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May 20, 2018

Journal of Clinical Oncology

Official Journal of the
American Society of Clinical Oncology

2018 ASCO Annual Meeting Proceedings

54th Annual Meeting
June 1-5, 2018
McCormick Place
Chicago, IL

ASCO®

54th
Annual Meeting of the American Society of Clinical Oncology
June 1-5, 2018
Chicago, Illinois

2018 Annual Meeting Proceedings

(a supplement to the *Journal of Clinical Oncology*)

ASCO®

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JOURNAL OF CLINICAL ONCOLOGY

Official Journal of the American Society of Clinical Oncology

CONTENTS

2018 ASCO ANNUAL MEETING PROCEEDINGS ABSTRACTS

continued on following page

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American Society of Clinical Oncology
54th Annual Meeting

2018 Abstracts

Descriptions of Scientific Sessions

Plenary Session
The Plenary Session includes abstracts selected by the Scientific Program Committee as having practice-changing findings of the highest scientific merit.

Highlights of the Day Sessions
Highlights of the Day Sessions invite expert discussants to provide an overview of the previous day's Oral Abstract presentations, focusing on key findings and putting abstracts into clinical context.

Oral Abstract Sessions
Oral Abstract Sessions include didactic presentations of abstracts of the highest scientific merit, as determined by the Scientific Program Committee. Experts in the field serve as discussants and provide comprehensive themed discussions of the findings from the abstracts.

Clinical Science Symposia
Clinical Science Symposia provide a forum for science in oncology, combining didactic lectures on a specific topic with abstract presentations. Experts in the field serve as discussants, placing studies in the appropriate context and critically discussing the applicability of the conclusions in clinical practice. Three special Clinical Science Symposia will be designated around specific topics that cut across cancer types.

Poster Discussion Sessions
Select posters from the Poster Sessions will be discussed by expert discussants, with the abstract authors participating in a question and answer period as panel members. These sessions will be followed by networking with the discussants and authors.

Poster Sessions
Poster Sessions include selected abstracts of clinical research in poster format. Trials in Progress (TPS) abstracts are presented within a track's Poster Session.

Publication-Only Abstracts
Publication-only abstracts were selected to be published online in conjunction with the Annual Meeting, but will not be presented at the Meeting.

All presented and publication-only abstracts are citable to this Journal of Clinical Oncology *supplement. For citation examples, please see the Letter from the Editor.*

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2018 Annual Meeting. Abstracts selected for electronic publication only are available in full-text versions online through ASCO.org and JCO.org. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Annual Meeting Program or the iPlanner, the online version of the Annual Meeting Program, available at am.asco.org.

Dates and times are subject to change.
All modifications will be posted on am.asco.org.

Letter From the Editor

The *2018 ASCO Annual Meeting Proceedings* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation at the 54th ASCO Annual Meeting. Accepted abstracts not presented at the meeting are included in the online supplement to the May 20 issue of *Journal of Clinical Oncology* at JCO.org.

The majority of abstracts selected for presentation are included here in full and are categorized by scientific track. Abstracts can be also accessed online through ASCO abstracts website (abstracts.asco.org) or Meeting Library (meetinglibrary.asco.org). Online abstracts include the full list of abstract authors and their disclosure information.

Late-Breaking Abstracts are represented here by abstract title and first author only. The full-text versions of these abstracts will be publicly released during the Annual Meeting. Print versions of these abstracts will be available onsite at the Annual Meeting in the *ASCO Daily News*.

All abstracts carry *Journal of Clinical Oncology* citations. The following are citation examples for print and electronic abstracts:

J Clin Oncol 36:5s, 2018 (suppl; abstr LBA1)

J Clin Oncol 36, 2018 (suppl; abstr e12000)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD
Editor, *2018 ASCO Annual Meeting Proceedings*

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Editorial Correspondence (manuscript-related inquiries):
Stephen A. Cannistra, MD, Editor-in-Chief
Journal of Clinical Oncology
2318 Mill Road, Suite 800
Alexandria, VA 22314
Phone: 703-797-1900; Fax: 703-684-8720
E-mail: jco@asco.org; Internet: jco.org

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4. Subscribers outside the US, add $150 per print subscription for expedited delivery.
5. Single-issue price: $40 US, $50 international.
6. Prices quoted are in US dollars, and payments must be made in US dollars.
7. Except on consortia orders, the publisher allows for a 5% discount on Tiers 1-3 to recognized subscription agents.

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Japan
USACO Corporation
2-17-12 Higashi-Azuba Minato-ku
Tokyo, Japan 106-0044
Phone: +81-3-3505-3256; Fax: +81-3-3505-6282
E-mail: import@usaco.co.jp; Internet: www.usaco.co.jp

China
Charlesworth China
Room 1105, Building 9, Jianwai SOHO
No. 39 Dongsanhuan Zhonglu
Chaoyang District, Beijing 100022
PR China
Phone: +86-10-58696201; Fax: +86-10-58696201
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India
BMJ
Mindmill Corporate Tower
6th Floor, 24 A, Film City, Sector 16 A
Noida, 201301, Uttar Pradesh
India
Phone: +91-120-4345733-38
E-mail: institutionalsales.india@bmj.com

South Korea
EBSCO Korea
Phone: +82-2-598-2571
E-mail: brendakim@ebsco.com

Taiwan
EBSCO Taiwan
Phone: +886 2-27751596
E-mail: dfeng@ebsco.com

Latin America, Caribbean, Middle East, and North Africa
Accucoms (US), Inc.
PO Box 1651
Lansdale, PA 19446
Phone: 1-267-646-1118
Fax: 215-660-5042
E-mail (Latin America): eva.barboza@accucoms.com
E-mail (Middle East): eyad@accucoms.com
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Australia and New Zealand
BMJ
Phone: +61-414-234-686
E-mail: thilker@bmj.com

Indonesia, Malaysia, Philippines, Singapore, Thailand, and Vietnam
BMJ
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Suntec Tower 2
Singapore 038983
Phone: +65-3157-1351
E-mail: dpeh@bmj.com

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Public Release of Abstracts

The abstracts published in the *2018 ASCO Annual Meeting Proceedings,* including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 16, 2018. These abstracts are publicly available online through ASCO.org, the official website of the Society. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released according to the following schedule:

- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Friday, June 1, will be publicly released Friday, June 1, through ASCO.org at 2:00 PM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Saturday, June 2, will be publicly released Saturday, June 2, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Sunday, June 3, will be publicly released Sunday, June 3, through ASCO.org at 7:30 AM (EDT).
- Late-Breaking Abstracts presented in a press briefing or scientific presentation (whichever comes first) on Monday, June 4, or Tuesday, June 5, will be publicly released Monday, June 4, through ASCO.org at 7:30 AM (EDT).

Late-Breaking Abstracts will be available in Section D of *ASCO Daily News* on the day of their scientific presentation, with the exception of abstracts presented on Friday (these will appear in the Saturday issue) and those presented on Tuesday (these will appear in the Monday issue).

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on ASCO.org.

Conflict of Interest Disclosure

As the CE provider for the Symposium, ASCO is committed to balance, objectivity, and scientific rigor in the management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. Participants in the Symposium have disclosed their financial relationships in accordance with ASCO's Policy for Relationships with Companies; review the policy at asco.org/rwc.

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ABSTRACTS
American Society of Clinical Oncology
54th Annual Meeting
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SPECIAL AWARD LECTURE ABSTRACTS

David A. Karnofsky Memorial Award and Lecture
Saturday, June 2, 9:30 AM

Oligometastasis from conception to treatment.
Ralph R. Weichselbaum, MD; The University of Chicago Medical Center, Chicago, IL

Metastases account for 80-90% of cancer deaths. Despite recent advances in systemic therapies, almost all patients who develop metastases from adult solid tumors are not cured. We proposed that a subset of patients develop few metastatic lesions within limited destination organs, termed oligometastasis. These patients may be amenable to cure by ablative therapies including radiotherapy and surgery. We also proposed that patients who respond well to systemic therapies, but later re-present with a limited number of persistent or oligo-progressive tumors, may be cured when ablative therapies are combined with systemic therapies. I will review laboratory data that provides clues regarding the biological basis of oligometastases, and discuss retrospective data and early level 1 evidence to demonstrate improved PFS and OS in patients with oligometastatic disease. Looking forward, I will discuss a rationale for designing clinical trials that integrate ablative therapies combined with systemic approaches including hormonal manipulation, targeted cytotoxic drugs, and immunotherapy in order to optimize cure in various stages of metastatic disease.

Science of Oncology Award and Lecture
Sunday, June 3, 1:00 PM

Preventing HPV-associated cancers by vaccination.
Douglas R. Lowy, MD; Deputy Director, National Cancer Institute, Bethesda, MD

The laboratory developed the virus-like particle technology that underlies the three FDA-approved HPV vaccines, which have the potential to prevent the majority of the HPV infections that lead to ~30,000 anogenital and oropharyngeal cancers annually in U.S. men and women, and to ~8% of all female cancers worldwide. They are the first vaccines that successfully target an infectious agent that mainly induces local sexually transmitted disease. The vaccines, which are given systemically, confer more than 90% protection against new mucosal and cutaneous infections.

We have studied the mechanisms that underlie the efficacy of the vaccine, using an HPV mouse genital tract challenge model after validating that it recapitulates vaccine responses that are similar to those observed in women. Passive transfer studies indicate that neutralizing antibodies induced by the vaccine account for its high protective efficacy, although the vaccine also induces cell-mediated responses. Factors that contribute to vaccine efficacy include: intrinsically high immunogenicity of the virus-like particle (VLP) structure of the vaccine immunogen, high in vivo sensitivity of HPV to neutralizing antibodies, and high antibody levels at potential sites of infection.

The HPV vaccines are already having an impact on HPV-induced early disease markers in vaccinated populations, including evidence of herd immunity. The high immunogenicity of the vaccines has led us to hypothesize that, in contrast to most other protein-based subunit vaccines, it may be possible to safely reduce the number of recommended vaccine doses from the current two or three to a single dose in young adolescents, who represent the main target group for the vaccine. A randomized clinical trial has been started to test this hypothesis.

Disclosure: I am an inventor of the virus-like particle technology that underlies the technology for the HPV vaccines. The technology has been licensed by the NIH to Merck and GlaxoSmithKline, the manufacturers of the FDA-approved vaccines.

ASCO–American Cancer Society Award and Lecture
Monday, June 4, 9:45 AM

Hereditary cancer genetic testing and risk reduction: Evolving strategies.
Karen H. Lu, MD; The University of Texas MD Anderson Cancer Center, Houston, TX

As a gynecologic oncologist, I have had an ongoing interest in the intersection of cancer treatment and cancer prevention. With the approval of parp inhibitors for BRCA-associated ovarian cancer and immune checkpoint blockade for MSI-H endometrial cancers, there has been increasing emphasis on universal genetic screening for women who have these cancers. However, the real impact on decreasing mortality will be in the "cascade testing" of family members, who can then undergo risk reduction strategies. Traditional models of delivering cancer genetics services and cascading the information to family members need to be re-examined. Strategies for genetic testing must focus on increasing access and using technology to provide genetic counseling. We are currently studying this paradigm in a national study called Making Genetic Testing More Accessible (MAGENTA). Described as "Genetic Testing from your Living room," the study aims to examine novel delivery models of genetic counseling and testing. Two other strategies need to be employed if we are to realize the full potential of cancer risk reduction through genetic risk assessment and testing. First, partnership with advocates at the time of research planning is essential, as the development of prevention strategies must consider patient preferences beyond efficacy. A national study of immediate salpingectomy and delayed oophorectomy in women at increased risk of ovarian cancer was based on scientific evidence that BRCA-associated ovarian cancer begins in the fimbriae of the fallopian tube, and was strongly driven by the advocacy community as an option to delay the effects of surgical menopause. Second, those of us in the cancer prevention community need to embrace a more patient-centered, multidisciplinary approach for care of these genetically high risk patients who are at risk for multiple cancers. As the number of "previvors" increases, we will need to continually innovate to develop novel approaches for multi-organ chemoprevention or coordinated screening.

B. J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
Monday, June 4, 3:00 PM

Honoring the preferences of older patients with cancer and caregivers through improved communication.
Supriya Gupta Mohile, MD, MS; University of Rochester Medical Center, Rochester, NY

Geriatric oncology has undergone a transformation over the last 15 years. Following advocacy from key leaders in research such as BJ Kennedy, Lodovido Balducci, and John Bennett, ASCO partnered with the John Hartford Foundation to invest in geriatric oncology fellowship training programs that spawned 28 fellows. These fellows, working with senior mentors in the field such as Harvey Cohen, Hyman Muss, Stuart Lichtman, and Martine Extermann, developed a cohesive voice dedicated to improving care delivery for older patients with cancer. To translate this voice and passion into action, geriatric oncology investigators, spearheaded by Arti Hurria, formed the Cancer and Aging Research Group. Three investigators (Hurria, Dale, and Mohile) organized 3 conferences through a U13 partnership with the NIH to develop the research priorities in aging and cancer. By partnering with ASCO, the Society of International Geriatric Oncology, the Alliance, and the NCI Community Oncology Research Program, geriatric oncology investigators are now taking action to improve policy, foster educational efforts in geriatric oncology, and conduct high quality, high impact research. Better care for older adults with cancer requires geriatric assessment and management; a new ASCO guideline highlights the high quality evidence developed by geriatric oncology investigators from around the world, which demonstrates that geriatric assessment measures can identify older patients at highest risk for adverse outcomes. Geriatric oncology research will now need to undergo another transformational shift and should focus on how best to improve communication around decisions for treatment for "real world" older patients. Geriatric assessment can enhance communication about risks and benefits and thus allow us as clinicians to elicit, respect, and honor what older patients with cancer and caregivers want and need. The transformational shift in geriatric oncology research will require strong partnerships with stakeholders, including older patients and caregivers, and will be enhanced by innovative research methods such as mixed methods, social network analyses, and machine learning.

Pediatric Oncology Award and Lecture
Monday, June 4, 1:15 PM

Facilitating precision oncology for children: Implementing new legislative provisions for the therapeutic orphans.
Gregory H. Reaman, MD, FASCO; U.S. Food and Drug Administration, Silver Spring, MD

Although the cure rates for childhood cancer have improved dramatically over the past several decades resulting in extended disease-free survival for >80% of those afflicted, cancer remains the leading cause of death from disease in children. This is a direct result of suboptimal treatment results for some specific cancers particularly when metastatic at diagnosis and when recurrent due to resistance to therapy. The dismal outcomes for some rare

pediatric cancers have not improved. In addition, the short and long term toxicities related to current therapies negatively impact quality of life and survivorship. The unmet clinical need for new drugs for children with cancer and cannot be overstated.

Molecularly targeted drugs developed for cancers which occur predominantly in adults have advanced the concept of precision medicine in oncology, which is transforming cancer care for adults. Similar treatment advances are yet to be realized in children. Although large scale efforts at genomic interrogation of various pediatric cancers have provided evidence that the genetic and epigenetic repertoire of driver gene aberrations differ between the cancers of adults compared to those which predominate in children, recent evidence reveals that many of the same genetic and other molecular biological vulnerabilities evident in many adult cancers may present opportunities for the use of certain targeted agents in up to 50% of children with tumors which are histologically and biologically different. Pediatric cancer drug development has historically leveraged adult drug discovery and development. Laws envisioned to assure equitable access to new therapies for both children and adults by requiring or incentivizing sponsors to conduct studies to evaluate efficacy and safety in children have greatly improved therapeutic options in many clinical areas except cancer. Recent amendments to Section 505B of the Food, Drug, and Cosmetic Act promise to change the landscape of pediatric cancer drug development. Responsible implementation of these new provisions to expedite evaluation of novel agents promises a change for children as therapeutic orphans.

Gianni Bonadonna Breast Cancer Award and Lecture
Monday, June 4, 4:45 PM

Mentoring, empowering, opening doors.

Gabriel N. Hortobagyi, MD, MACP, FASCO; The University of Texas MD Anderson Cancer Center, Houston, TX

Gianni Bonadonna was an outstanding oncologist, clinical investigator, academic leader, educator, role model, writer, philosopher and most importantly, a dear friend. Our 40-year friendship started in 1975 and continued through collaborations in clinical research, publishing, international speaking, mentoring and sharing the finer aspects of life. At the top of his career, a sudden illness transformed his life; he then became an example to all of us about how to overcome adversity with dignity, persistence and grace. His continued productivity during the last decade of life is a testimony to his willpower, creativity, intelligence and dedication to oncology and medicine.

My own career focused on clinical and translational research in breast cancer and the training and mentoring of a number of young oncologists from around the world. My initial focus was the development and implementation of neoadjuvant chemotherapy, first, in the management of locally advanced and inflammatory breast cancer, later, in the curative therapy of earlier stages of operable breast cancer. I was fortunate to work with outstanding colleagues in surgical, radiation and medical oncology, as well as imagers and pathologists at one of the premier cancer centers in the world. Our multidisciplinary approach to the management of malignant disease was the cornerstone of our practice since the early 1970s. Since then, it has been adopted by many other institutions around the world as a superior method to manage all solid tumors. Other major research interests resulted in the development and implementation of clinical trials that demonstrated the role of multiple new drugs (anthracyclines, taxanes, bisphosphonates, everolimus and ribociclib) in the management of advanced and early breast cancer, the development of gene expression profiling for prognostication, classification and prediction of benefit from treatment, and the initial steps in gene therapy for solid tumors. However, the most satisfying aspect of my career has been the opportunity to interact with, mentor and empower my younger colleagues (residents, fellows, junior faculty) and open doors for successful career development. Many of them occupy today leadership positions in oncology all around the world. They will carry the torch and will train the next generation of oncologists to move the field forward.

Allen S. Lichter Visionary Leader Award and Lecture
Saturday, June 2, 3:00 PM

Serendipity and purpose.

Nancy E. Davidson, MD, FASCO; Fred Hutchinson Cancer Research Center, Seattle, WA

Reducing the burden of cancer is a daunting task and requires vision, collaboration, and hard work from all. During my career as a physician-scientist working in the biology and treatment of breast cancer and inspired by our patients, I worked in the nascent fields of apoptosis and epigenetics of breast cancer, moving lab discoveries from bench to bedside. Our teams at Johns Hopkins, University of Pittsburgh, and Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance enabled this work. The imperative to work nationally and internationally led us to found the Translational Breast Cancer Research Consortium and initiate the AURORA project in metastatic breast cancer to accelerate our goals to bring scientific discovery to patient care. My service as director of an NCI Cancer Center and advisor to many others crystallized the need for and importance of collaborative and visionary

leadership. The unusual honor of serving as president of both the American Society of Clinical Oncology and the American Association for Cancer Research provided an extraordinary platform to champion the vital roles of the entire community of cancer practitioners, researchers, and advocates to catalyze progress and change.

LBA1 **Plenary Session, Sun, 1:00 PM-4:00 PM**

TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score. *First Author: Joseph A. Sparano, Montefiore Medical Center, Bronx, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA2 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Maintenance low-dose chemotherapy in patients with high-risk (HR) rhabdomyosarcoma (RMS): A report from the European Paediatric Soft Tissue Sarcoma Study Group (EpSSG). *First Author: Gianni Bisogno, Department of Women and Children Health, University Hospital of Padova, Padova, Italy*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA3 **Plenary Session, Sun, 1:00 PM-4:00 PM**

CARMENA: Cytoreductive nephrectomy followed by sunitinib versus sunitinib alone in metastatic renal cell carcinoma—Results of a phase III noninferiority trial. *First Author: Arnaud Mejean, Department of Urology, Hôpital Européen Georges-Pompidou - Paris Descartes University, Paris, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

LBA4 **Plenary Session, Sun, 1:00 PM-4:00 PM**

Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) $\geq$ 1%: Open-label, phase 3 KEYNOTE-042 study. *First Author: Gilberto Lopes, Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Sunday, June 3, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

100 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Ado-trastuzumab emtansine (T-DM1) in patients (pts) with HER2 amplified (amp) tumors excluding breast and gastric/gastro-esophageal junction (GEJ) adenocarcinomas: Results from the National Cancer Institute (NCI) Molecular Analysis for Therapy Choice (MATCH) trial. *First Author: Komal L. Jhaveri, New York University Cancer Institute, New York, NY*

Background: The NCI-MATCH is the largest national signal-finding trial incorporating centralized genomic testing to direct pts to molecularly targeted phase 2 treatment arms. HER2 gene amp is observed in many different tumor types. **Methods:** HER2 amp was defined as copy number (CN) ≥7 based on tumor sequencing on an adapted Oncomine AmpliSeq™ panel under FDA investigational device exemption. Pts with prior trastuzumab, pertuzumab or T-DM1 treatment were excluded. Pts received T-DM1 at 3.6 mg/kg IV Q3 weeks until toxicity or disease progression. Tumor assessments occurred Q3 cycles for 33 cycles and Q4 cycles thereafter. Primary endpoint was objective response. Correlative studies included correlating HER2 CN, HER2 protein levels by IHC, HER2:CEP17 ratio (by FISH), PTEN loss, MYC amplification and PIK3CA mutation status with response. **Results:** 37 eligible pts were treated between 11/15-3/17. Median age was 65 (range 39-80). 33% had received > 3 lines of prior therapy. Median HER2 CN was 17 (7-139). Various histologies were treated: colon carcinoma (ca) (n = 7), ovarian ca (n = 6), rare tumors such as cholangioca (n = 1), carcinosarcoma of the uterus (n = 1), salivary gland ca (n = 3), among others. 3/37 (8.1%, 90% CI 2.2%-19.6%) had a confirmed partial response including 1 patient each with salivary duct ca of parotid gland, squamous cell ca of parotid gland and extramammary Paget's disease of the scrotum. Additionally, 43% had stable disease (SD) including 3/3 evaluable ovarian and uterine ca respectively. Median duration of SD was 4.6 months. The 6-month PFS rate was 24.8% (90% CI 15.0%-41.1%). Common toxicities included fatigue, anemia, fever and thrombocytopenia with no new safety signals. Median treatment duration was 4 cycles (range 1- 23). Data from correlative analysis will be presented at the meeting. **Conclusions:** T-DM1 was well tolerated. Clinical activity was observed in HER2 amp non breast and gastric/GEJ adenoca pts warranting further study either alone or in combinations particularly in some histologies such as salivary gland tumors. Clinical trial information: NCT02465060.

101 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Results from molecular analysis for therapy choice (MATCH) arm I: Taselisib for PIK3CA-mutated tumors. *First Author: Ian E. Krop, Dana-Farber Cancer Institute, Boston, MA*

Background: MATCH is a trial that assigns patients (pts) with solid tumors, lymphomas, or multiple myeloma to specific targeted therapies based on genetic alterations identified in fresh tumor biopsies. Arm I evaluated the PI3-kinase inhibitor taselisib in pts with activating mutations in PIK3CA, the catalytic subunit of PI3-kinase. **Methods:** Pts with KRAS mutations or PTEN mutation or loss were excluded, as were pts with breast or squamous lung cancer. Pts received taselisib 4 mg po daily on 28 d cycles until progression or intolerable toxicity. Staging was every 2 cycles. The primary endpoint was objective response (OR); secondary endpoints were PFS, 6-month PFS, and predictive biomarkers. **Results:** 65 pts (enrolled 3/2016-4/2017) received ≥1 dose of study therapy; 45 tumor types were represented; 38% of pts had > 3 prior lines of therapy. There were no ORs, but prolonged stable disease was observed (estimated PFS6 rate 27%, 90% CI 19%-39%), and 2 pts remain on study > 1 yr. The most common toxicities were fatigue (38%), diarrhea (38%) and nausea (34%), all predominately grade 1-2, with 2% of pts requiring dose reductions, and 11% discontinuing taselisib because of toxicity. No hyperglycemia or rash were observed. PIK3CA mutations occurred in the helical domain (HD, 69%), kinase domain (KD, 17%), or other domains (14%). There was an observed trend (non-significant) toward longer PFS in tumors with KD mutations compared to HD or other mutations (median PFS 4.6 mo vs 3.5 mo vs 1.8 mo, respectively). Co-occurring mutations were detected in 67% of tumors. In exploratory analyses, TP53/MDM2 alterations (n = 24) were associated with PFS < 6 mo, and enrichment for PFS ≥ 6 mo was observed in pancreatic-biliary tumors/cholangiocarcinoma (3/6) and adenoid cystic carcinoma (3/4). Only 1 of 9 pts with BRAF, NRAS, HRAS, MAP2K1, MAPK1, or NF1 mutations achieved PFS ≥ 6 mo. **Conclusions:** In a mixed histology cohort selected for activating PIK3CA mutations, taselisib did not achieve any ORs, although 27% of pts had PFS ≥ 6 mo. PIK3CA mutation independent of histology is an insufficient predictor of taselisib activity. Associations of individual histologies and PIK3CA mutation subtypes with PFS may be worthy of further study. Clinical trial information: NCT02465060.

102 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with *RET*-altered cancers. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Multikinase inhibitors (MKIs) have limited activity in *RET* fusion-positive (+) and *RET*-mutant cancers, questioning the therapeutic potential of these targets. LOXO-292 selectively targets RET and has preclinical activity against activating *RET* fusions/mutations, potential resistance mutations, and brain metastases. **Methods:** This global phase 1 study for patients (pts) w/ advanced solid tumors included *RET* fusion+ NSCLC and papillary thyroid cancer (PTC), *RET*-mutant medullary thyroid cancer (MTC), and any other cancer w/ these alterations. Pts were dosed orally in 28-day cycles. Dose escalation followed a 3+3 design. The primary endpoint was MTD determination. Secondary endpoints included safety, overall response rate (ORR, RECIST 1.1) and duration of response (DoR). **Results:** As of 05-Jan-18, 57 pts were treated at 7 doses (20 mg QD→160 mg BID), including 35 *RET* fusion+ tumors (27 NSCLC, 7 PTC, 1 pancreatic) and 20 *RET*-mutant MTCs. 67% were MKI pre-treated (median 1, range 1-4; included pts w/ acquired MKI resistance). No DLTs were observed. The MTD was not reached. AEs (≥10% of pts) were fatigue (16%), diarrhea (16%) and dyspnea (12%); most were grade 1-2. No AEs ≥ grade 3 were attributed to LOXO-292. The ORR in evaluable *RET* fusion+ pts was 69% (95% CI 50%-84%, n = 22/32, 11 pending confirmation, 9/13 MKI-naïve,13/19 MKI pretreated): 65% (n = 17/26) in NSCLC and 83% (n = 5/6) in PTC. 84% (27/32) had radiographic tumor reduction (range -19% to -67%). NSCLC responses occurred independent of upstream partner when known (9/13 *KIF5B* vs 7/9 non-*KIF5B*) and included 3 pts w/ baseline brain metastases. Tumor reduction was achieved in 79% of MTC pts (n = 11/14 evaluable, range -9% to -45%), including 2 PRs, 1 in a patient w/ a hereditary *RET* V804M gatekeeper mutation treated w/ 3 prior MKIs. 79% (n = 11/14) of MTCs had a ≥50% decrease in serum calcitonin (for ≥4 weeks). Most pts (n = 52/57) remained on treatment. The median DoR was not reached (all responses ongoing, longest > 6 months). **Conclusions:** LOXO-292 was well-tolerated and had marked antitumor activity in pts w/ *RET*-altered cancers, including those w/ resistance to prior MKIs and brain metastases. Rapid development w/ registrational intent is planned. Clinical trial information: NCT03157128.

103 Clinical Science Symposium, Sat, 8:00 AM-9:30 AM

Impact of next-generation sequencing (NGS) on treatment selection in acute myeloid leukemia (AML). *First Author: Rita Elias Assi, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Until recently, therapy options for AML patients (pts) were limited. The advent of NGS and novel targeted agents raise the question of how broader use of testing will impact treatment and outcomes. **Methods:** From October 2012 to June 2016, we included 1470 AML pts with available NGS-based detection of somatic mutations. 17 genes (*ALK, CSF1R, FGFR1/2/3, FLT3, IDH1/2, JAK2, KDR, KRAS/NRAS, NPM1, PDGFRA, PTPN11, RET and TP53)* were considered potentially actionable due to the possibility to be directly or indirectly targeted with standard or investigational agents. **Results:** of the 1271 treated pts, 982 (77%) had a median of 2 actionable mutations (AMs) (1-5): *TP53* (n = 241; 16%), *IDH2* (n = 240; 16%), *IDH1* (n = 238; 16%), *FLT3* (200; 14%), *NPM1* (n = 195; 13%), *NRAS* (n = 175; 12%), *JAK2* (103; 7%), *KRAS* (n = 82; 6%). 41% (271/518) of pts started new therapy after NGS results availability. NGS guided targeted therapy in 36% of pts: 53% of these enrolled on clinical trials (CT) and 6% received off-label agents. Considering AMs only, relapsed/refractory (R/R) pts were more likely to receive targeted therapy than newly diagnosed (51% vs 23%, p < 0.0001). At different timepoints, the probability of receiving targeted agent for pts with AMs was 9% (13/140) for the period 2012-Sept 2013, 21% (143/685) for Oct 2013-2014 and 23% (147/645) in 2015-June 2016 (p = 0.001). Pts who received targeted therapy had higher response rate compared to those who did not whether newly diagnosed (72% vs 60%;p = 0.04) or R/R (31% vs 21%; p = 0.001). **Conclusions:** NGS can impact therapy decision in more than 30% of AML pts when performed in a timely manner. R/R pts were more likely to receive targeted agents than newly diagnosed. Possible reasons are delays in NGS results, urgency to start therapy and presumption that standard therapy may be better than investigational targeted agents. The results of current CT may change the way we treat AML pts.

Treated pts		**1271/1470 (86%)**	
Median age		63 yrs (17-92)	
Male		782 (62%)	
Median time to inform results		9 days (3-90)	
		Newly diagnosed (N = 519)	**R/R (N = 463)**
Actionable mutation(s)		390 (75%)	338 (73%)
Subsequent targeted therapy	p < 0.0001	91/390 (23%)	173/338 (51%)
On CT		75 (19%)	149 (44%)
Off-label		16 (4%)	24 (7%)
Alive at last follow-up		55%	76%

104 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). *First Author: Sibylle Loibl, German Breast Group (GBG), Neu-Isenburg, Germany*

Background: Combining immune-checkpoint inhibitors with chemotherapy yielded high response rates in patients (pts) with metastatic TNBC. Therefore, we evaluated the addition of durvalumab, an anti-PD-L1 checkpoint inhibitor, to standard neoadjuvant chemotherapy in pts with primary TNBC. **Methods:** GeparNuevo randomized pts to durvalumab (D) 1.5 g i.v. or placebo every 4 weeks (wks). D/placebo monotherapy (0.75 g i.v.) was given for the first 2 wks (window phase), followed by a biopsy and D/placebo plus nab-paclitaxel (nP) 125 mg/m^2 weekly for 12 wks, followed by D/placebo plus epirubicin/cyclophosphamide (EC) q2 wks for 4 cycles. Randomization was stratified by stromal tumor infiltrating lymphocyte (sTILs) (low (≤10%), intermediate (11-59%), high (≥60%)). Pts with primary cT1b-cT4a-d disease, centrally confirmed TNBC and sTILs status were included. Primary objective compares pCR (ypT0 ypN0) rates. Secondary objectives are pCR rates in stratified subpopulations and according to other pCR definitions; response rates; breast conservation rate; toxicity; compliance and survival. Sample size was planned assuming a pCR rate of 48% for placebo based on the GeparSepto results and 66% for D (as clinically meaningful benefit), requiring 158 pts to show superiority of D (2-sided α=0.2, 80% power). Assuming a 10% drop-out rate, randomization of 174 pts was planned. **Results:** A total of 174 pts were enrolled between June 2016 and September 2017 and all pts had completed treatment. Median age was 49.5 years [range 23.0-76.0]; 44.5% of pts had cT1, 49.7% cT2, 3.5% cT3, 2.3% cT4; 83.3% G3 and 31.4% cN-positive tumors assessed by sonography; sTILs categories were 37.9% low, 47.7% intermediate, and 14.4% high; median Ki67 was 49.0% [range 3.0%-96.0%]. A total of 86 SAEs and 65 immune related AEs of special interest (irAESI) were reported; 34.5% of pts had at least one SAE and 27.6% had at least one irAESI. Overall, 84 of 174 pts (48.3% 95%CI [40.7-56.0]) had a pCR. **Conclusions:** Combination of chemotherapy with durvalumab/placebo yielded a high pCR rate in TNBC. Treatment was feasible. Unblinded results will be presented at the meeting. Funding and drug was provided by AstraZeneca and Celgene. Clinical trial information: NCT02685059.

105 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). *First Author: Luis G. Paz-Ares, University Hospital 12 de October, Madrid, Spain*

Background: Pembro plus pemetrexed and carboplatin resulted in superior objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) for untreated pts with non-sq NSCLC. Pembro is active in sq NSCLC, so combining with chemo is a rational next step. **Methods:** KEYNOTE-407 (NCT02775435) is a randomized, placebo-controlled, global study of 560 untreated pts with metastatic sq NSCLC with ECOG 0-1. Pts were stratified by type of taxane, PD-L1 (TPS <1% vs ≥1%), and site (East Asia vs other). Investigators chose taxane. Pts were randomized 1:1 to receive carboplatin 6 mg/mL/min and paclitaxel 200 mg/m^2 every 3 weeks or nab-paclitaxel 100 mg/m^2 weekly plus pembro or saline placebo for 4 cycles followed by pembro/placebo for a total of 35 treatments. Imaging is sent for blinded independent central review (BICR) per RECIST 1.1. The primary endpoints are PFS by BICR and OS in the intent-to-treat population. Alpha is strictly controlled at 0.025 one-sided; PFS and OS each have 0.01. A key secondary endpoint is ORR by BICR in about the first 200 pts randomized with 0.005 alpha. A second interim analysis will be performed on PFS and OS when approximately 332 PFS events will have occurred. The hazard ratio (target 0.7) will be estimated using a stratified Cox regression model. The arms will be compared with a stratified log-rank test. Enrollment completed at the end of 2017. **Results:** In the first interim analysis, the initial 204 pts were randomized 101 to pembro + chemo and 103 to chemo with median follow-up of 7.7 m (range 0.4, 13.9). Pts were 78% male, 48% < 65 y, and 28% ECOG PS 0. PD-L1 status was 35% TPS<1%. 32% used nab-paclitaxel. Per BICR pembro + chemo had an ORR of 58.4% compared to 35.0%, p-value 0.0004. Duration of response ≥6m was 65.8% for pembro + chemo and 45.6% for chemo by Kaplan-Meier estimates. Incidence grade ≥3 AEs was 64.4% for pembro + chemo and 74.5% for chemo. No new safety concerns were observed. **Conclusions:** Adding pembro almost doubled the ORR of chemo for pts with untreated metastatic sq NSCLC. Pembro + chemo has a tolerable safety profile. Results from a second interim analysis may be available prior to the meeting. Clinical trial information: NCT02775435.

106 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort. *First Author: Panagiotis A. Konstantinopoulos, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Platinum-resistant OC (PROC) has few treatment options. Niraparib is an oral PARP inhibitor (PARPi) approved for maintenance treatment of ROC. Anti–programmed death (PD)–1 monotherapies (eg, pembrolizumab) have shown low level activity in ROC, and beyond *BRCA*-mut, PARPi have shown minimal activity in PROC. Preclinical data demonstrate synergy with PARPi + anti-PD-1 combinations. **Methods:** Eligible pts must have experienced a response lasting ≥6 months to first-line platinum therapy and were considered to have PROC per investigator's assessment (eg, pts not eligible for further platinum) and no more than 5 prior treatment lines. While primary platinum-refractory (PRef) disease was excluded, secondary PRef disease was not. A phase 1 study previously established RP2D of niraparib 200 mg orally once daily + pembrolizumab 200 mg IV every 21 days. Primary and secondary endpoints included objective response rate (ORR = CR+PR) and disease control rate (DCR = CR+PR+SD). Genetic biomarkers were assessed by Stand Up To Cancer (SU2C) Ovarian Cancer Dream Team. **Results:** As of Jan 2018, 60/62 pts were evaluable for response assessment (≥1 on-study scan). Median age was 60 years. Median prior lines of chemotherapy was 2 (range: 1-5). Based upon platinum-free interval (PFI) to last platinum treatment, 64% of pts had PROC (PFI < 6 months), 19% had PRef disease (PFI < 30 days), and 17% had platinum-sensitive (PSens; PFI ≥6 months) disease. Twenty pts remain on treatment and 11 have received treatment for ≥6 months. Among the 60 evaluable pts, ORR/DCR were 25%/68%; among the 11 tumor *BRCA* (t*BRCA*) mut evaluable pts, ORR/DCR were 45%/73%. Responses were observed in 11/38 PROC pts, 2/11 PRef pts, and 1/10 PSens pts (platinum status unknown in 1 responder). Durability of response data will be presented. Follow-up is ongoing. The most common grade ≥3 TEAEs were anemia (19%) and thrombocytopenia (9%). **Conclusions:** With ORR of 25% in all PROC and ORR of 45% in t*BRCA*mut pts, niraparib + pembrolizumab appears promising. Additional evaluation of this combination in ROC is warranted. No new safety signals were identified with the combination. Clinical trial information: NCT02657889.

108 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Epacadostat (E) plus pembrolizumab (P) versus pembrolizumab alone in patients (pts) with unresectable or metastatic melanoma: Results of the phase 3 ECHO-301/KEYNOTE-252 study. *First Author: Georgina V. Long, Department of Medical Oncology and Translational Research, Melanoma Institute Australia, The University of Sydney, Mater Hospital and Royal North Shore Hospital, Sydney, Australia*

Background: In a phase 1/2 study, the combination of E, a selective oral inhibitor of the IDO1 enzyme, plus P, a PD-1 inhibitor, suggested promising antitumor activity with minimal additive toxicity. ECHO-301/KEYNOTE-252 (NCT02752074) is a phase 3, randomized, double-blind study evaluating the efficacy and safety of E + P vs placebo + P in pts with untreated unresectable or metastatic melanoma. **Methods:** Pts had histologically confirmed unresectable stage III or IV melanoma and were treatment naive for advanced or metastatic disease, except for pts with the *BRAF* V600 mutation who could have received prior BRAF/MEK therapy. Pts were stratified by PD-L1 expression and *BRAF* mutation status (*BRAF* mutant with prior BRAF-directed therapy, *BRAF* mutant without prior BRAF-directed therapy, and *BRAF* wild type) and randomized 1:1 to E 100 mg BID + P 200 mg Q3W or matched E placebo + P 200 mg Q3W. Response was assessed per RECIST v1.1 and irRECIST (both by central review). The primary endpoints were PFS per RECIST v1.1 and OS. Secondary endpoints were ORR per RECIST v1.1, duration of response, and safety. This is the final analysis for PFS and interim analysis for OS. **Results:** A total of 706 pts were randomized (354 to E + P and 352 to placebo + P); 72.5% of tumors were PD-L1 positive, 44.5% *BRAF* mutant (12.2% received prior BRAF/MEK therapy). Median follow-up was ~14 mo. E + P did not result in a significantly longer PFS vs placebo + P (median 4.7 vs 4.9 mo; HR=1.00; CI, 0.83-1.21; P=0.517). PFS rate at 12 mo was 37% in both groups. Findings were consistent across PD-L1 and *BRAF* subgroups. OS was not expected to reach statistical significance based on the results of this interim analysis (HR=1.13; CI, 0.86-1.49; P=0.807). The OS rate at 12 mo was 74% in both groups. ORR was 34.2% and 31.5% in the E + P and placebo + P groups, respectively. Grade ≥3 treatment-related AEs occurred in 21.8% of patients receiving E + P and 17.0% receiving placebo + P. **Conclusions:** The addition of E to P did not result in greater clinical benefit over P alone in pts with unresectable or metastatic melanoma. The safety profile was consistent with that observed in previously reported studies of this combination. Clinical trial information: NCT02752074.

109 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

A comparative clinical study of PF-06439535, a candidate bevacizumab biosimilar, and reference bevacizumab, in patients with advanced non-squamous non-small cell lung cancer. *First Author: Mark A. Socinski, Florida Hospital Cancer Institute, Orlando, FL*

Background: This ongoing, double-blind, randomized, global clinical trial (NCT02364999) evaluated the efficacy, safety, and immunogenicity of PF-06439535 vs. reference bevacizumab sourced from the EU (bevacizumab-EU), in combination with paclitaxel (P) and carboplatin (C), as first-line therapy in patients with advanced non-squamous non-small cell lung cancer (NSCLC). **Methods:** Eligible pts were randomized 1:1 to PF-06439535 or bevacizumab-EU plus P/C on Day 1 of every 3-week (wk) cycle followed by PF-06439535 or bevacizumab-EU blinded monotherapy until disease progression or unacceptable toxicity. The primary objective was to compare objective response rate (ORR) by Wk 19 between treatment arms. Secondary objectives included safety, 1 year (yr) PFS, 1 yr survival rate and immunogenicity. **Results:** 719 pts were randomized: PF-06439535 (n = 358) and bevacizumab-EU (n = 361). The majority of patients were male (65%) with a median age of 61y and newly diagnosed Stage IV NSCLC (76%). For the primary endpoint, relative risk of ORR was 1.015. The 90% confidence interval (CI), 0.886-1.163, was contained within the FDA pre-specified therapeutic equivalence margin of 0.73–1.37. Secondary endpoints further support similarity between the 2 treatment arms (Table). Incidence of treatment-emergent adverse events (AEs) (all-causality) was similar (PF-06439535: 96.6%) and (bevacizumab-EU: 96.1%). AE results indicate no clinically meaningful differences between the two arms for arterial thromboembolic event (TE)/venous TE events, bleeding events, hypertension, GI perforation, and proteinuria. **Conclusions:** In patients with advanced non-squamous NSCLC, PF-06439535 and bevacizumab-EU showed similar ORR (primary endpoint) PFS, OS, safety and immunogenicity. Clinical trial information: NCT02364999.

Efficacy endpoints.

	PF-06439535	Bevacizumab-EU
ORR	45.3% (95%: 40.01%, 50.57%)	44.6% (95%: 39.40%, 49.89%)
1 yr PFS rate	29.4% (95% CI: 23.2%, 35.9%)	29.3% (95% CI: 23.5%, 35.3%)
1 yr survival rate	65.2% (95% CI: 59.0%, 70.7%)	66.4% (95% CI: 59.9%, 72.0%)

110 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Biosimilar trastuzumab-dkst monotherapy versus trastuzumab monotherapy after combination therapy: Toxicity, efficacy, and immunogenicity from the phase 3 Heritage trial. *First Author: Aleksei Manikhas, City Clinical Oncology Dispensary, St. Petersburg, Russian Federation*

Background: The Heritage trial is a multicenter, double-blind, randomized, parallel-group, phase 3 study (NCT02472964) evaluating efficacy and safety of trastuzumab-dkst (Ogivri), a trastuzumab biosimilar, vs trastuzumab, in combination with taxane as first-line therapy for patients with HER2+ metastatic breast cancer. The primary endpoint, overall response rate on combination therapy at week 24, was previously reported (Rugo et al, *JAMA* 2017). **Methods:** Eligible patients were randomized 1:1 to trastuzumab-dkst or trastuzumab, combined with taxane. After 24 weeks, patients with responding or stable disease received monotherapy as per randomization. Here, we describe secondary endpoints of safety and immunogenicity during monotherapy and cumulative through 48 weeks; progression-free survival (PFS) and event-based overall survival (OS) will be presented in the future. **Results:** 500 patients were randomized, 342 continued treatment after 24 weeks, and 214 continued through 48 weeks. Treatment-emergent adverse event (TEAE) rates during monotherapy were similar (trastuzumab-dkst, 54.7%; trastuzumab, 60.1%); most were low grade. Grade ≥3 TEAEs were more frequent with trastuzumab (11.7%) vs trastuzumab-dkst (6.7%); serious TEAE rates were similar (trastuzumab-dkst, 2.8%; trastuzumab, 2.5%). When assessed over 48 weeks of combination and monotherapy, cumulative rates of TEAEs of special interest were similar for pulmonary events, significant cardiac disorders, and infusion-related events (trastuzumab-dkst, 13.0%, 4.9%, and 9.3%; trastuzumab, 12.2%, 4.1%, and 8.1%, respectively). Immunogenicity and incidence of left ventricular ejection fraction < 50% ≥1 time postbaseline and ≥10% reduction at week 48 were similar between groups (trastuzumab-dkst, 3.9% and 3.6%; trastuzumab, 4.4% and 2.8%, respectively). No new safety signals were detected. At week 48, median PFS was 11.1 months in both groups and OS curves were similar. **Conclusions:** Maintenance monotherapy with FDA-approved trastuzumab-dkst after combination with taxane was well tolerated, with safety and efficacy profiles similar to originator trastuzumab. Clinical trial information: NCT02472964.

111 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Comparison of efficacy and safety of biosimilar filgrastim in a RCT (PIONEER) and real-world practice (MONITOR-GCSF). *First Author: Nadia Harbeck, Brustzentrum der Universität München (LMU), Munich, Germany*

Background: Sandoz biosimilar filgrastim has been approved in the US since 2015 for several indications including prevention of chemotherapy-induced neutropenia. US approval was based on results from PIONEER, a phase III confirmatory trial in breast cancer (BC) patients receiving chemotherapy randomized to either Sandoz biosimilar or reference filgrastim (Blackwell et al. Ann Oncol 2015;26:1948-53). BC is considered a sensitive indication to demonstrate filgrastim biosimilarity. Post-approval, safety of Sandoz biosimilar filgrastim has been monitored in MONITOR-GSCF, an observational study in patients with solid or hematological malignancies undergoing chemotherapy (Gascon et al. Support Care Cancer 2016;24:911-25). The results from PIONEER were compared to the MONITOR-GCSF BC cohort to evaluate Sandoz biosimilar filgrastim in a RCT and a real-world practice setting in BC. **Methods:** Results were compared for corresponding endpoints. Patient- and cycle-level comparisons were made between patients in PIONEER, and all BC patients receiving biosimilar filgrastim in MONITOR-GCSF. **Results:** There were 217 evaluable patients in PIONEER and 466 in MONITOR-GCSF. Patients were generally younger in PIONEER (mean age, years ± SD: 48.9 ± 11.3 vs 56.2 ± 11.7). Patient level results are reported. Febrile neutropenia (FN) was reported in 5.1% (PIONEER) vs 6.2% (MONITOR-GCSF). All grade adverse events (AEs) were generally reported at a higher level in PIONEER than MONITOR-GCSF, including musculoskeletal/connective tissue disorders (PIONEER: 261, MONITOR-GCSF: 20 [absolute numbers]); infections/infestations (PIONEER: 31, MONITOR-GCSF: 3); skin/subcutaneous tissue disorders (PIONEER: 258, MONITOR-GCSF: 5) and general disorders/administration site conditions (PIONEER: 673, MONITOR-GCSF: 7). Cycle level results were generally similar between studies. **Conclusions:** Sandoz biosimilar filgrastim prevented FN in a RCT and in real-world practice in BC patients receiving (neo-)adjuvant chemotherapy. In real-world practice, experiencing AEs may be perceived as unavoidable in order to achieve clinical efficacy. Thus Phase III RCTs remain an effective tool to assess and monitor AEs.

112 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Treatment approach for non-Hodgkin lymphoma patients since first biosimilars of rituximab approved in EU5. *First Author: Alessandra Franceschetti, Ipsos Healthcare, London, United Kingdom*

Background: Non-Hodgkin Lymphoma (NHL) is the tenth most common cancer in Europe. In 2017, the first biosimilars of rituximab were approved in Europe to treat NHL. Using real world data from Ipsos' Global Oncology Monitor, this study explores prescription patterns of rituximab biosimilars in EU5 to determine if biosimilars are favoured over branded versions for certain patient types. **Methods:** An online multi-country, multi-centre medical chart review study of NHL patients; 97 physicians provided de-identified data on 640 patients treated with anti-cancer drugs in France (117), Germany (73), Italy (117), Spain (136) and UK (197) between July and September 2017. Physicians were geographically representative and screened for treatment involvement levels and number of patients managed per month. Reporting on patients seen in consultation, they provided date of diagnosis, current and historic treatment, and reasons for prescribing/discontinuing anti-cancer drug treatment. Data on patients treated with and without a rituximab biosimilar were compared using descriptive statistics. **Results:** Of the 640 NHL patients studied, 77% were treated with a regimen that included branded rituximab. Prescribing of rituximab biosimilars was highest in Germany and UK (14% and 13%, respectively). For recently-initiated patients in Germany and UK, prescription of biosimilars increased towards 2nd and 3rd lines of treatment (1L: 11%; 2L:18%; 3L:30%). A profile comparison of German and UK patients treated with a rituximab biosimilar (27) vs. branded rituximab (179) shows that the former is more likely to have: ECOG 0-1 (93% vs. 82%); no comorbidities affecting cancer drug treatment (52% vs. 31%); indolent vs. aggressive status (70% vs. 52%); and Follicular Lymphoma as sub-type of cancer (56% vs. 35%). **Conclusions:** Physicians responsible for the drug treatment of NHL patients in EU5 have begun prescribing rituximab biosimilars. This seems to be more frequent after first line treatment, in fitter patients, and for those with indolent disease and Follicular Lymphoma.

	Total EU5	France	Germany	Italy	Spain	UK
	640	**117**	**73**	**117**	**136**	**197**
Rituximab (branded version)	**70%**	68%	66%	75%	76%	66%
Rituximab (biosimilar version)	**7%**	0%	14%	3%	5%	13%

500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Adjuvant denosumab in early breast cancer: Disease-free survival analysis of 3,425 postmenopausal patients in the ABCSG-18 trial. *First Author: Michael Gnant, Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria*

Background: Adjuvant aromatase inhibitors (AI) are standard of care for postmenopausal women with hormone receptor positive (HR+) early stage breast cancer but cause osteoporosis and fractures. ABCSG-18 showed previously that adjuvant denosumab significantly reduces clinical fractures (primary endpoint, HR = 0.5, $p < 0.0001$, Lancet 2015). Here, we present the impact of adjuvant denosumab on disease-free survival. Patients and **Methods:** 3,425 postmenopausal patients with early HR+ BC receiving adjuvant AI were recruited in 58 trial centers into this prospective, double-blind, placebo-controlled, phase-III trial. Patients were randomized 1:1 to receive either denosumab 60mg s.c. (N = 1712) or placebo (N = 1713) q6 months during AI therapy. We here present results of ABCSG-18's secondary endpoint disease-free survival (DFS), including relevant subgroup and sensitivity analyses (accounting for cross-over either by censoring or by using a rank preserving structural failure time model). **Results:** After a median follow-up (FU) of 72 months, 287 events occurred in the placebo group, and 240 in the denosumab group. DFS was significantly improved in the denosumab arm (HR = 0.823, 95% CI 0.69-0.98, Cox p = 0.026*). In the denosumab group, DFS was 89.2% (95% CI 87.6-90.7) at 5 years and 80.6% (78.1-83.1) at 8 years of FU, compared to 87.3%, (85.7-89.0) at 5 years and 77.5% (74.8-80.2) at 8 years for patients who received placebo. Similar results were obtained from sensitivity analyses. No case of osteonecrosis of the jaw (ONJ) was recorded so far, despite proactive adjudication of potential cases by an independent expert panel. One potential atypical femur fracture was seen in the denosumab arm. **Conclusion:** Adjuvant denosumab improves disease-free survival of HR+ postmenopausal breast cancer patients receiving AI. Based on these results and the previously reported dramatic reduction of fractures, adjuvant denosumab 60mg s.c. q6 months should be offered to postmenopausal HR+ breast cancer patients receiving AI. ** descriptive, without controlling for multiplicity.* Clinical trial information: EudraCT #: 2005-005275-15.

501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Adjuvant denosumab in early breast cancer: First results from the international multicenter randomized phase III placebo controlled D-CARE study. *First Author: Robert E. Coleman, University of Sheffield, Weston Park Hospital, Sheffield, United Kingdom*

Background: Denosumab (Dmab) is a potent RANK ligand inhibitor approved for the management of treatment induced bone loss in early breast (EBC) and prevention of skeletal morbidity associated with metastatic bone disease. Preclinical data suggested that Dmab could prevent development of bone metastases. This trial evaluated the addition of Dmab to standard (neo) adjuvant therapy for high-risk EBC patients (pts). **Methods:** 4509 pts with EBC (93.5% node+) from 407 centers were randomized to standard loco-regional and (neo)adjuvant therapy plus either Dmab 120mg sc or matching placebo (P) monthly x 6 then 3 monthly for up to 5 years. In addition to routine clinical follow-up, pts underwent annual CT and bone scan imaging to screen for recurrence. Primary endpoint was bone metastasis free survival (BMFS) defined as first bone metastatic event confirmed by central imaging review or death from any cause. Secondary endpoints included disease free survival (DFS), DFS in the postmenopausal (PM) subgroup, overall survival (OS) and safety. **Results:** Patient groups were balanced for baseline characteristics with median age 51y, 77% ER+, 20% Her2+ and use of anthracycline and/or taxane chemotherapy in 95.9%. No benefits for the addition of Dmab were seen at a time-driven analysis performed after a median follow-up of 67 months that allowed for the full 5 years of treatment in all pts. Hazard ratio (HR) for BMFS (597 events) was 0.97, 95%CI 0.82-1.14, p = 0.70 and 1.04, 95%CI 0.91-1.19, p = 0.57 for DFS (875 events). OS (412 events) was similar in both groups (HR = 1.03, 95%CI 0.85-1.25). Dmab did not improve BMFS, DFS or OS in the PM subset (n = 2149). Exploratory analysis of time to bone metastases as first recurrence suggested benefit for Dmab (HR = 0.76, 95%CI 0.59-0.97) for this endpoint. Time to on-study fracture prior to bone recurrence was reduced with Dmab (HR = 0.76, 95%CI 0.63-0.92). 122 (5.4%) pts on Dmab and 4 (0.2%) on P developed osteonecrosis of the jaw. 9 (0.4%) pts on Dmab experienced an atypical femoral fracture. **Conclusions:** Adjuvant Dmab does not reduce breast cancer recurrences or deaths in EBC pts receiving optimal loco-regional and standard of care systemic adjuvant therapy. Clinical trial information: NCT01077154.

502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Role of adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: The ASTRRA study. *First Author: Woo Chul Noh, KIRAMS, Seoul, Republic of Korea*

Background: The role of adding ovarian function suppression (OFS) to tamoxifen (T) for premenopausal patients with breast cancer after completing (neo) adjuvant chemotherapy is uncertain. The prospective randomized phase III trial was conducted to evaluate the efficacy of adding OFS to T in patients with hormone receptor-positive breast cancer who remain in premenopausal status or resume ovarian function after chemotherapy (NCT00912548). The primary and key secondary endpoints were to compare the 5-year disease-free survival and overall survival, respectively, between patients who received T and those who received T and OFS. **Methods:** We enrolled 1483 premenopausal women (aged ¡Â45 years) with estrogen receptor-positive breast cancer who were treated with definitive surgery after completing neoadjuvant or adjuvant chemotherapy. Ovarian function was assessed every 6 months for 2 years since enrollment based on follicular-stimulating hormone levels and menstruation history. If ovarian function was confirmed to be premenopausal at each visit, the patient was randomized to receive 5 years of T (T-only group) or 5 years of T plus 2 years of OFS by monthly goserelin (T + OFS group). A total of 1282 patients was randomly assigned. Disease-free survival was defined as the time from enrollment to the detection of recurrence of breast cancer, contralateral breast cancer, secondary malignancy, or death by any cause. **Results:** After a median follow-up of 63 months, the estimated disease-free survival rate at 5 years was 91.1% in the T + OFS group and 87.5% in the T-only group (hazard ratio 0.686; 95% confidence interval [CI], 0.483 to 0.972; P = 0.033). The estimated overall survival rate after 5 years was 99.4% in the T + OFS group and 97.8% in the T-only group (hazard ratio 0.310; 95% CI, 0.102 to 0.941; P = 0.029). **Conclusions:** Ovarian function needs to be monitored for at least 24 months after completing chemotherapy to establish eligibility for OFS. Adding 2 years of OFS to T significantly improved disease-free survival as compared to T alone in those who remained premenopausal or resumed ovarian function after chemotherapy. Clinical trial information: NCT00912548.

503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with hormone receptor-positive (HR+) HER2-negative breast cancer (BC): Results from TEXT and SOFT. *First Author: Meredith M. Regan, Dana-Farber Cancer Institute, Boston, MA*

Background: The TEXT and SOFT trials randomly assigned premenopausal women with HR+ BC to exemestane plus ovarian function suppression (E+OFS), tamoxifen+OFS (T+OFS) and T alone. We previously examined absolute treatment effects on any BC recurrence across a continuum of recurrence risk to individualize endocrine therapy decision making. After 8.5 yrs median follow-up we now consider effects on freedom from distant recurrence. **Methods:** The TEXT and SOFT HR+/HER2- analysis population included 4891 pts and was stratified by chemotherapy use. The endpoint was distant recurrence-free interval (DRFI; time from randomization to first appearance of DR). For each pt, a previously defined continuous, composite recurrence risk index (CRI) was calculated from a Cox model incorporating age, nodal status, tumor size and grade, and ER, PgR and Ki-67 expression levels. Subpopulation Treatment Effect Pattern Plot (STEPP) methodology estimated 8yr absolute treatment effects for subpopulations defined by CRI values. **Results:** Overall 8yr DRFI was 91% (433 DRs) and ranged from ~100% to 63% across lowest CRI of 0.2 to highest CRI of 3.4. TEXT pts (n = 2267) had median [IQR] CRI of 1.7 [1.2-2.3]. Overall 8yr DRFI was 92% (194 DRs) and absolute benefit of E+OFS vs T+OFS was 3%; benefit ranged from 0% at lowest CRI (both therapies having 100% 8yr DRFI) to 15% at highest CRI. SOFT pts who remained premenopausal after chemo (n = 1271) had median CRI of 2.1 [1.5-2.7]. Overall 8yr DRFI was 82% (216 DRs) and absolute benefit of E+OFS vs T was 5%; benefit ranged from 2% to 10% across CRI. For T+OFS vs T the absolute benefit ranged 0% to 5%. The SOFT no-chemo cohort (n = 1353) had median CRI of 1.1 [0.3-1.4]. Overall 8yr DRFI was 99% (23 DRs), and across CRI exceeded 97% with all three endocrine therapies. **Conclusions:** Premenopausal pts with HR+/HER2- BC and high recurrence risk, as defined by clinicopathological characteristics, may experience 10-15% absolute improvement in 8yr DRFI with E+OFS vs T+OFS or T alone. Potential benefit of escalating endocrine therapy vs T alone is minimal for those at low risk, and may be 4-5% for pts at intermediate risk. Clinical trial information: NCT00066690, NCT00066703.

504 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Fifteen-year results of the randomised EORTC trial 22922/10925 investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. *First Author: Philip Poortmans, Institut Curie, Paris, France*

Background: EORTC trial 22922-10925 investigates whether internal mammary and medial supraclavicular (IM-MS) lymph nodes (LN) irradiation improves outcome for stage I-III breast cancer patients (Clinicaltrials.gov NCT00002851). The 10 years analysis showed an improvement of 3.0% in metastases free survival (p = 0.02) and of 1.6% in overall survival (p = 0.056). Toxicity was limited and no increased lethal side effects were seen. This is the second of 3 scheduled analyses, at 15-year follow-up. **Methods:** Eligible patients had involved axillary nodes and/or a medially located primary tumour. Randomisation was to irradiate or not the IM-MS. The final trial design aimed at detecting a 4% increase in 10-year overall survival (OS) (from 75 to 79%, HR = 0.82) with 2-sided unadjusted Log-rank test at the 5% significance level. Secondary endpoints are disease-free survival (DFS), metastases-free survival (MFS) and cause of death. Two long-term analyses were planned, at respectively 15 and 20 years of follow-up. **Results:** Between 1996 and 2004, 4004 patients were randomized in 43 centres. Median age was 54 years; 59.0% were postmenopausal; 55.6% had involved axillary LN; 33.8%, 52.0% and 14.2% had stage I, II and III, respectively. Nearly all LN-positive (99.0%) and 66.3% of LN-negative patients received adjuvant systemic treatment. At a median follow-up of 15.7 years, 1117 patients died. At 15 years, overall survival was 73.2% in the nodal-irradiation group and 70.8% in the control group (HR IM-MS RT vs. control = 0.95; 95%CI, 0.84-1.06;P = 0.358).). Regional recurrences in IM-MS LN occurred in 1.8% vs. 3.1% of patients. Distant disease-free survival rate was 70.1% vs. 68.1% (HR = 0.92; 95%CI, 0.83-1.04; P = 0.178), breast-cancer mortality was 15.8% vs. 19.7% (HR = 0.81; 95%CI, 0.69-0.94; P = 0.005). Probability of breast cancer recurrence was 24.5% vs. 27.1% (HR = 0.87; 95%CI, 0.77-0.98; P = 0.024. No difference was observed in the incidence of second malignancies, contralateral breast cancer or cardiovascular deaths. **Conclusions:** The 15-years results show a significant reduction of breast cancer mortality and breast cancer recurrence by internal mammary and medial supraclavicular lymph node irradiation in stage I-III breast cancer. However, this is not converted in improved overall survival without a clear explanation for this. Subgroup analyses and continued follow-up will be performed to better define patients that may benefit from this treatment and define the causes of death. Clinical trial information: NCT00002851.

505 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

A gene expression assay for prediction of radiotherapy benefit in breast cancer. *First Author: Laura A Knight, Almac Diagnostics, Craigavon, United Kingdom*

Background: We have previously developed and clinically validated a 44-gene DNA damage response deficiency (DDRD) assay in breast cancer for predicting response to adjuvant anthracycline based chemotherapy. The assay defines a molecular group of patients with loss of the DNA damage response FA/BRCA pathway. We investigate a further utility of the assay as a predictor of response to radiotherapy in the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) cohort. **Methods:** The DDRD assay was applied to RNA-seq data for 1904 patients from the METABRIC study. Of these patients, 1137 (59.7%) had received adjuvant radiotherapy. Chi-squared tests were applied to test the association between DDRD and clinical factors (ER, PR, HER2, Grade, and tumour stage). 396 patients that received chemotherapy were excluded, and a multivariable Cox model was performed to test the effect of radiotherapy on overall survival (OS) within DDRD positive and DDRD negative groups respectively. **Results:** 635 patients were classified as DDRD positive and 1269 as DDRD negative. A statistically significant association was observed between DDRD groups and ER ($p < 0.0001$), HER2 ($p < 0.0001$), PR ($p < 0.0001$), grade ($p < 0.0001$) and tumour stage ($p < 0.0001$). The effect of radiotherapy was evaluated in a multivariable analysis for DDRD positive and DDRD negative respectively, whereby clinical factors known to be associated to DDRD status were adjusted for. In the DDRD positive group, a significant improvement in overall survival was observed in patients treated with adjuvant radiotherapy (adjusted HR = 0.65 [0.49-0.87], p = 0.0043). In the DDRD negative group, no significant effect on survival was observed with radiotherapy treatment (adjusted HR = 0.95 [0.78-1.16], p = 0.6203). **Conclusions:** The DDRD assay detects a molecular subgroup of patients with DNA repair defects through loss of the FA/BRCA pathway. Previous studies have demonstrated that the assay is predictive in the context of DNA damaging chemotherapy, such as anthracycline. Here we show that the DDRD assay has further utility for predicting patients that are most likely to derive benefit from adjuvant radiotherapy in breast cancer.

506 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

PERSEPHONE: 6 versus 12 months (m) of adjuvant trastuzumab in patients (pts) with HER2 positive (+) early breast cancer (EBC): Randomised phase 3 non-inferiority trial with definitive 4-year (yr) disease-free survival (DFS) results. *First Author: Helena Margaret Earl, University of Cambridge, Department of Oncology & NIHR Cambridge Biomedical Research Centre & Cambridge University Hospitals NHS Foundation Trust, Cambridge Breast Cancer Research Unit, Cambridge, United Kingdom*

Background: Adjuvant trastuzumab has significantly improved outcomes for HER2+ EBC pts, using the 12m duration empirically adopted from the pivotal registration trials. A shorter duration could reduce toxicities and cost whilst providing similar efficacy. No reduced-duration trial to date has demonstrated non-inferiority. **Methods:** PERSEPHONE is a randomised phase 3 non-inferiority trial comparing 6 to 12m trastuzumab, the largest reduced-duration non-inferiority trial internationally. Mapping onto standard UK practice, all HER2+ EBC pts were eligible. Stratification is by ER status, chemotherapy (CT) type, and CT and trastuzumab timing. The primary endpoint is DFS from diagnosis (first relapse or death from any cause). Randomising 4000 pts (1:1) enabled the trial to assess the non-inferiority of 6m (5% 1-sided significance, 85% power), defining non-inferiority as 'no worse than 3%' below the 12m arm's assumed 80% 4-yr DFS. The pre-planned definitive DFS analysis required 500 events. **Results:** 4089 pts were randomised from 152 UK sites (Oct'07 – Jul'15). ER+ 69%; CT - 41% anthracycline (A)-based / 49% A and taxane (T)-based / 10% T-based; adjuvant CT 85%; sequential trastuzumab 54%. At 4.9 yrs median follow-up, there were 319 (8%) deaths and 500 (12%) DFS events. With a 4-yr DFS rate of 89% (95%CI 88 – 91) in both arms, the hazard ratio (HR) non-inferiority limit was set at 1.29. The calculated HR was 1.05 (95%CI 0.88 – 1.25, 95th percentile = 1.22) demonstrating non-inferiority (HR < 1.29) of 6m trastuzumab (1-sided p = 0.01). Congruent results were found for overall survival (OS) and for the pre-planned DFS and OS landmark analyses (after 6m of trastuzumab). Heterogeneity was observed in some stratification variables. Cardiac events were reduced in 6m pts (4% v 8% of 12m pts stopping treatment due to cardiotoxicity ($p < 0.0001$)). **Conclusions:** PERSEPHONE has demonstrated 6m of trastuzumab as non-inferior to 12m (3% non-inferiority margin). Given cardiac and other toxicities during months 7-12 of treatment, our results would support a reduction of standard trastuzumab duration to 6 months. Clinical trial information: 52968807.

507 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

De-escalated treatment with trastuzumab-pertuzumab-letrozole in patients with HR+/HER2+ operable breast cancer with Ki67 response after 2 weeks letrozole: Final results of the PerELISA neoadjuvant study. *First Author: Valentina Guarneri, Department of Surgery, Oncology and Gastroenterology, University of Padua, Medical Oncology 2, Instituto Oncologico Veneto IRCCS, Padova, Italy*

Background: Neoadjuvant trials with chemotherapy plus anti-HER2 agents consistently showed a lower rate of pathologic complete response (pCR) in HER2+/HR+ vs HER2+/HR-tumors. Here we report the final results of the PerELISA study, aimed to evaluate the efficacy of a de-escalated, chemotherapy-free neoadjuvant regimen in HER2+/HR+ patients (pts) selected on the basis of Ki67 response after a short course letrozole (L). **Methods:** PerELISA is a phase II, multicentric, non-profit study for postmenopausal, operable HER2+/HR+ BC pts. Eligible pts received 2 wks window therapy with L, then underwent re-biopsy for Ki67 evaluation. Pts classified as Ki67 responders (relative Ki67 reduction ≥20% from baseline) continued L and started trastuzumab (T) and pertuzumab (P) q21 days for 5 cycles. Pts without Ki67 response discontinued L and started wkly paclitaxel for 13 wks combined with P and T. Primary aim was breast and axillary pCR. At least 8 pCR in 43 Ki67 responders were required to satisfy the study hypothesis in a two-step Simon's design. Correlative analyses included: PAM50, TILs, PIK3CA. **Results:** 64 pts from 8 centers were enrolled: median age 63 yrs (49-83 yrs); stage IIA 67%, IIB 23%; IIIA 9%. Median (range) ER, PgR and ki67 expression: 90% (10-100), 14% (0-100); 30% (7-90). Median TILs level 10% (Q1 2%-Q3 15%). PIK3CA mutation was reported in 25% of the cases. 44 pts (69%) achieved a Ki67 response after 2 wks L and underwent surgery after L+T+P (breast conserving 66%; mastectomy 34%). A pCR was observed in 9 cases (20.5%). pCR rate was significantly higher in HER2-E vs other subtypes (45.5% vs 13.8%, p = 0.042). Intrinsic subtype was significantly associated with ki-67 response ($p < 0.001$).The proportion of pts with a Ki67 response in Luminal vs non Luminal subtypes was 92.6% and 44% respectively. **Conclusions:** The PerElisa study met its primary aim: a chemotherapy-free regimen for patients with Ki67 response after short term L warrants further investigation. Among Ki67 responders, the HER2-E subtype can identify pts most likely to benefit from de-escalated therapy. Clinical trial information: NCT02411344.

508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Neoadjuvant talazoparib (TALA) for operable breast cancer patients with a BRCA mutation (BRCA+). *First Author: Jennifer Keating Litton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TALA has demonstrated efficacy in patients (pts) with BRCA+ metastatic breast cancer. We previously reported a window trial with median 88% tumor volume reduction after 2 months for early stage breast cancer. This study expanded to evaluate the pathologic response of TALA alone x 6 months in BRCA+ pts and operable breast cancer. **Methods:** The study was approved by the Institutional Review Board. Eligibility included ≥ 1 cm tumor and BRCA+. HER2+ tumors were excluded. Twenty pts underwent a pre-treatment biopsy, 6 months of once daily oral TALA (1 mg), followed by definitive surgery. Pts received adjuvant therapy at physician's discretion. Endpoint was residual cancer burden (RCB). With 20 patients, the RCB0 + RCB1 response rate can be estimated with a 95% confidence interval with half width < 20%. **Results:** All 20 planned pts have enrolled from 08/2016-09/2017: median age = 38 (range 23-58); BRCA1+ = 16 and BRCA2+ = 4; 17 patients had triple negative breast cancer (TNBC, ER/PR < 10%) and 3 had hormone+ disease; Clinical stage I = 5, stage II = 12, Stage III = 3 including 1 patient with inflammatory breast carcinoma (IBC) and 1 with metaplastic chondrosarcomatous carcinoma (MpBC). One pt chose to receive chemotherapy prior to surgery so no RCB obtained. To date 18 pts have completed TALA and 17 surgery. This report will be updated with the final 2 patients scheduled for surgery in 03/2018. RCB0 = 9 (including the 1 pt with IBC and 1 pt with MpBC, 8 pts had TNBC and 1 with ER+ invasive lobular). RCBI = 1; RCB II = 5, RCBIII = 2. RCB0/1 rate = 10/17 = 59%, 95% CI = (36%, 78%). There was 1 grade 4 toxicity of thrombocytopenia. Grade 3 toxicities included: anemia = 8; neutropenia = 3, UTI = 1. Most common grade 1/2 toxicities included: nausea, fatigue, neutropenia, alopecia, dizziness and dyspnea. Toxicities were managed by dose reduction and transfusions. Nine pts required dose reduction. **Conclusions:** Single agent oral TALA once daily given preoperatively without chemotherapy produced significant pathologic complete responses with manageable toxicity. This pilot trial exceeded our expectations and is novel to demonstrate RCB0 in TNBC by a single targeted therapy. These results warrants a larger study for this pt population. Clinical trial information: NCT02282345.

509 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

HER2-enriched subtype and ERBB2 mRNA as predictors of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer: A combined analysis of TBCRC006/023 and PAMELA trials. *First Author: Aleix Prat, Department of Medical Oncology, Hospital Clinic, Barcelona, Spain*

Background: HER2-Enriched (HER2-E) intrinsic subtype within HER2-positive breast cancer is characterized by high expression of ERBB2 and related genes. Here we retrospectively evaluated the value of the HER2-E subtype and ERBB2 mRNA expression alone to predict pathological complete response (pCR) in tumor samples from PAMELA and TBCRC 006/023 trials. **Methods:** All patients had HER2-positive early breast cancer and were treated with neoadjuvant lapatinib and trastuzumab. Patients with hormone receptor-positive tumors were also treated with letrozole or tamoxifen. In PAMELA (NCT01973660), 151 patients were treated for 18 weeks. TBCRC 006 (NCT00548184) treated 66 patients for 12 weeks and TBCRC 023 (NCT00999804) randomized 97 patients to 12 vs. 24 weeks of treatment. pCR was defined as no residual invasive carcinoma in the breast. Baseline intrinsic subtypes and ERBB2 mRNA expression were determined using the nCounter-based PAM50 predictor. ERBB2 expression was dichotomized as low (lowest 1/3) vs high (highest 1/3) as used in PAMELA. **Results:** Two-hundred and sixty-five tumors (84.4%) were profiled; 65.7% were classified as HER2-E. pCR was more likely to occur if HER2-E (35.1% vs. 9.9%; odds ratio [OR] = 4.92; 95% CI 2.31-10.50; P < 0.001) or ERBB2-high (36.1% vs. 8.2%; OR = 6.51; 95% CI 2.96-14.31; P < 0.001). HER2-E subtype represented 84.0% and 46.0% of ERBB2-high and ERBB2-low groups, respectively. Rates of pCR in HER2-E/ERBB2-high, nonHER2-E/ERBB2-high, HER2-E/ERBB2-low, and nonHER2-E/ERBB2-low groups were 45.0%, 16.1%, 10.8%, and 6.7%, respectively. Finally, the HER2-E/ERBB2-high group independently predicted pCR (adjusted OR = 6.0; 95% CI [3.1-11.8]; *P*< 0.001). **Conclusions:** Combining HER2-E subtype and ERBB2 mRNA levels better identifies anti-HER2 sensitivity than each variable alone in HER2-positive breast cancer. The combined biomarker identified nearly 50% of patients with pCR to an all-biologic regimen, and if validated may provide a means for rational therapeutic de-escalation.

510 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Evaluation of trastuzumab without chemotherapy as a postoperative adjuvant therapy in HER2-positive elderly breast cancer patients: Randomized controlled trial (RESPECT). *First Author: Masataka Sawaki, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: The relative value of trastuzumab (H) monotherapy as an adjuvant treatment compared to the standard combination treatment with chemotherapy (CT) is not clear for elderly breast cancer (BC) patients (pts). **Methods:** We randomly assigned pts over 70 years (yrs) old with HER2-positive invasive BC who received curative surgery into either H (H group) or H plus CT (H+CT group) selected from pre-specified regimens (PTX/DTX/TC/AC/EC/FEC/CMF/TCb [CBDCA]). The primary endpoint was disease-free survival (DFS), and the total required numbers of events and pts were set to 120 and 260, respectively, for assuring a statistical power of 80% for a 95% confidence interval (CI) with a hazard ratio (HR) of H to H+CT not to exceed 1.69. Restricted mean survival time (RMST) was calculated as a supplementary endpoint for interpreting the relative benefit of H because the blinded interim analysis showed the number of events was much fewer than expected, and the statistical power of the non-inferiority test based on HR is not assured. **Results:** A total of 275 pts were randomized from 2009 to 2014. The median age was 73.5 (70-80) yrs and the median follow up time was 3.52 yrs. Stage I (pT > 0.5cm) 43.6%, IIA 41.7%, IIB 13.5%, IIIA 1.1%. The planned analysis showed that DFS at 3 yrs was 94.8% in H+CT (n = 131, 12 events) vs 89.2% in H (n = 135, 18 events) (HR = 1.42; 95% CI, 0.68 to 2.95, P = 0.35). The difference in RMST between arms at 3 yrs was 0.45 months (mo). Relapse-free survival at 3 yrs was 95.6% (9 events with 4 deaths) in H+CT vs 91.7% (13 events with 5 deaths) in H. Common adverse events (AE) in H+CT vs H were anorexia (44.3% vs 7.4%, P < 0.0001), alopecia (71.8% vs 2.2%, P < 0.0001) and grade 3/4 non-hematological AE were 29.8% vs 11.9% (P = 0.0003). The total score of FACT-G improved more in H at 12 mo (H: 42.9% vs H+CT: 25.3%, P = 0.021). **Conclusion:** Small number of events precluded the evaluation of H monotherapy based on HR of DFS, and comparison of RMSTs revealed the lost survival due to omitting CT was less than 1 mo at 3 yrs. In light of less toxicity and a better QOL profile, H monotherapy can be an option as an adjuvant therapy for elderly HER2-positive BC pts. Clinical trial information: NCT01104935.

511 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

TBCRC026: Phase II clinical trial assessing the correlation of standardized uptake value (SUV) on positron emission tomography (PET) with pathological complete response (pCR) to pertuzumab and trastuzumab in patients with primary operable HER2-positive breast cancer. *First Author: Roisin M. Connolly, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD*

Background: Predictive biomarkers to identify patients with HER2-positive breast cancer (BC) that may be treated with targeted therapy alone are of great interest. We hypothesized that early changes in tumor standardized uptake values corrected for lean body mass (SULmax) on FDG-PET/CT would predict pathologic complete response (pCR) to pertuzumab and trastuzumab (PT) in early stage BC. **Methods:** The multicenter phase II TBCRC026 trial administered 4 cycles of neoadjuvant PT in women with stage II/III, ER-negative, HER2-positive BC (NCT01937117). FDG-PET/CT were performed at baseline and C1D15. Primary Objective: Correlate baseline and change in SULmax on PET with pCR (no invasive cancer breast/axilla). We correlated baseline, D15 and % reduction in SULmax with pCR using logistic regression and compared median values between those with pCR vs no pCR using Wilcoxon rank-sum tests. We evaluated odds ratio (OR), positive (PPV) and negative predictive value (NPV) with selected cutoffs for response assessment. Fisher's exact tests evaluated null hypothesis that OR = 1. **Results:** Between 01/2014-08/2017, 88 enrolled (83 evaluable) with median age 58 (range 29-82), median tumor size 3.9cm (range 2-15). 85% (75/88) completed all 4 cycles PT. pCR after PT alone was 34% (28/83). In an intent to treat analysis (n = 83 evaluable), baseline SULmax did not predict pCR. We observed a significant difference in median % reduction in SULmax between pCR vs no pCR (63.8 % vs 33.5%, p < 0.001), and higher proportion of SULmax reduction ≥40% in pCR vs no pCR (86% vs 54%, p < 0.001, OR 7.2, PPV 49%, NPV 88%). We observed a significant difference in median D15 SULmax between pCR vs no pCR (1.6 vs 3.9, p < 0.001), and a higher proportion of D15 SULmax ≤ 3 in pCR vs no pCR (93% vs 62%, p < 0.001, OR 21, PPV 55%, NPV 94%). **Conclusions:** Percent reduction and D15 SULmax significantly differ between those with pCR versus not, after 4 cycles PT, in ER-negative/HER2-positive BC. This strategy, once optimized, may facilitate escalation and de-escalation of therapy in this setting. Clinical trial information: NCT01937117.

513 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Factors associated with lymphedema in patients/women with node positive breast cancer treated with neoadjuvant chemotherapy and axillary dissection on a prospective clinical trial. *First Author: Judy Caroline Boughey, Mayo Clinic, Rochester, MN*

Background: Lymphedema (LE) is a known complication of breast cancer treatment. Herein we report the factors associated with LE after neoadjuvant chemotherapy (NAC) and axillary dissection (ALND) in the ACOSOG Z1071 (Alliance for Clinical Trials in Oncology) trial of patients with node-positive breast cancer. **Methods:** Patients who consented to the LE substudy underwent prospective arm measurements and symptom assessment after completion of NAC and at 6, 12, 18, 24, and 36 months after surgery. All patients had node-positive disease and underwent ALND after NAC. LE was defined based on symptoms of arm heaviness or swelling (LE-symptoms) or by arm volume increase of $>$ 10% (LE-V10); severe LE was defined as volume increase $>$ 20%. Kaplan-Meier methods were used to determine cumulative incidence. **Results:** 488 of 701 eligible patients consented to the LE substudy. Cumulative incidence of LE at 3 years was 37.8% (33.0-43.1%) by LE-symptoms; 58.6% (53.4-64.4%) by LE-V10; 37.2% (32.2-42.9%) for severe LE. In a univariable analysis, patient age, type of chemotherapy regimen used, breast surgical procedure, number of positive lymph nodes, and use of adjuvant radiation were not associated with risk of LE. Incidence of LE-symptoms was higher in obese patients (BMI $>$ 30, p = 0.02) and in patients with NAC duration $>$ 144 days (p = 0.029). Severe LE incidence was also higher with longer duration of NAC (p = 0.01). LE-V10 incidence was highest in patients with 30+ lymph nodes removed and lower when fewer lymph nodes were removed (p = 0.009). On multivariable analysis, obesity and length of NAC remained significant for LE-symptoms. **Conclusions:** In patients treated with NAC and ALND for node-positive breast cancer, risk of LE-symptoms increases with longer duration of neoadjuvant chemotherapy and obesity. Patients in these groups may benefit from closer surveillance for LE to allow early intervention. Support: U10CA180821, U10CA180882, UG1CA189823; Clinical trial information: NCT00881361.

514 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase II national clinical trial of prophylactic irradiation to the contralateral breast for BRCA mutation carriers treated for early breast cancer (EBC). *First Author: Ella Evron, Assaf Harofeh Medical institution, Zerifin, Israel*

Background: Women who carry germ line mutations in BRCA1/2 face a very high risk of breast and ovarian cancer. Recommendations for BRCA mutation carriers advocate intensified screening and BSO. Risk-reducing bilateral mastectomy is considered by healthy BRCA mutation carriers and by carrier patients who already developed breast cancer. Yet, the procedure is disfiguring. Women fear its effects on body image, sexuality and sensation and seek alternative preventive measures. Most studies found that breast conserving therapy was associated with similar risk of ipsilateral cancer recurrence in BRCA carriers compared to non-carriers. However, the risk of subsequent contralateral (CLT) breast cancer in carriers was markedly increased. In Israel, BRCA associated breast cancer is relatively common. Accordingly, a national protocol was devised for this enriched population. **Methods:** In this IRB-approved trial, the choice of prophylactic irradiation to the CLT breast, in addition to radiation of the involved side, was offered to BRCA carrier patients treated for EBC who declined CLT mastectomy. Radiation to both sides was delivered by the same schedule and dose. The primary end point was CLT breast cancer. **Results:** Between May 2007 and October 2017, 162 patients were enrolled. 81 opted for standard treatment including surgery and radiation to the involved side only (control group) and 81 chose additional radiation to the CLT breast (intervention group). At a median follow up of 60 months, 9 patients developed CLT breast cancer in the control group within a median of 24 months, as compared to 2 patients in the intervention group who developed CLT breast cancer 80, 109 months after bilateral breast irradiation (log-rank P = 0.027). One patient developed sarcoma in the muscle behind a CLT breast, 5 years after bilateral irradiation. There was no increase in other early or late radiation toxicities among the intervention group. **Conclusions:** Among BRCA carrier patients treated for EBC, the addition of CLT breast irradiation significantly reduces the risk of subsequent CLT breast cancer and constitutes a viable option for high-risk women declining mastectomy. Clinical trial information: NCT00496288.

515 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Persistence of circulating tumor cells in high risk early breast cancer patients five years after adjuvant chemotherapy and late recurrence: Results from the adjuvant SUCCESS A trial. *First Author: Wolfgang Janni, University of Ulm, Ulm, Germany*

Background: Recent data suggest that circulating tumor cells (CTCs) are of prognostic relevance in early as well as metastatic breast cancer. However, there is a lack of data on the prognostic impact of CTCs to predict late recurrences during long-term follow-up, especially in patients with hormone receptor positive tumors. **Methods:** The SUCCESS A trial is a randomized Phase III study, in which patients with high-risk early breast cancer were first randomized to 3 cycles of epirubicin-fluorouracil-cyclophosphamide followed by either 3 cycles of docetaxel or 3 cycles of gemcitabine-docetaxel, followed by a second randomization to 2 vs. 5 years of zoledronate treatment. Presence of CTCs 5 years after chemotherapy was assessed using the CellSearch System (Janssen Diagnostics, LLC), and CTC positivity was defined as $\geq$ 1 CTC in 7.5 ml whole blood. Recurrence-free survival (RFS) was analyzed by univariable and multivariable Cox regressions. Survival time was measured as of the date of blood sampling for CTC assessment. **Results:** Follow-up data for patients with known CTC status 5 years after chemotherapy were available for 206 (5.5%) of 3754 randomized patients (median time interval of CTC assessment 62.4 months since randomization). The CTC status was positive in 16 (7.8%) patients (range 1 – 53 CTCs). Median follow-up time after CTC assessment was 360 days (range 1 – 911 days). Overall, 13 late recurrences were observed; 11 in 153 hormone receptor positive patients and 2 in 53 hormone receptor negative patients. In hormone receptor positive patients, CTC status was a significant prognostic factor for RFS in univariable (hazard ratio [HR] 5.14, 95% confidence interval [CI] 1.47 – 18.03, p = 0.011) and in multivariable cox regressions adjusted for age, tumor stage, nodal stage, grade, histological type, and HER2 status (HR 5.95, 95%CI 1.14 – 31.16, p = 0.035). **Conclusions:** The presence of CTCs 5 years after chemotherapy was associated with decreased RFS, suggesting that persisting CTCs during long term follow-up independently predict late recurrences in hormone receptor positive patients. Extended follow-up data will be presented at the meeting. Clinical trial information: NCT02181101.

516 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Genomic stratification with BCI of ER+ early breast cancer patients with limited long-term risk of breast cancer death. *First Author: Virginia G. Kaklamani, Northwestern University Division of Hematology/Oncology, Chicago, IL*

Background: An increasing body of evidence from extended endocrine therapy trials underscores the unmet need to manage risk-benefit at the individual patient (pt) level. Breast Cancer Index (BCI) is a multigene assay that identified women with a 4.8%-6.6% low risk of cumulative recurrence (0-10y) and a low risk of late recurrence of 2.5%-3.5% in validation studies. In this post-hoc analysis, an optimized assay threshold to identify patients with favorable long-term breast cancer–specific survival was developed and characterized. **Methods:** An adjusted BCI cut point for indolent disease was trained using a cohort of node-negative, post-menopausal women with HR+ breast cancer from the Stockholm trial treated with surgery alone (UNT, n = 283). Initial performance of the optimized model was evaluated in tamoxifen-treated HR+ patients (TAM, n = 317). Breast cancer–specific survival (BCSS) was the primary analysis using Kaplan-Meier estimates over 0-20y and 5-20y. Subsets based on tumor size and tumor grade were also analyzed for BCSS. Median follow-up was 17 years. **Results:** Long-term survival analysis demonstrated that BCI optimized for minimal risk classified pts into 4 distinct risk groups for years 0-20 ($p < 0.0001$) and 5-20 (p = 0.032), with an 8% risk of breast cancer–specific death for the minimal risk group in the UNT arm. BCI classified 27% of pts treated with adjuvant TAM into a BCI minimal risk group with 98% and 99% BCSS for years 0-20 and 5-20, respectively. Among clinically high-risk grade 2 and 3 tumors (n = 250), BCI classified 20% of pts as BCI minimal risk with 98% BCCS for years 0-20 and 5-20. **Conclusions:** In this analysis, a BCI minimal risk group identified more than 1/4 of pts as having favorable long-term outcome (2% risk of breast cancer death) over 20 years after 2-5 years of tamoxifen therapy. Results suggest that the specific gene characteristics of BCI, which combine measures of cell proliferation and estrogen signaling, are an effective prognostic marker of indolent disease. BCI stratification of a genomic subset with favorable long-term outcome may identify node-negative pts with early-stage breast cancer in which more than 5 years of endocrine therapy is unlikely to be of benefit.

517 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Molecular alterations and late recurrence in postmenopausal women with hormone receptor-positive node-positive breast cancer (BC): Results from the "SOLE" trial. *First Author: Elena Guerini Rocco, Department of Pathology, European Institute of Oncology, Milan, Italy*

Background: Women with hormone receptor-positive BC have an ongoing risk of relapse. We performed molecular analyses of primary BC from postmenopausal patients (pts) enrolled in the extended adjuvant intermittent letrozole vs. continuous letrozole (SOLE) trial to identify prognostic factors and potential targets. **Methods:** From 4884 pts enrolled, 3162 had FFPE tumor samples and were eligible. A case-cohort design selected 599 pts, and 499 DNA samples underwent next-generation sequencing of 35 and 19 actionable genes for mutation (SNV) and copy number gain (CNG) analyses. Correlations of SNV/CNG with clinicopathologic factors were analyzed. Associations with breast cancer free-interval (BCFI) and distant recurrence free-interval (DRFI) were assessed using weighted proportional hazards models to obtain unbiased and consistent estimates representing the overall trial population. With 403 pts there was 90% power to detect a hazard ratio (HR) = 2.0 (SNV/CNG+ vs. -; assuming a 40% mutation prevalence), with 0.05 two-sided significance level and adjusted standard error estimate from the weighed Cox model. **Results:** SNV and CNG data were available for 403 (81%) and 350 (70%) of 499 samples, respectively. 294 samples had ≥1 SNV or CNG; 132 had concurrent alterations. *PIK3CA* was the most frequently mutated gene (42%). Other genes showed < 5% SNV rate. Recurrent CNGs were seen in *CCND1* (15%), *ERBB2* (10%), *FGFR1* (8%) and *MYC* (8%). *PIK3CA* SNVs and *MYC* CNG were associated with low (p = 0.032) and high (p = 0.004) tumor grade. Ki-67 index was high in tumors with CNG of *CCND1*, *ERBB2* and *MYC* (each p < 0.01). No association was seen between *PIK3CA* SNV and recurrence. *FGFR1* CNG was associated with worse outcomes (BCFI: HR = 3.2; 95% CI, 1.5-6.9, p = 0.003; and DRFI: HR = 3.5; 95% CI, 1.6-7.7, p = 0.002). The results were consistent in multivariable models adjusting for clinicopathologic factors. **Conclusions:** We showed that pts with hormone receptor-positive node-positive BC with *FGFR1* CNG had an increased risk of late recurrence despite extended therapy. *FGFR1* analysis may improve the risk stratification in this population and represent a potential therapeutic target. Clinical trial information: NCT00553410.

518 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Precision neoadjuvant therapy (P-NAT): A planned interim analysis of a randomized, TNBC enrolling trial to confirm molecular profiling improves survival (ARTEMIS). *First Author: Stacy L. Moulder, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ARTEMIS is a double blind, randomized trial to determine if P-NAT impacts rates of excellent pathologic response [Residual Cancer Burden (RCB) 0-I]. P-NAT used a CLIA-certified chemosensitivity mRNA gene signature (GES) and subtyping of triple negative breast cancer (TNBC) by immunohistochemistry (IHC) to select targeted therapy (TT) trials for chemo insensitive tumors. **Methods:** ARTEMIS planned to randomize 360 TNBC patients (pts) 2:1 to 'know' vs. 'not know' P-NAT results using a group sequential design with one-sided O'Brien-Fleming boundaries and two interim tests for futility and superiority; overall α set at .05 with 80% power to detect improved RCB 0-1 rate from 50% to 64%. After biopsy, pts began a planned 4 cycles of Adriamycin-based chemo (AC). Volumetric change by ultrasound (US) upon completion of AC (or at progression) combined with GES results (if known) determined sensitivity using a protocol defined algorithm. Pts with sensitive disease received subsequent taxane-based (T) therapy. Pts with insensitive disease were offered phase II trials (TT; table) using IHC results, if known. To gauge impact of TT independently from GES, pts having < 50% volumetric reduction by US to AC were evaluated (US-resistant cohort). **Results:** The first interim analysis (n = 133 pts with RCB status) revealed a RCB 0-1 rate of 56% (know P-NAT) v 62% (not know P-NAT); p = 1.0; thus, randomization was discontinued for futility. In total 232 pts were enrolled; 168 evaluable for RCB. In the US-resistant cohort (n = 43), RCB 0-I rates were higher in pts treated with TT (n = 30) v AC-T (n = 13); (30% v 8%; odds ratio = 5.1 with 95% CI = (0.6-45.7); Fisher's exact test 1-sided p-value = 0.11). **Conclusions:** GES failed to improve rates of RCB 0-I in TNBC; however, in pts with resistant disease identified by US after AC, RCB 0-I rates were higher in pts treated with targeted therapy compared to chemo alone. Clinical trial information: NCT02276443.

Regimen	Entry criteria (IHC)	# pts treated
Atezolizumab + nab-paclitaxel	None	19
Panitumumab + paclitaxel + carboplatin	None	14
Liposomal doxorubicin + bevacizumab + everolimus	Vimentin > / = 50% or metaplastic	12
Enzalutamide + paclitaxel	Androgen receptor > / = 10%	11
AC-T	None	153

519 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Evaluation of homologous recombination deficiency (HRD) status with pathological response to carboplatin +/- veliparib in BrighTNess, a randomized phase 3 study in early stage TNBC. *First Author: Melinda L. Telli, Stanford University School of Medicine, Stanford, CA*

Background: HRD status is significantly associated with a higher rate of response to neoadjuvant platinum-based therapy and improved PFS following adjuvant doxorubicin and cyclophosphamide (AC) in TNBC. We assessed the prognostic and predictive role of the HRD assay for platinum and PARP inhibitor response in BrighTNess. **Methods:** 634 stage II-III TNBC pts were randomized 2:1:1 to: Arm A: Paclitaxel (T) q wk x 12 + carboplatin (P) (AUC 6) q3 wk x 4 + veliparib (TPV) - > AC q2-3 wk x 4; Arm B: T + P + placebo (TP) - > AC; or Arm C: T + dual placebo (T) - > AC. HRD status was defined as HRD+ (HRD score ≥ 42 or a tumor *BRCA1/2* mutation) or HRD- (HRD score < 42 and no tumor *BRCA1/2* mutation). An exploratory HRD threshold of ≥ 33 vs < 33 was also assessed. **Results:** HRD status was available for 438 pts. HRD data by arm for pCR for the 42 and 33 cut-offs are shown. Within each arm using the 42 and 33 cut-offs, respectively, ORs for pCR by HRD status (HRD +/HRD-) were 2.85 (p = 0.0005) and 3.10 (p = 0.004) for Arm A, 1.55 (p = 0.30) and 2.28 (p = 0.10) for Arm B and 2.13 (p = 0.13) and 1.52 (0.48) for Arm C. Comparing between arms using the 42 threshold, ORs for pCR (Arm A/Arm B, Arm A/Arm C, Arm B/Arm C) in the HRD+ group were 1.04, 3.02 and 2.90 and were not statistically significantly different than in the HRD- group (0.57 [p = 0.23], 2.26 [p = 0.60] and 4.0 [p = 0.61]). Similar results were observed with the 33 cut-off. **Conclusions:** In BrighTNess, higher rates of pCR were observed in HRD+ pts across all treatment arms. However, pts treated with P had higher rates of pCR in both HRD+ and HRD- subsets. The exploratory HRD threshold of 33 appeared to provide greater sensitivity to identify responders with the addition of P + V. Receipt of AC in all pts may have contributed to the lack of interaction observed between HRD status and P +/- V treatment. Clinical trial information: NCT02032277.

Arm	pCR HRD+ ≥ 42	pCR HRD- < 42	pCR HRD+ ≥ 33	pCR HRD- < 33
TPV-AC (A) n = 213	87/141 (61.7%)	26/72 (36.1%)	93/153 (60.8%)	20/60 (33.3%)
TP-AC (B) n = 116	51/84 (60.7%); p = 0.88#	16/32 (50%); p = 0.18#	57/92 (62%); p = 0.89#	10/24 (41.4%); p = 0.61#
T-AC (C) n = 109	24/69 (34.8%); p = 0.0003‡	8/40 (20%); p = 0.08‡	25/79 (31.6%); p = < 0.0001‡	7/30 (23.3%); p = 0.46‡

= for TPV-AC vs TP-AC; ‡ = for TPV-AC vs T-AC

520 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Residual cancer burden (RCB) as prognostic in the I-SPY 2 TRIAL. *First Author: William Fraser Symmans, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: I-SPY2 is a multicenter phase 2 trial in high risk stage II/III breast cancer (BC) using adaptive randomization within biomarker subtypes to evaluate novel treatment agents added to standard neoadjuvant chemotherapy (NAC) in different phenotypic subsets of breast cancer. Residual cancer burden (RCB) quantifies the extent of residual disease (RD) for patients who did not achieve pathologic complete response (pCR = RCB-0). **Methods:** Local site pathologists reported RCB in the I-SPY2 trial. We performed a pooled analysis of 678 patients in I-SPY2 with RCB data and known follow-up (median 2.5 years). Cox models for event-free survival (EFS) were evaluated for RCB index (continuous) and RCB classes (hazard ratio; 95% CI) in all patients and in subtypes defined by hormone receptor (HR) and HER2 status. We separately compared experimental and control arms (Wilcoxon rank sum test) in a pooled analysis of RCB index (498 patients in total) from the first six treatment comparisons that "graduated" a therapy based on ≥85% predicted probability of increasing pCR rate over control therapy in a future 300-patient phase 3 trial. **Results:** RCB index was prognostic overall (hazard ratio; 95% CI: 1.86; 1.62-2.14) and in each subtype: TNBC (2.09; 1.70-2.57, N = 224), HR-/HER2+ (2.91; 1.79-4.73, N = 69), HR+/HER2+ (1.41; 1.00-1.99, N = 134), and HR+/HER2- (2.08; 1.54-2.81, N = 251). Overall, estimates of 3-year EFS for RCB classes were: pCR 94%, RCB-I 87%, RCB-II 80%, RCB-III 62%. The distribution of RCB index decreased with graduating treatments, relative to control therapy, in TNBC (p < 0.001) and HER2+ (p = 0.03), but not in HR +/HER2- (p = 0.21). In those with RD (excluding pCR), there was a trend for decreased RCB index with graduating treatments, relative to control therapy, in TNBC (P = 0.08), but not in HER2+ (p = 0.43) or HR+/HER2- cancers (p = 0.94). **Conclusions:** RCB determined by local site pathologists was prognostic in all subtypes of breast cancer. Observed differences in RCB index distribution between randomized treatments suggested different patterns, possibly by class of experimental treatment and phenotype of disease. Clinical trial information: NCT01042379.

521 Poster Session (Board #13), Sat, 8:00 AM-11:30 AM

Patient (pt)-reported function and symptoms in APHINITY: A randomized comparison of chemotherapy (C) + trastuzumab (H) + placebo (Pla) versus C + H + pertuzumab (P) as adjuvant therapy in pts with HER2-positive early breast cancer (EBC). *First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In APHINITY (NCT01358877), adding P to H + C significantly improved invasive disease-free survival in pts with HER2-positive EBC (von Minckwitz, *NEJM* 2017). Pt-reported health-related quality of life (HRQoL; symptoms of therapy, patient functioning, and global health status) was a secondary outcome, assessed by EORTC QLQ-C30, QLQ-BR23, and EQ-5D 3L questionnaires. **Methods:** Pts received 1 year (18 cycles) of P or Pla and H + standard adjuvant C (3–4 cycles of anthracycline-based C followed by 3–4 cycles of taxane, or 6 cycles of docetaxel + carboplatin). Pts completed measures until recurrence or 36 months post-randomization (whichever was first). Assessments were performed at screening, end of anthracycline, taxane, and HER2-targeted therapy, at Week 25, and at 6, 12, and 24 months following the end of HER2-targeted therapy. Mean and mean change from baseline (BL) scores were assessed in each arm and time point; results were defined as clinically meaningful if they differed by ± 10 points (Osoba, *JCO* 1998). **Results:** Questionnaire completion rates were > 85% throughout. Mean physical function scores (SD; 95% CI) decreased from BL to Week 13 (end of taxane): –10.7 (17.2; –11.4, –10.0) with P and –10.6 (17.7; –11.4, –9.9) with Pla during C. Scores returned to BL during HER2-targeted treatment. There was no clinically meaningful decline in role function from BL to Week 13 in either arm: –8.0 (28.6; –9.2, –6.8) with P and –8.5 (29.5; –9.8, –7.3) with Pla during C. Diarrhea symptom score differences from BL were clinically meaningful with P (at Week 13), and scores returned to BL at the end of targeted therapy (P + H). Diarrhea symptom scores were worst at Week 13 in both arms (P +22.3 [29.8; 21.0, 23.6]; Pla +9.2 [23.9; 8.2, 10.2]). **Conclusions:** In one of the largest HRQoL data sets reported to date in HER2-positive EBC, there was no clinically meaningful worsening of role function, indicating that patients' abilities to conduct daily activities did not differ by treatment arm. Patient-reported diarrhea symptoms worsened to a greater extent in the P arm during both C and HER2-targeted treatment. Clinical trial information: NCT01358877.

522 Poster Session (Board #14), Sat, 8:00 AM-11:30 AM

Pooled analysis of two randomized phase III trials (PlanB/SuccessC) comparing six cycles of docetaxel and cyclophosphamide to sequential anthracycline taxane chemotherapy in patients with intermediate and high risk HER2-negative early breast cancer (n=5,923). *First Author: Wolfgang Janni, University of Ulm, Ulm, Germany*

Background: Recent studies draw different conclusions concerning whether omission of anthracyclines (A) in adjuvant chemotherapy for HER2-negative early breast cancer (EBC) may reduce toxicity without compromising efficacy. **Methods:** The prospectively randomized PlanB and Success C trials compared 6 cycles of docetaxel (D) and cyclophosphamide (C) with either 4 cycles of epirubicin (E) and C, followed by 4 cycles of D (EC-D, PlanB) or 3 cycles of 5-FU, E and C, followed by 3 cycles of D (FEC-D, SuccessC). Disease-free survival (DFS) was analyzed using univariable and multivariable Cox models adjusted for hormone receptor status (HRS) and histologic grade (G), age, menopausal status, type of surgery, pT, pN, and histologic type. **Results:** Overall, 5923 patients with follow-up data were available for this pooled analysis, with 2979 and 2944 patients randomized to A-free and A-containing chemotherapy, respectively. After 62 months median follow-up, DFS of patients receiving A-free vs A-containing chemotherapy was quite similar in univariable analysis (hazard ratio, HR = 1.04; 95% confidence interval, CI: 0.88 – 1.22, p = 0.64) and in multivariable analysis (HR = 1.00, 95% CI: 0.85 – 1.19, p = 0.96). Defining biological subtypes "luminal A-like" as HRS positive, G1/2, "luminal B-like" as HRS positive, G3, and TN (triple negative), no significant differences were seen in DFS between A-free and A-containing chemotherapy in luminal A-like (HR = 1.06, 95% CI 0.81 – 1.39, p = 0.66), luminal B-like (HR = 1.07, 95% CI 0.78 – 1.48, p = 0.68), or TN tumors (HR = 0.99, 95% CI 0.76 – 1.30, p = 0.95). However, in high-risk patients with four or more affected lymph nodes (pN2-3), A-containing chemotherapy was associated with significantly better DFS (HR = 0.69, 95%-CI 0.48- 0.98, p = 0.04). **Conclusions:** Our results suggest that 6 cycles of DC provide sufficient efficacy compared to an anthracycline-containing regimen in most patients with HER2-negative EBC. However, subgroup analyses indicate that high-risk patients might benefit from anthracycline-containing chemotherapy.

523 Poster Session (Board #15), Sat, 8:00 AM-11:30 AM

A prospective study on the effect of endoxifen concentration and CYP2D6 phenotypes on clinical outcome in early stage breast cancer patients receiving adjuvant tamoxifen. *First Author: Anabel Beatriz Sanchez-Spitman, Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, Netherlands*

Background: It has been postulated that endoxifen levels are better predictors of tamoxifen efficacy than CYP2D6 phenotype. Although in a retrospective study an endoxifen threshold of 5.9 ng/ml for efficacy was described, confirmation based on prospective studies is lacking. The objective of the prospective CYPTAM study (NTR1509) is to associate endoxifen levels and, CYP2D6 phenotypes with clinical outcome in early stage breast cancer patients receiving tamoxifen. **Methods:** Breast cancer patients who were receiving adjuvant tamoxifen were included. Blood samples were used for CYP2D6 genotyping and endoxifen levels by Amplichip and high-performance liquid chromatography-tandem mass spectrometry assay, respectively. Endoxifen levels and CYP2D6 phenotypes were associated with relapse-free survival (RFS) by using Cox-regression analysis. Patients who changed to an aromatase inhibitor, were censored at the time of switch. **Results:** A total of 667 pre and post-menopausal patients were enrolled. No association was found between endoxifen serum levels used as a continuous variable and RFS (Adjusted Harzard Ratio (HR): 0.991, 95 % CI: 0.946-1.038, p-value: 0.691). Categorizing endoxifen levels in quartiles, or using 5.9 ng/ml as threshold did not alter these results. In addition, no association was observed between CYP2D6 phenotypes and RFS (Adjusted HR: 0.929, 95 % CI 0.525-1.642, p-value 0.799). **Conclusions:** This first prospective clinical study shows no association between endoxifen levels and CYP2D6 phenotypes with RFS in early breast cancer patients using adjuvant tamoxifen. These results do not support the use of therapeutic drug monitoring based on endoxifen levels or CYP2D6 genotyping. Associations between Endoxifen levels and CYP2D6 phenotypes with RFS. Clinical trial information: NTR1509.

	Multivariable analysis		
	HR	95 % CI	p
Endoxifen	0.991	0.946-1038	0.691
Threshold (ng/ml):			
< 5.9	1.000	Reference	
> 5.9	1.538	0.719-3.290	0.267
Quartiles (ng/ml):			
Q1 (< 6.6)	1.000	Reference	
Q2 (6,6-10,3)	1.986	0.909-4.340	0.085
Q3 (10,3-14,1)	1.331	0.580-3.059	0.500
Q4 (> 14.1)	0.950	0.399-2.262	0.907
CYP2D6 phenotypes			
UM/EM	1.00	Reference	
hetEM/IM/PM	0.929	0.525-1.642	0.799

524 Poster Session (Board #16), Sat, 8:00 AM-11:30 AM

Duration of extended adjuvant therapy with neratinib in early-stage HER2+ breast cancer after trastuzumab-based therapy: Exploratory analyses from the phase III ExteNET trial. *First Author: Michael Gnant, Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria*

Background: The optimal duration of adjuvant therapy with targeted agents remains a question of ongoing relevance in oncology. ExteNET, an international, randomized, placebo-controlled phase III trial, showed that neratinib given for 12 months after trastuzumab-based therapy significantly improved 2- (HR 0.67, p = 0.009) and 5-year (HR 0.73, p = 0.008) invasive disease-free survival (iDFS) in early-stage HER2+ breast cancer [Chan et al. *Lancet Oncol* 2016; Martin et al. *Lancet Oncol* 2017]. We examined the influence of duration of neratinib therapy on efficacy in the ExteNET study. **Methods:** Patients with early-stage HER2+ breast cancer were randomly assigned to oral neratinib 240 mg/day or placebo for 12 months (or until disease recurrence) after standard primary therapy and trastuzumab-based (neo)adjuvant therapy. Patients who received neratinib for ≤3 or ≥11 months (the median duration of neratinib treatment) were each compared with the ITT placebo group. iDFS (primary endpoint) was analyzed using Kaplan-Meier methods and Cox proportional-hazards models adjusted for prognostic factors. Data cut-off: March 1, 2017. Clinicaltrials.gov: NCT00878709. **Results:** ITT population comprised 2840 patients (neratinib, n = 1420; placebo, n = 1420). Median treatment duration (ITT population) was 11.6 and 11.8 months in the neratinib and placebo groups, respectively. 391 patients received neratinib for ≤3 months. 872 patients received neratinib for ≥11 months or stopped treatment prior to 11 months due to recurrence. Results after a median of 5.2 years follow-up are shown below. **Conclusions:** These exploratory data suggest that patients who remained on neratinib for ≥11 months derived clear benefits from therapy, whereas neratinib efficacy was considerably reduced in those who stopped treatment early (≤3 months).Clinical trial information: NCT00878709.

		5-year iDFS rate, %		
Duration of neratinib	**N**	**Neratinib**	**Placebo**	**HR (95% CI)**
≤3 months	1811	88.4	87.7	0.90 (0.591.32)
≥11 months	2292[a]	91.0	87.7	0.67 (0.500.88)
ITT	2840	90.2	87.7	0.73 (0.570.92)[b]

[a]14 patients stopped treatment before 11 months due to recurrence.
[b]Adjusted for stratification factors.

525 Poster Session (Board #17), Sat, 8:00 AM-11:30 AM

Predicting expected absolute chemotherapy treatment benefit in women with early-stage breast cancer using a 12-gene expression assay. *First Author: William John Gradishar, Feinberg School of Medicine, Northwestern University, Chicago, IL*

Background: Previous studies have validated the ability of a 12-gene expression assay to predict risk of distant recurrence (DR) in women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) early stage breast cancer. Here, we employed a mathematical approach to estimate an expected absolute chemotherapy benefit based on the 12-gene expression test results. **Methods:** Data was included for patients who had clinical testing with the 12-gene expression assay in the US (Myriad Genetic Laboratories Inc., Salt Lake City, Utah) or Germany (Myriad GmbH, Munich, Germany). FFPE breast resections of treatment-naïve ER+, HER2- breast tissue were tested to generate a combined molecular and clinical score (EPclin score). For the entire group, the *relative* chemotherapy benefit was assumed to be 30% based on meta-analyses from the Early Breast Cancer Trialists' Collaborative Group. This was used to calculate the expected *absolute* chemotherapy benefit across the EPclin score continuum. This was first done in a conservative scenario where chemotherapy benefit was assumed to be independent of EPclin score (no interaction). The degree of interaction between expected chemotherapy benefit and the EPclin score was then systematically increased until the maximum possible EPclin score was associated with the maximum chemotherapy benefit. The mean *absolute* benefit was calculated for patients at high risk (EPclin $\geq$3.3) or low risk (EPclin $<$ 3.3) of distant recurrence. **Results:** Overall, 2,205 ER+, HER2- breast resections (303 tested in USA, 1902 tested in Germany) were included here [1286 samples (58%) with low EPclin scores; 919 (42%) with high EPclin scores]. The mean absolute benefit ranged from 1.5% to 1.8% (mean 10-year risk of DR 4.6% to 4.3%) for patients with low risk EPclin scores compared to 5.3% to 7.3% (mean 10-year risk of DR 14.7% to 12.8%) for patients with high risk EPclin scores. **Conclusions:** In this analysis, the 12-gene expression assay was able to predict *absolute* benefit from adjuvant chemotherapy in women with ER+, HER2- early stage breast cancer, regardless of which EPclin score cohorts accrued maximal *relative* treatment benefit.

527 Poster Session (Board #19), Sat, 8:00 AM-11:30 AM

Tumor infiltrating lymphocytes to predict DFS from intense dose-dense (idd) EPC regimen: Results from the German Adjuvant Intergroup Node-positive study (GAIN-1). *First Author: Aurelia Noske, Institut für Pathologie, Technische Universität München, München, Germany*

Background: Immunogenic infiltrate in breast cancer (BC) may influence the prognosis and response to systemic therapies. The association and prognostic role of tumor infiltrating lymphocytes (TILs), PD-1 and PD-L1 expression were investigated in high-risk, node positive breast carcinomas. **Methods:** The prospective adjuvant phase III GAIN trial compared two dose-dense regimens, iddEPC (epirubicin (E), paclitaxel (P), cyclophosphamide (C)) vs. EC-PX (capecitabine (X)) and Ibandronate vs. observation in patients with node-positive primary breast cancer. A total of 1318 FFPE tumor samples were available for analysis of TILs by HE morphology, and PD-1, and PD-L1 by immunohistochemistry. The association of immune parameters and their prognostic and potential predictive role were analyzed by Cox regression models. The median FU was 74.3 months (range: 0.1-113.7). **Results:** Increased TILs, PD-1 and PD-L1 positive TILs were significantly associated with higher grade, higher Ki67, ER/PR negative and triple negative BC (each $p < 0.0001$). TILs and PD-L1 positive TILs were slightly more frequent in HER2 positive BC ($p = 0.005$). Spearman analysis revealed positive, moderate to low correlations between TILs, PD1 and PD-L1. At multivariate Cox regression analysis with clinical covariables, TILs had a significant positive impact on DFS in the iddEPC-arm (HR = 0.57 [0.39-0.84], $p = 0.0043$) but not in the EC-PX-arm (HR = 1.26 [0.86-1.87], $p = 0.2384$, interaction $p = 0.0336$). Especially, HR+/HER2- BC with TILs and treated with iddEPC had a better DFS compared to no TILs (HR = 0.59 [0.38-0.93], $p = 0.0227$). PD-1 positive TILs in TNBC were associated with a significant better DFS (HR = 0.50 [0.25-0.99], $p = 0.0457$). PD-L1 expression had no impact on patient outcome. **Conclusions:** TILs and expression of immune checkpoints are common in high-grade, highly proliferative, triple negative and in part in HER2 positive BC. Tumor infiltrating lymphocytes predict the benefit from intense dose-dense EPC whereas the prevalence and prognostic impact of PD-1 /PD-L1 seem to play an inferior role in this node-positive breast cancer cohort with adjuvant chemotherapy.

529 Poster Session (Board #21), Sat, 8:00 AM-11:30 AM

Residual risk assessment with the Breast Cancer Index (BCI) for prediction of late distant recurrence (DR) in patients from the TransATAC study. *First Author: Ivana Sestak, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom*

Background: The Breast Cancer Index (BCI) is a gene-expression based signature comprised of two complementary functional domains: the molecular grade index (MGI) for tumor proliferation, and the HoxB13/IL17BR ratio (H/I) for estrogen signalling. BCI provides a quantitative assessment of the likelihood of overall (0-10yr), late (5-10yr) DR and reported to show endocrine benefit in patients with estrogen receptor positive (ER+) breast cancer. The aim of the current study was to further characterize BCI performance to predict late DR for postmenopausal women with N- and N+ disease treated with either anastrozole or tamoxifen. **Methods:** 883 women with ER+, N- or N+ (1 to 3 nodes) breast cancer from TransATAC study who were recurrence free at 5 years were included in this analysis. Time to late DR (5 years after diagnosis) was the primary endpoint. Cox regression models were utilized to determine the prognostic value of the BCI and KM-estimates were used to determine 5-10 year DR. **Results:** 75 late DRs were recorded in all 883 patients who were recurrence free at 5 years. Patients with a high BCI score were associated with a significantly worse outcome compared to those with a low BCI score (HR = 1.88 (1.49-2.39)). This relationship was observed for both N- (HR = 1.96 (1.41-2.72)) and N+ (HR = 1.51 (1.08-2.12)) patients. BCI added significant prognostic information beyond that from CTS in all patients (ΔLR-χ^2= 11.51, P = 0.0007). For women with N- disease, significant differential risk stratification was observed between low and intermediate groups and between low and high groups. For N+ patients a significant difference was observed between low and high risk groups (HR = 3.10 (1.28-7.49)), but not low and intermediate or intermediate and high. For N+ patients, a BCI model integrating tumor size and grade provided significantly more prognostic value than BCI alone (LR-χ^2= 21.34 vs. LR-χ^2= 5.86, respectively). **Conclusions:** In this post-hoc analysis with an expanded group of patients from the TransATAC cohort, BCI was a significant prognostic factor for late DR in both N- and N+ patients, with a combined BCI model providing more prognostic value in N+ patients.

530 Poster Session (Board #22), Sat, 8:00 AM-11:30 AM

Overall survival in female Medicare beneficiaries with early stage breast cancer receiving bisphosphonates or denosumab. *First Author: Raul A Herrera Pena, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Adjuvant bisphosphonates in early breast cancer (BC) have resulted in reduction in bone metastasis and improved overall survival (OS), particularly in post-menopausal women. We aim to evaluate the effect of bone-modifying agents (BMA) on survival in a population based cohort of older BC patients. **Methods:** Patients aged $\geq$ 66 yo diagnosed with stage I-III BC between 2007 and 2013 were identified in SEER-Medicare and TCR-Medicare database. Patients were required to have Medicare Parts A, B and D coverage. Patients receiving at least 6 months of an oral bisphosphonate, two doses of ibandronate or one dose of zoledronate or denosumab at doses equivalent or higher to those approved for osteoporosis, during the first two years of BC diagnosis were identified as having received a BMA. Five year-OS was estimated with Kaplan-Meier with groups compared with the log rank test. Cox proportional hazards models were fitted to determine the association of BMA and OS after propensity score adjustment. Subgroup analysis were stratified by stage. **Results:** The final cohort included 37,604 patients. Median age was 75 years. 32,045 (85.2%) of the patients had hormone receptor-positive tumors. Overall, 8,591 (22.8%) of the patients were treated with BMA. Of these, 7,349 (85.5%) received bisphosphonates only. The unadjusted 5 year OS was 81% and 77 % for those who did and did not receive BMA, respectively ($P < 0.0001$). After multivariate analysis including propensity scores adjustment, treatment with BMA was associated with a statistically significant increased survival (Hazard ratio [HR] 0.91, 95% CI = 0.85-0.96). When stratified by stage, BMA vs no BMA showed an improvement in unadjusted 5 year OS in patients with Stage II (5y OS 79% vs 72%, $P < 0.0001$) and Stage III (64% vs 57%, $P = 0.002$) but not for Stage I (86% vs 85%, $P = 0.88$). After multivariate adjustment, survival remained significant for Stage II (HR 0.81, 95% CI = 0.73-0.90) but not for Stage III (HR 0.91, 95% CI = 0.78-1.07). **Conclusions:** Use of BMA in post-menopausal woman with early stage BC patients was associated with improved 5 year OS. Stage stratified subgroup analysis showed that the difference in survival was significant only for patients with stage II.

531 Poster Session (Board #23), Sat, 8:00 AM-11:30 AM

Safety and tolerability of adjuvant enzalutamide for the treatment of early stage androgen receptor positive (AR+) triple negative breast cancer. *First Author: Tomas Lyons, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A subset of triple negative breast cancer (TNBC) is characterized by androgen receptor (AR) expression and dependence on AR signaling (Doane Oncogene 2006; Gucalp CCR 2013). Enzalutamide (ENZA), an AR-antagonist, has a clinical benefit rate of 33% in evaluable patients(pts) with metastatic AR+ TNBC (Traina et al, JCO 2018). This study tests the feasibility of 1 year (y) of adjuvant ENZA for the treatment (tx) of early stage, AR+ TNBC (NCT02750358). We now report safety data observed in our phase II trial. **Methods:** Eligible pts have centrally confirmed, Stage I-III, ER/PR $<$ 1%, HER2(-) AR $\geq$1% BC and completed all planned tx (surgery, (neo)adjuvant chemotherapy and radiation) within 6 months of study start. Tx consists of ENZA 160mg orally daily for 1y with option for 2y at pt discretion. Toxicity assessment per NCI CTCAEv4 every 4 weeks for 12 weeks, then every 3 months. Primary endpoint: feasibility of 1y ENZA, measured as the tx discontinuation rate due to toxicity, withdrawal of consent or tolerability. 46 evaluable pts are required to discriminate between feasibility of 50% and 70%, with type I error 5% and 88% power. Secondary endpoints: feasibility rate at 1y in adherent pts, safety of extended duration ENZA and 3y DFS and OS. Exploratory endpoints: pt reported outcomes and biomarker development. **Results:** Between 5/2016-1/2018, 38 pts on tx, with complete accrual planned by 6/2018. Pt characteristics: median age 53y(32-80), Stage I/II 81%, III 19%, Grade 2 21%, Grade 3 79%. 35(92%) received chemo: Neo 49%, Adj 51%; Anthracycline/Taxane-based 29 (83%), Platinum 2 (6%), Other 6 (17%). 5(14%) received adjuvant capecitabine for lack of pCR. 79% received XRT. AR $>$ 10% in 24 pts(63.2%) and AR $\leq$10% in 14(36.8%). Any grade (gr) AE possibly attributed to ENZA: fatigue (31.5%), hot flashes (21%), reduced white blood cells (7.9%), nausea (5.3%) and increased alkaline phosphatase (5.3%). The only ENZA-related gr $\geq$3 AE was fatigue (1pt, 3%). No seizures were observed. 3 pts had dose reduction due to AE. **Conclusions:** ENZA administered in the adjuvant setting is well tolerated following definitive locoregional tx and standard of care chemotherapy. No new safety signals were observed. Clinical trial information: NCT02750358.

532 Poster Session (Board #24), Sat, 8:00 AM-11:30 AM

Adherence to hormonal therapy among commercially insured breast cancer patients. *First Author: Hui Zhao, Health Services Research Department, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tamoxifen and aromatase inhibitors (AI) are adjuvant hormone therapy (HT) routinely used for the treatment of early-stage estrogen-positive breast cancer, their use reduces the risk of breast cancer recurrence by about 30%. Despite the survival benefit, the side effects of HT and other factors may affect patients' adherence. No large observational study has assessed the 5 year HT adherence for breast cancer. We evaluated HT adherence over a five-year course using the commercial health claims data provided by Truven Health Analytics. **Methods:** Breast cancer patients who received mastectomy or lumpectomy aged 18 years and older between 1999 to 2014 and initiated HT within 1 year since surgery were selected. The outcome variable was HT adherence rate from years 1 to 5. HT adherence was defined as proportion of days covered (PDC) $\geq$ 80% during a treatment year. HT adherence rate was computed as adherence patients in a given year divided by all HT users who had insurance coverage in that year. Covariates included patient's age, geographic region, type of health insurance plan, year at cancer surgery, comorbidity, type of HT drugs, and primary cancer treatment such as surgery, chemotherapy, and radiation treatment. Logistic regression was used to evaluate factors associated with HT adherence. **Results:** 27,790 patients initiated HT within 1 year of breast cancer surgery. The median age was 55 years old and the median time from breast cancer surgery to HT initiation was 114 days. 29.2% of patients used tamoxifen, 28.2% used anastrozole, 8.9% used letrozole, 1.4% used exemestane, and 32.3% used more than one type of HT drugs. Each year, about 60 to 70% patients were adherent to the treatment. The five year adherence rate decreased from 81.4% in the first year to 21.1% in the 5th year. Patients who were $\geq$ 50 years old, lived not in the South, with insurance other than HMO, received lumpectomy or mastectomy combined with chemotherapy and radiation therapy, with no comorbidity, used AI, and received surgery in 2003 were more likely to be adherent to HT. **Conclusions:** The five year HT adherence rates were low among breast cancer patients. Health care providers need to identify ways to improve HT adherence to prevent breast cancer recurrence. [1996 characters]

533 Poster Session (Board #25), Sat, 8:00 AM-11:30 AM

Selection for Oncotype Dx testing among young women with early-stage ER+/HER2- breast cancer. *First Author: Philip Daniel Poorvu, Dana-Farber Cancer Institute, Boston, MA*

Background: The Oncotype Dx Recurrence Score (RS) predicts distant recurrence risk and benefit from chemotherapy for women with early-stage estrogen receptor (ER) positive (+)/human epidermal growth factor receptor 2 (HER2) negative (-) breast cancer (BC). Due to the independent risk of young age and small proportion of young women in the validation studies, providers may be hesitant to rely on the RS among young women. **Methods:** Using a multi-center, prospective cohort study of women newly diagnosed with BC at age $\leq$40 years enrolled from 2006-2016, we identified participants with stage I-III, ER+/HER2- BC. Clinical data were obtained through patient surveys and medical record review. Factors associated with RS testing by univariable analyses ($p < 0.20$) were used to generate a multivariable logistic regression model. **Results:** 182 (32%) of 575 eligible women had a RS performed (Table 1). Younger women ($OR_{age \leq 30 \text{ vs } 36\text{-}40} = 0.49$, $p = 0.03$) and those with larger ($OR_{> 2cm \text{ vs } \leq 2cm} = 0.54$, $p = 0.007$), node positive ($OR_{pos \text{ vs } neg} = 0.14$, $p < 0.0001$) or high grade tumors ($OR_{high \text{ vs low/intermediate}} = 0.37$, $p < 0.0001$) were less likely to have a RS performed. Of women who had a RS performed, chemotherapy usage was 21/88 (24%), 44/77 (57%), and 17/17 (100%) among those with low, intermediate, and high RS, respectively. Most women with low risk RS who received chemotherapy had other low risk features: 67% T1, 67% N0, and 86% low/intermediate grade. **Conclusions:** Despite the development of multigene testing to assess the benefit of chemotherapy, many young women with node-negative ER+/HER2- BC are not tested, and when tested, a substantial percentage receive chemotherapy despite a low RS. This highlights an opportunity to improve individualized care for young women with BC.

Recurrence score testing.

	RS/N (%)	OR (95% CI)	p-value
Age ≤30	18/75 (24)	0.49 (0.26,0.93)	0.03
31-35	48/158 (30)	0.87 (0.55,1.34)	0.57
36-40	116/342 (34)	Ref	
Tumor size ≤ 2cm	137/326 (42)	Ref	
> 2cm	45/249 (18)	0.54 (0.35,0.85)	0.007
Nodal status N0	154/322 (48)	Ref	
N+	25/249 (10)	0.14 (0.09,0.24)	< 0.0001
Grade Low/Intermediate	146/357 (41)	Ref	
High	35/213 (16)	0.37 (0.24,0.59)	< 0.0001

* Missing data and factors not associated with RS testing not included

534 Poster Session (Board #26), Sat, 8:00 AM-11:30 AM

Assessment and management of bone health in women treated with adjuvant anastrozole in the DATA study. *First Author: Irene Van Hellemond, Maastricht University Medical Centre, Maastricht, Netherlands*

Background: The phase III DATA study (NCT00301457) investigates the efficacy of 6 versus 3 years of adjuvant anastrozole (AI) after an initial 2-3 year treatment with tamoxifen in postmenopausal women with breast cancer. In a planned side study, we assessed patterns of care in detection and treatment of osteopenia/osteoporosis and linear trends over time in bone mineral density (BMD). **Methods:** BMD measurements and bisphosphonate use in the DATA study were left to the treating physician. We registered all BMD measurements and start of bisphosphonate-use. BMD was measured by a dual-energy x-ray absorptiometry (DEXA) scan of the lumbar spine and/or the hip and transformed to a T-score. Time to osteopenia or osteoporosis was analysed by reverse Kaplan Meier methodology. For the linear trend in BMD T-score, linear mixed models with random effects for patient were used. **Results:** Of the 1860 eligible patients in the DATA study, 910 (48.9%) had a BMD measurement at the start of anastrozole (baseline). In 417 (45.8%) patients the baseline measurement indicated a normal BMD, in 408 (44.8%) osteopenia, and in 85 (9.3%) osteoporosis. In patients with a normal baseline BMD, osteopenia was observed in 53.5% of patients in the 6-year group, and 55.4 % in the 3-year group ($p = 0.18$), while none developed osteoporosis within 6 years after randomization. Of the patients with osteopenia at baseline, 24.4 % developed osteoporosis in the 6-year group and 20.4% in the 3-year group ($p = 0.89$). The yearly BMD change in the lumbar spine showed a decline of the mean T score of 0.075. When bisphosphonates were added the decline became 0.047 per year ($p < 0.001$), and when the AI was stopped and bisphosphonates continued the BMD increased yearly with 0.047. **Conclusions:** In postmenopausal women who had been treated with 2-3 years of adjuvant tamoxifen, BMD measurement showed osteopenia in 44.8% of women and osteoporosis in 9.3%. Although subsequent AI-use was associated with a further decrease of BMD, none of the patients with a normal BMD at baseline developed osteoporosis regardless of treatment arm. Clinical trial information: NCT00301457.

535 Poster Session (Board #27), Sat, 8:00 AM-11:30 AM

Comprehensive transcriptomic profiling to identify breast cancer patients that may be spared adjuvant systemic therapy. *First Author: Martin Sjostrom, Lund University, Department of Oncology and Pathology, Lund, Sweden*

Background: Some women with early stage breast cancer (BC) may not require additional systemic therapy after breast-conserving surgery (BCS). While this subgroup of ultra low-risk women has been difficult to identify with conventional clinical metrics, transcriptomic profiling may offer improved risk stratification. Previously described genomic signatures perform well on the group level, but reports indicate that there may be substantial disagreement between signatures for an individual patient. **Methods:** We analyzed tumors from 765 patients in the SweBCG91-RT trial, which randomized node-negative BC patients to +/- radiation following BCS, with minimal use of adjuvant systemic treatment (9%). Median follow-up was 18.6 years for breast cancer-specific survival (BCSS). The original study demonstrated a benefit from radiation on locoregional events, but not BCSS. Tumors were profiled with the Affymetrix Human Exon 1.0 ST microarray and 14 genomic signatures from literature (including Mammaprint-like, OncotypeDX-like and PAM50-like signatures) were calculated. The average of all signatures was used as an average genomic risk (AGR), which was further used to derive a novel 141-gene signature, with independent features from the previous signatures. **Results:** Most previously described signatures performed well in our data and were highly prognostic for BCSS. The performance of AGR was in line with the best individual genomic signatures, and among the systemically untreated, ER+, HER2- and postmenopausal patients (N = 454, 59% of the entire study population), the BCSS at 15 years for the 50% of patients with lowest AGR was 93% (95%CI 90-97%). The 141-gene signature had a similar performance with 92% (95%CI 88-96) BCSS for the 50% of patients with lowest risk at 15 years. **Conclusions:** AGR, based on 14 previously published signatures, is highly prognostic for BCSS and identifies a large proportion of patients with an excellent outcome. An associated novel 141-gene signature performs similarly and identifies patients that may be spared adjuvant systemic treatment. Based on several individual signatures, AGR and the novel 141-gene signature may be more robust on an individual patient level.

536 Poster Session (Board #28), Sat, 8:00 AM-11:30 AM

Breast cancer cell-free DNA (cfDNA) profiles reflect underlying tumor biology: The Circulating Cell-Free Genome Atlas (CCGA) study. *First Author: Minetta C. Liu, Mayo Clinic, Rochester, MN*

Background: New breast cancer screening approaches are needed to detect clinically aggressive subtypes that may not be detected by mammography or are detected late in unscreened populations. CCGA (NCT02889978) is a prospective multi-center observational study for the development of a noninvasive assay for cancer detection. A preplanned substudy of a Women-Only Cohort is reported. **Methods:** Blood was prospectively collected (N = 1627) from 878 participants (pts) with newly diagnosed untreated cancer (20 tumor types, all stages) and 749 pts with no cancer diagnosis (controls, C) for plasma cfDNA extraction. This substudy included 358 pts with invasive breast cancer (IBC) and 452 C. Three prototype sequencing assays were performed: paired cfDNA and white blood cell (WBC) targeted sequencing (507 genes, 60,000X) for single nucleotide variants/indels, paired cfDNA and WBC whole genome sequencing (WGS, 30X) for copy number variation, and cfDNA whole genome bisulfite sequencing (WGBS, 30X) for methylation; WBC sequencing identified the contribution of clonal hematopoiesis (CH). For each assay, a classification model using 10-fold cross-validation was developed to discriminate IBC from C using a subset of women; sensitivity was estimated at 95% specificity. **Results:** IBC pts and C had similar age (mean yrs±SD: 58±13 IBC, 59±12 C). 46% of IBC pts were symptomatic (a subset were documented interval cancers), 82% were stage I/II. The subtype breakdown of HR+/HER2+/triple-negative breast cancer (TNBC) was 65%/17%/15%. WGBS returned the highest sensitivity of the 3 assays and is reported here; results were consistent across all assays. Sensitivity (95% CI) was higher for TNBC vs HER2+ vs HR+/HER2- (58% [43-72] vs 40% [28-54] vs 15% [10-20]), and higher for symptomatic vs screen-detected breast cancer (44% [36-52] vs 10% [6-16]). Comparison to tumor WGS and multi-assay classification will be reported. **Conclusions:** Breast cancers with detectable cfDNA signals at time of diagnosis included clinically aggressive subtypes and symptomatic presentation. Further assay and clinical development in the intended use population is ongoing (NCT03085888). Clinical trial information: NCT02889978.

538 Poster Session (Board #30), Sat, 8:00 AM-11:30 AM

Dose tailoring of breast cancer adjuvant chemotherapy aiming at avoiding both over and undertreatment: Results from the prospective PANTHER study. *First Author: Alexios Matikas, Department of Oncology, Karolinska Institutet and University Hospital, Stockholm, Sweden*

Background: Adjuvant breast cancer chemotherapy (ACT) improves relapse free (BCRFS) and overall survival (OS). Differences in terms of efficacy and toxicity could partly be explained by the significant interpatient variability in pharmacokinetics which cannot be captured by dosing according to body surface area. Consequently, tailored dosing was prospectively evaluated in the phase III PANTHER trial with 2017 patients. **Methods:** PANTHER is a multicenter, open-label, randomized phase III trial which compared tailored, dose dense epirubicin/cyclophosphamide (EC) and docetaxel (D) (group A) with standard interval 5-fluorouracil/E/C and D (group B), with identical duration of therapy in both arms. The primary endpoint was BCRFS. The primary efficacy analysis revealed an improved event free survival and favorable trends for BCRFS, OS and distant disease free survival compared with standard ACT. In this secondary analysis, we aimed to explore the concept of dose tailoring. Our two hypotheses regarding patients treated at group A were that BCRFS would not differ according to the cumulative administered dose; and that dose tailoring would lead to appropriate dosing and improved outcomes for obese patients. **Results:** Patients randomized in group A had similar BCRFS regardless of the cumulative epirubicin (p = 0.495) or docetaxel dose (p = 0.575). There were consistent, non-statistically significant trends in favor of patients receiving < 360 mg/m^2 epirubicin compared to 360-420 and > 420 mg/m^2. In addition, there were no differences in outcomes between patients receiving tailored ACT with a body mass index (BMI) of < 24 (n = 307), 24-28 (n = 296) and 28-40 (n = 312) (p = 0.384). Patients with a BMI of 28-40 had a non-significant trend for improved BCRFS, using BMI < 24 as reference (HR = 0.73, 95% CI 0.45-1.18) **Conclusions:** Dose tailoring could spare patients from unnecessary overdosing without compromising outcomes and may overcome the negative impact on prognosis conferred by obesity. Although exploratory, these results highlight the feasibility of tailored ACT, and underscore the need for further studies. An in-depth discussion will be presented at the ASCO meeting. Clinical trial information: NCT00798070.

539 Poster Session (Board #31), Sat, 8:00 AM-11:30 AM

In silico evaluation of the 12-gene molecular score (EndoPredict) and the recurrence score (Oncotype DX) as predictors of response to neo-adjuvant chemotherapy in estrogen receptor positive (ER+), HER2 negative (HER2-) breast cancer. *First Author: Hatem Hussein Soliman, Moffitt Cancer Center, Tampa, FL*

Background: Neo-adjuvant chemotherapy (NaCT) facilitates complete surgical resection in locally advanced, ER+, HER2- breast cancer. Due to its association with improved outcome, pathologic complete response (pCR) to NaCT treatment has been accepted as a surrogate for long-term outcome in clinical trials of patients with HER2+, triple-negative, or luminal B breast cancer. However, only 7-10% of patients with ER+, HER2- disease who receive NaCT achieve pCR. Biomarkers predictive of NaCT response would facilitate patient stratification and enable individualized therapeutic strategies. Here we evaluated the ability of two prognostic biomarker assays to predict NaCT response in ER+, HER2- breast cancer by means of a microarray-based in silico analysis. **Methods:** Expression and corresponding clinical data associated with pre-treatment biopsies obtained from patients with breast cancer who subsequently received NaCT were obtained from public datasets (GSE entries 16716, 20271, 25066, 32646, 41656, 41998). ER+, HER2- samples were selected based on available immunohistochemistry (IHC) data. The 12-gene molecular score (12-MS) and 21-gene recurrence score (21-RS) were approximated in silico according to published algorithms using expression means of array probes corresponding to the respective genes. Association with pCR was tested by logistic regression with adjustment for cohort. **Results:** A total of 764 patients with ER+, HER2- disease had available IHC data; 59 experienced pCR (response rate 8%). 12-MS and 21-RS were moderately well correlated (0.71). Both scores were predictive of pCR (12-MS p = 6.9×10^{-5}; 21-RS p = 0.0023). In bivariate analysis the 12-MS remained a significant predictor of response (p = 0.01) while the 21-RS did not (p = 0.73). **Conclusions:** In this microarray-based in silico analysis, 12-MS was highly predictive of ER+, HER2- response to NaCT. Optimal stratification of patients with ER+, HER2- breast cancer for NaCT offers the opportunity to individualize care, improve response rates, and possibly avoid ineffective treatment.

540 Poster Session (Board #32), Sat, 8:00 AM-11:30 AM

Image-based risk score to predict recurrence of ER+ breast cancer in ECOG-ACRIN Cancer Research Group E2197. *First Author: Nishant Verma, Inspirata, Tampa, FL, US*

Background: Tumor grade is a predictor of breast cancer recurrence, independent of gene expression assays such as Oncotype Dx (ODx). However, grade suffers from significant intra- and inter-observer variability, limiting its clinical utility. Advances in whole slide imaging facilitate computerized analysis of H&E slides. We have developed a prognostic assay called Image-based Risk Score (IbRiS) which extracts and leverages morphometric signatures from H&E slides to classify patients into low- vs. high-risk groups for recurrence. **Methods:** IbRiS was evaluated on 378 ER+ patients treated with chemo-hormonal therapy obtained from ECOG-ACRIN study E2197; patients had 0-3 positive axillary nodes and H&E slides of acceptable quality; 60 patients suffered recurrence. A subset of 124 patients (27 recurrences) were HER2-. Another (enriched) subset (116 patients with 27 recurrences) had accompanying ODx scores. To establish IbRiS low- and high-risk groups, we determined (over the 378 patients) a cutoff such that the low-risk group had a 10-year recurrence rate of ~10%. We evaluated IbRiS risk groups using Cox proportional hazard analysis, controlling for node status, age, and tumor size. We also compared the recurrence rates in the IbRiS risk groups to those of ODx and a combined assay (IbRiS + ODx). **Results:** IbRiS risk groups predicted recurrence with a hazard ratio of 2.41 (n = 378, 95% CI = 1.21-4.79, $p = 0.01$) and 2.52 (n = 124, 95% CI = 0.85-7.46, $p = 0.09$) for the HER2- subset. Over the 378 patients, IbRiS classified as low-risk 35.3% of the patients who did not suffer recurrence. Table 1 compares the low-/high- risk stratifications of IbRiS, ODx, and the combined assay. **Conclusions:** IbRiS assay is a significant predictor of breast cancer recurrence and contributes prognostic information independent of ODx. The combined genomic and morphometric assay outperforms either individual assay. Also, while ODx was reported to lose prognostic ability when restricted to HER2- patients in E2197, IbRiS remains a predictor of recurrence.

Performance of assays (N = 116).

	% of patients without recurrence classified as low-risk	10-year recurrence rate in low-risk group
IbRiS	37.5%	17.2%
ODx	56.3%	19.6%
IbRiS + ODx	75.0%	20.0%

541 Poster Session (Board #33), Sat, 8:00 AM-11:30 AM

Long-term benefit from tamoxifen therapy for patients with Luminal A and Luminal B breast cancer: Retrospective analysis of the STO-3 trial. *First Author: Linda Lindström, Karolinska Institutet, Stockholm, Sweden*

Background: Breast cancer patients with estrogen receptor (ER)-positive disease have a continuous long-term risk for fatal breast cancer spanning more than 20 years, but the biological factors influencing this risk are unknown. Here we aimed to investigate the long-term survival and benefit from tamoxifen therapy for patients with Luminal A and Luminal B subtype tumors. **Methods:** The Stockholm Tamoxifen (STO-3) trial enrolled 1780 postmenopausal patients from 1976 until 1990 with lymph node-negative breast cancers and tumors less than or equal to 30 mm in diameter, randomly assigned to at least two years of adjuvant tamoxifen (40 mg daily) vs no adjuvant treatment. All patients had a complete long-term follow-up until December 31, 2012, and detailed patient and clinical information. Gene expression data was generated using custom designed Agilent arrays from FFPE breast cancer tumor tissue and was used to define Luminal A and Luminal B subtype tumors. ER, PR, HER2 and Ki-67 were also reassessed in 2014. Long-term breast cancer-specific survival was performed using Kaplan-Meier analysis and flexible parametric survival models were used to estimate the time-varying hazard ratios (HRs) adjusting for patient and tumor characteristics. **Results:** A statistically significant difference in long-term survival (25 years) by Luminal subtype and trial arm was seen (Log Rank, $P < 0.0001$). For Luminal A and Luminal B patients, the 25 year survival was 88% versus 69% for treated patients and 73% versus 58% for untreated patients. Luminal A patients in the tamoxifen treated arm had a significantly reduced long-term risk of fatal breast cancer up to 20 years after breast cancer diagnosis (HR at 15-years: 0.59; 95% CI, 0.35-0.98; and HR at 20-years: 0.65; 95% CI, 0.32-1.30) as compared to the untreated arm. However for patients with Luminal B tumors, a significantly reduced long-term risk was only seen up to 10 years after diagnosis (HR at 5-years: 0.37; 95% CI, 0.18-0.73; and HR at 10-years: 0.68; 95% CI, 0.31-1.47). **Conclusions:** Patients with Luminal A subtype tumors have a long-term benefit from tamoxifen therapy, whereas the benefit for patients with Luminal B tumors is up to ten years after diagnosis. Clinical trial information: STO-3 trial from 1976 no registration# at the time.

542 Poster Session (Board #34), Sat, 8:00 AM-11:30 AM

Next-generation targeted sequencing (NGTS) investigating *CDK4* as a prognostic driver in pure invasive lobular breast carcinoma (ILC): Preliminary results in early-stage patients (pts) stratified according to a validated clinico-pathological model. *First Author: Luisa Carbognin, University of Verona, Verona, Italy*

Background: The aim of this analysis was to investigate the distribution of molecular abnormalities and their potential role as therapeutic targets (with particular regard to CDK4/6 alterations) in resected ILC pts, grouped according to prognosis. **Methods:** Clinico-pathological multi-center data of early-stage pure ILC pts were correlated to disease-free survival (DFS). A continuous score was derived according to multivariate Hazard Ratios, to develop a 3-class model. The model was validated in an external pts' cohort. Mutational and Copy Number Variation (CNV) analyses by NGTS, including 26 genes, were performed for pts at Poor and Good Prognosis (PP/GP). Quantitative-PCR analysis was applied for CNV validation; IHC for CDK6 was accomplished. Fisher's exact test and *Peto* Odds Ratio (OR) were adopted for comparison. **Results:** Data from 773 pts (Training/Validation Set [TS/VS]: 491/282) were gathered. At multivariate analysis, T-size and N-status were independent predictors for DFS. A significant difference between pts at low/intermediate/high risk was found (10-yrs DFS: 76.3%/67.6%/39.8%, respectively, $p < 0.0001$) in the TS. The model discriminated DFS in the VS ($p < 0.0001$). According to the developed model, 20 PP and 14 GP pts underwent molecular analysis. In PP group, *CDH1* was the most mutated gene (50.0%) followed by *PIK3CA* (35.0%). *MAP3K1* (10.0%), *ERBB2* and *PTEN* were mutated with low frequency (6.1%), only in the PP group. With regard to CNV, *CDH1* loss (55.0%) were the most frequent event, followed by gain in *ESR1*, *FGFR1* and *CDK4* (35.0%), which was present exclusively in PP group ($p = 0.03$) and validated by quantitative-PCR. Moreover, *CDK4* gain reported a significant higher chance to be associated with PP (OR = 7.98, 95%CI 1.51-42.1, $p = 0.014$). CDK6 overexpression showed a trend toward an association with PP (OR = 3.29, 95%CI 0.56-19.25, $p = 0.18$). **Conclusions:** These preliminary data first suggest that *CDK4* gain is potentially associated with PP. The potential *druggable* of this alteration deserves further clinical investigations in the context of ILC.

543 Poster Session (Board #35), Sat, 8:00 AM-11:30 AM

Association of a low-expression SLCO1B1 polymorphism with estrogen concentrations before and during aromatase inhibitor treatment for breast cancer. *First Author: Jacqueline M Dempsey, University of Michigan College of Pharmacy, Ann Arbor, MI*

Background: Three aromatase inhibitors (AI), the steroid exemestane, and the azoles anastrozole and letrozole, are effective in the treatment of estrogen receptor positive (ER+) breast cancer by preventing biosynthesis of estrogens including estradiol (E2), estrone (E1), and estrone-sulfate (E1S) in postmenopausal women. OATP1B1, encoded by *SLCO1B1*, transports E1S into the liver for desulfation to active E1. Women carrying the low-expression *SLCO1B1* rs4149056 single nucleotide polymorphism (SNP) have higher E1-conjugate levels (Dudenkov Breast Cancer Res Treat 2017). We hypothesized that patients carrying this SNP would have increased E1S at baseline, and this E1S reserve could resupply E1 and E2 resulting in detectable estrogen levels during AI treatment. **Methods:** Five hundred postmenopausal women with ER+ breast cancer were randomized 1:1 to either exemestane 25 mg/day or letrozole 2.5 mg/day. Plasma estrogen concentrations were measured prior to and after 3 months of AI treatment using LC/MS/MS (LLOQ for E2 = 0.625 pg/mL, E1 = 1.56 pg/mL, E1S = 3.13 pg/mL). The additive genetic associations between rs4149056 and 1) log-transformed concentrations of E2, E1, and E1S at baseline and 2) detectable (> LLOQ) concentrations of E2, E1, and E1S after 3 months of AI treatment, were tested using linear and logistic regression, respectively. **Results:** Patients carrying the low-expression rs4149056 (minor allele frequency = 0.18) SNP had 51% (per allele) higher baseline E1S concentrations (n = 438, 95% CI (29%-76%), $p < 0.0001$). After 3 months of AI treatment, 15% (58/378) of patients had detectable E1; carrying rs4149056 increased risk of maintaining detectable E1 by 84% (per allele) (odds ratio = 1.84, 95% CI (1.08-3.14), p = 0.025). **Conclusions:** Patients carrying a low-expression OATP1B1/*SLCO1B1* SNP have higher pre-treatment E1S and greater risk of maintaining detectable E1 during AI treatment, possibly due to replenishment from E1S reserves. Further studies are needed to assess whether this common SNP is associated with increased risk of AI treatment failure.

544 Poster Session (Board #36), Sat, 8:00 AM-11:30 AM

Patient(Pt)-reported toxicities by chemotherapy regimen for early breast cancer (BC) (LCCC1334/1440). *First Author: Kirsten A. Nyrop, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Pt-reported outcomes reflect toxicity of anticancer drugs, and can be measured using "moderate, severe or very severe" ratings (MSVS) that mirror physician-assessed CTCAE grades 2-4. **Methods:** We prospectively collected pt-reported MSVS in pts with stage I-III BC at each cycle of conventional (neo)adjuvant chemotherapy. **Results:** In 135 patients, mean age was 52, 26% non-white, 32% ≤high school education. Fatigue, arthralgia, constipation, diarrhea, nausea, myalgia, and peripheral neuropathy toxicities varied significantly by chemotherapy regimen ($p < 0.05$). Pts who received anthracycline-based chemotherapy reported significantly more MSVS toxicities compared those who did not (mean 5.3 vs 3.5, $p < 0.001$). **Conclusions:** Modern (neo)adjuvant chemotherapy has substantial toxicity that varies by regimen; anthracycline-based regimens appear particularly difficult. These findings support efforts to tailor therapy and minimize overtreatment. Clinical trial information: NCT02328313.

Patient-reported MSVS toxicities, by chemotherapy regimen.

Toxicities	All Regimens N = 135		Doxorubicin + cyclophosphamide à paclitaxel + carboplatin N = 18	Doxorubicin + cyclophosphamide à paclitaxel N = 49	Docetaxel + carboplatin* N = 22	Docetaxel + cyclophosphamide** N = 46	*p* value
	Moderate	Severe/ Very Severe	Combined Moderate/Severe/ Very Severe (MSVS)				
Fatigue	59 (44%)	30 (22%)	14 (78%)	40 (82%)	14 (64%)	21 (46%)	**.002**
Insomnia	50 (37%)	27 (20%)	12 (67%)	32 (65%)	9 (41%)	25 (52%)	.20
Anxiety	46 (34%)	15 (11%)	10 (56%)	22 (45%)	8 (36%)	21 (46%)	.68
Arthralgia	42 (31%)	15 (11%)	9 (50%)	27 (55%)	5 (23%)	16 (35%)	**.04**
Constipation	34 (25%)	19 (14%)	12 (67%)	22 (45%)	6 (27%)	13 (28%)	**.02**
Myalgia	40 (30%)	11 (10%)	11 (61%)	24 (49%)	4 (18%)	12 (26%)	**.005**
Diarrhea	34 (25%)	15 (11%)	3 (17%)	14 (27%)	15 (68%)	17 (37%)	**.004**
Nausea	31 (23%)	16 (12%)	12 (67%)	19 (39%)	8 (36%)	8 (17%)	**.002**
Peripheral neuropathy	31 (23%)	8 (6%)	9 (50%)	21 (43%)	5 (23%)	4 (9%)	**.0002**
Depression	30 (22%)	9 (7%)	7 (39%)	16 (33%)	6 (27%)	10 (22%)	.47
Dyspnea	15 (11%)	7 (6%)	3 (17%)	10 (20%)	3 (14%)	6 (13%)	.80
Vomiting	6 (4%)	6 (4%)	2 (11%)	4 (8%)	4 (18%)	2 (4%)	.25

*Two patients anti-HER2 therapy; **four patients anti-HER2 therapy

545 Poster Session (Board #37), Sat, 8:00 AM-11:30 AM

Impact of high deductible insurance on out-of-pocket cost burden in breast cancer. *First Author: Christine Lu, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*

Background: High-deductible health plans (HDHP) requiring out-of-pocket (OOP) costs for most services may place heavy economic burden on patients. This study examined the impact of modern HDHPs on OOP costs among women with early-stage breast cancer. **Methods:** We included 886 women with incident early-stage breast cancer, age 25 to 64 years, who were insured by employers that mandated a transition from low-deductible (< = $500/year) to high deductible (> = $1000/year) coverage, and 3099 exact matched contemporaneous patients whose employers offered only low-deductible plans. Measures were pharmacy and medical OOP costs per person-year. Medical services were categorized as inpatient, emergency room (ER), primary care visits, and outpatient care which included specialist visits, radiology, lab tests, and chemotherapy. We calculated OOP costs as the sum of deductibles, copays, and coinsurance. Effect estimates of changes between study groups were established using difference-in-differences analyses. **Results:** HDHP members faced an absolute baseline-to-follow-up increase in total OOP costs of $1067 per person-year compared to controls ($p = < 0.001$). The absolute change in medical OOP costs per person-year among HDHP members compared to controls from baseline to follow-up was significant ($1004, 95% CI: [$580, $1429]) and the relative change was also significant (41.2%, 95% CI: [17.8%, 64.5%]). The increase in medical OOP costs was driven by increases in outpatient care OOP costs. The absolute change in outpatient care OOP costs per person-year among HDHP members compared to controls from baseline to follow-up was $919 (95% CI: [$506, $1332]; relative change: 43.7%, 95% CI: [17.0%, 70.5%]). Changes in OOP costs for pharmacy, inpatient, ER, and primary care visits were not significant. **Conclusions:** In this rigorous, natural experimental study, women with incident breast cancer experienced increases in total OOP costs after employer-mandated HDHP switches, a change driven by a 44% increase in outpatient care OOP costs. Further research should examine which outpatient services contributed to this substantial economic burden, when the differences occur and the proportion of women reaching their annual deductible.

546 Poster Session (Board #38), Sat, 8:00 AM-11:30 AM

Patient(Pt)-reported toxicities during breast cancer (BC) chemotherapy (CRx): Associations with pre-treatment (Tx) measures of quality of life (QOL) and Tx discontinuation. *First Author: Kirsten A. Nyrop, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: CRx completion is essential to Tx effectiveness and may depend on pt-reported toxicities rated "moderate, severe or very severe" (MSVS) that mirror physician-assessed CTCAE grades 2-4. Methods: We prospectively collected pt-reported MSVS in pts with stage I-III BC at each cycle of conventional (neo) adjuvant CRx. Pts also completed a pre-Tx measure of QOL (Functional Assessment of Cancer Therapy-General). Results: 158 pts were mean age 54, 28% non-white, 37% ≤high school (HS), 56% married. 44% received anthracycline-based CRx. Pt-rated maximum toxicity level was 12% mild, 37% moderate, 33% severe, and 18% very severe. Mean number of toxicities rated MSVS was 4.5 (range 0-12), with 51% rating ≥4 toxicities as MSVS. In multivariable analysis (R^2= 45%), un-married ($p = .04$), ≤HS ($p = .03$), lower pre-Tx QOL ($p < .0001$), and anthracycline-based CRx ($p = .001$) were associated with increased number of MSVS toxicities. 28 pts (18%) discontinued CRx. Mean number of MSVS toxicities was 5.5 (range 1-7) in pts who discontinued CRx compared to 4.3 (range 0-11) in pts who completed CRx ($p = .08$). Mean number of severe/very severe toxicities was 2.0 (range 1-7) in pts who discontinued CRx compared to 1.3 (range 0-9) in pts who completed CRx ($p = .01$). Conclusions: Pt characteristics and pre-Tx QOL are associated with pt reports of Tx toxicities. Cumulative number of higher severity toxicities is associated with CRx discontinuation. Patients whose chemotherapy treatment was discontinued, by patient-reported symptom severity Clinical trial information: NCT02328313.

Symptom	None/Mild	Moderate/Severe/ Very Severe	p value (2-sided)
Fatigue	5/54 (9%)	23/104 (22%)	***.05***
Insomnia	12/69 (17%)	16/89 (18%)	.92
Anxiety	15/88 (17%)	13/70 (19%)	.80
Arthralgia	16/93 (17%)	12/65 (18%)	.84
Constipation	14/99 (14%)	14/59 (24%)	.13
Myalgia	16/98 (16%)	12/60 (20%)	.56
Diarrhea	17/94 (18%)	11/64 (17%)	.89
Nausea	14/102 (14%)	14/56 (25%)	.08
Peripheral neuropathy	17/107 (16%)	11/51 (22%)	.38
Depression	19/112 (17%)	9/46 (20%)	.70
Dyspnea	17/127 (13%)	11/31 (35%)	***.004***
Vomiting	21/142 (15%)	7/16 (44%)	***.004***

547 Poster Session (Board #39), Sat, 8:00 AM-11:30 AM

Treatment and outcomes in older women with DCIS: SEER-Medicare 2007-2013. *First Author: Mary Chen Schroeder, University of Iowa, Iowa City, IA*

Background: Ductal carcinoma in situ (DCIS) is a low-risk precursor lesion for which hormonal therapy (HT) has been shown in clinical trials to lower risk of subsequent (subs) breast cancer (bc) but not improve overall survival (OS). We report population-based uptake of HT and outcomes by type of local therapy. **Methods:** SEER-Medicare data identified women (wm) with no comorbidity, ages 66+ and diagnosed 2007-2013 with DCIS as first cancer. Wm were required to have Medicare Parts A, B & D at diagnosis. Treatments were identified with Medicare claims (2007-2014): surgery within 6 months and HT within one year of diagnosis. Outcome and survival analyses included 2007-2009 diagnoses, for adequate follow up. Subs breast events were identified: any bc and ipsilateral invasive bc (ips ibc). Local therapy included NONE, lumpectomy (BCS), BCS with radiation (w/XRT), and mastectomy (MAST). **Results:** 4,098 wm with DCIS were studied. 40.7% of wm received HT: 26.7% Tamoxifen, 14.0% an aromatase inhibitor. HT use varied by local therapy [BCS (32.8%), BCS w/XRT (52.0%), MAST (28.0%), NONE (19.6%), $p < 0.01$] but not race [white (40.4%), black (46.3%), other (38.7%), $p = 0.13$]. More wm ages 66-74 received HT than wm aged 75+ (45.9% v 32.7%, $p < 0.01$). Outcomes for the full cohort are shown (Table). For wm ages 66-74 outcomes did not differ between those having NONE v any local therapy [5yr OS (95.7% v 96.9%, $p = 0.71$), subs bc (0% v 4.2%, $p = 0.31$), subs ips ibc (0% v 1.0%, $p = 0.64$)]. On multivariate Cox model of wm 66-74, HT was associated with better OS (HR = 0.60, CI: 0.40-0.9992, $p = 0.0497$) but not marital status or age (66-69 v 70-74, HR = 1.56, $p = 0.10$); blacks had worse OS than whites (HR = 2.45, $p = 0.01$). **Conclusions:** In this large population-based cohort of older wm with DCIS, about half received HT. Wm who received HT had fewer subs bc and superior survival. OS for wm who elected NONE was inferior to those undergoing local therapy, though this was not significant for wm ages 66-74. These findings suggest opportunities remain to improve outcomes for wm with DCIS.

	NONE (N = 44)		BCS (N = 408)		BCS w/XRT (N = 834)		MAST (N = 393)		
	No HT	HT	No HT	HT	No HT	HT	No HT	HT	p*
Subs bc (%)	2.9	0	11.2	5.3	3.8	2.4	7.6	0.9	< 0.01
Subs ips ibc (%)	2.9	0	6.1	3.1	0.7	0.2	0.4	0	0.02
5yr OS (%)	80.0	66.7	89.2	92.4	94.7	95.9	90.2	92.3	0.03

* No HT v HT

548 Poster Session (Board #40), Sat, 8:00 AM-11:30 AM

Urgent hypertension as a biomarker for bevacizumab in the curative setting. *First Author: Nawal Kassem, Indiana University School of Medicine, Indianapolis, IN*

Background: Bevacizumab is FDA approved across many tumors including lung, colon, and glioblastoma. It is unclear which patients are destined to respond and/or experience the most toxicity. We previously demonstrated that bevacizumab-induced hypertension (HTN) in the metastatic breast cancer setting (E2100) was correlated with an improved overall survival (OS). In this study we evaluated the impact of bevacizumab-induced urgent HTN on outcome in the curative setting in E5103 and BEATRICE. We further evaluated for germline biomarkers to predict patients destined to experience HTN using whole exome sequencing (WES). **Methods:** Cases were defined as those who experienced urgent HTN (systolic blood pressure (SBP) $>$ 180 mmHg) and controls included those with SBP $<$ 160 mmHg. Log rank test was used to compare DFS and OS between cases and controls. WES was performed using germline DNA from patients in E5103 and BEATRICE. Exomes were enriched via Ion AmpliSeq Exome RDY kits. Templates were prepared on Ion Chef Systems and sequenced on Ion Proton Sequencers. Rare variants with a minor allele frequency $<$ 3% and those which were predicted to be deleterious by standard protein prediction programs were retained. A gene-based, case-control analysis using SKAT was performed to generate level of significance. **Results:** There were 93 cases of urgent HTN and 3000 matched controls. Patients with urgent HTN had a markedly superior DFS (p-value = 0.01) and superior OS (p-value = 0.02). There was no effect seen in the control arm. We also identified rare variants in SLC7A7 as predictors of urgent hypertension. **Conclusions:** Urgent HTN is associated with improved outcomes in the curative setting. We have also identified rare variants associated with severe HTN through WES. Exploring the biology of those who experience bevacizumab-induced HTN may help explain the heterogeneity of outcomes and elucidate secondary drug targets.

549 Poster Session (Board #41), Sat, 8:00 AM-11:30 AM

Timing of initiation of neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ hormone receptor (HR)-negative breast cancer: Exploratory analyses from the phase III ExteNET trial. *First Author: Bent Ejlertsen, Department of Oncology, Rigshospitalet, Copenhagen, Denmark*

Background: ExteNET, an international, randomized, placebo-controlled phase III trial, showed that neratinib given for 1 year after trastuzumab-based adjuvant therapy significantly improved 2- (HR 0.67, p = 0.009) and 5-year (HR 0.73, p = 0.008) invasive disease-free survival (iDFS) in early-stage HER2+ breast cancer [Chan et al. 2016; Martin et al. 2017]. Pre-specified subgroup analyses showed greater benefit with neratinib in HR+ than HR tumors, and in patients who initiated neratinib ≤12 months of completing trastuzumab. To better understand the effects of neratinib in patients with HR disease, we examined the impact on efficacy of the interval from prior trastuzumab to start of neratinib in the HR subpopulation. **Methods:** Patients with early-stage HER2+ breast cancer received oral neratinib 240 mg/day or placebo for 1 year after standard trastuzumab-based (neo)adjuvant therapy. iDFS, the primary study endpoint, was examined in subgroups categorized according to the interval between completing trastuzumab and randomization (i.e. 06, 612 and $>$ 12 months). Data cut-off: March 1, 2017. Clinicaltrials.gov: NCT00878709. **Results:** The ITT population comprised 2840 patients; 1209 (43%) had HR disease (neratinib, n = 604; placebo, n = 605). Results after a median of 5.2 years in the HR subgroup are shown below. **Conclusions:** Patients with HER2+ HR tumors tend to recur early. The risk of recurrence is higher in patients who have recently completed trastuzumab-based therapy (reflected in the iDFS rates of the placebo group). Consistent with these observations, our analyses suggest that the benefits of neratinib in HR disease are greater when treatment is started closer to completion of trastuzumab (i.e. ≤6 months). Clinical trial information: NCT00878709.

Interval between prior trastuzumab and randomization, months	n	5-year iDFS rate, %		Hazard ratio (95% CI)[a]
		Neratinib	Placebo	
06	695	88.9	86.1	0.73 (0.471.14)
612	268	86.1	91.7	1.61 (0.733.70)
> 12	246	91.3	93.7	1.39 (0.523.90)
Overall	1209	88.8	88.9	0.95 (0.661.35)

[a]Neratinib vs placebo

550 Poster Session (Board #42), Sat, 8:00 AM-11:30 AM

Adjuvant tamoxifen adherence in men with early stage breast cancer. *First Author: Oluchi Oke, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Most male breast cancers (MBC) are hormone-receptor positive, part of the standard treatment of these patients includes adjuvant tamoxifen. Prior small, single-institution studies have suggested that men may have high rates of discontinuing adjuvant endocrine treatment. We examined rates of tamoxifen discontinuation and medication adherence in a large population-based cohort of MBC patients. **Methods:** In the SEER-Medicare database male patients with non-metastatic MBC, diagnosed between 2007-2013, age 65 and older, with Part D coverage, and with tamoxifen prescriptions within one year of diagnosis were identified. The cumulative incidence of drug discontinuation was calculated for each year after diagnosis. Adherence was defined as a medication possession ratio (MPR) of $>$ -80% among those patients who were filling tamoxifen prescriptions. A logistic regression model was used to assess predictors of tamoxifen adherence. **Results:** We identified 451 patients who met eligibility criteria. Median age at diagnosis was 75 years. Median follow-up was 32.5months. 34% of patients had Stage I breast cancer, 48% Stage II, and 18% Stage III. Among those with known hormone receptor status, 99% had hormone receptor positive cancer. Rates of tamoxifen discontinuation were 19.8%, 30.7%, 39.6%, 46.8% and 61.4% at 1, 2, 3, 4, and 5 years after diagnosis, respectively. Among the men who were still taking tamoxifen, the corresponding adherence rates were 77.4%, 75.2%, 71.4%, 67.9%, and 63.5%. In the adjusted model, significant predictors of lower adherence included residing in a high poverty area (OR 0.26, 95% CI 0.08-0.86) and Charlson comorbidity score of ≥2 (OR 0.46, CI 0.21-1.00). **Conclusions:** Older men with breast cancer have high rates of tamoxifen discontinuation, with 61% of patients discontinuing tamoxifen before the end of year 5. In addition, even among those patients continuing tamoxifen, a substantial number of patients are non-adherent. Further research should evaluate potentially modifiable reasons for treatment discontinuation and lack of adherence to tamoxifen.

551 Poster Session (Board #43), Sat, 8:00 AM-11:30 AM

Predicting Oncotype DX scores using clinicopathologic features: A report from the National Cancer Database. *First Author: Catherine Pesce, Department of Surgery, NorthShore University Health System, Evanston, IL*

Background: The Oncotype DX recurrence score is used to predict the benefits of chemotherapy added to adjuvant hormone therapy in ER positive early-stage breast cancer. While its use has been validated and cost effectiveness has been established, its expense remains a concern in some health care systems and communities. Using clinical and pathologic features and the National Cancer Data Base (NCDB) we aim to predict patients with low or high Oncotype DX scores. **Methods:** From 2010-2014, 78,663 breast cancer patients with Oncotype DX scores were selected from the NCDB. Seven clinical and pathologic variables including age, ER, PR, histologic subtype, lymphovascular invasion (LVI), grade, and tumor size were used to predict high-risk ($>$30) or low-risk ($<$18) Oncotype DX scores using logistic regression. Data were split into training (70%) and testing (30%) sets for external validation. The predictive accuracy of the regression model was assessed using a Receiver Operator Characteristic (ROC) analysis. Model fit was analyzed by plotting the predicted probabilities against the actual probabilities. Nomograms were created for visualization of the high-risk and low-risk models using bootstrap estimation method of the model coefficients. **Results:** Estrogen receptor status, progesterone receptor status, and grade were the strongest predictors of both low-risk and high-risk Oncotype DX scores, followed by age, histology, tumor size, and LVI, yielding AUC of 0.70 for the low-risk model and 0.86 for the high-risk model. **Conclusions:** We have developed a model that can predict high-risk Oncotype DX scores with very good reliability. Such a tool may be useful in health care systems with limited resources. Model Coefficients of Strongest Predictors of High-Risk Oncotype DX Score

Factors		Coefficients
ER	negative	2.977
PR	negative	2.095
Grade	well differentiated	0.000
	moderately differentiated	1.356
	poorly differentiated	3.374
Tumor size	$<$ 10mm	0.000
	10-20mm	0.264
	20-30mm	0.584
	30mm+	0.78

552 Poster Session (Board #44), Sat, 8:00 AM-11:30 AM

Estimation of historical control rate for a single arm de-escalation study: Application to the POSITIVE trial. *First Author: Zhuoxin Sun, IBCSG Statistical Center, Boston, MA*

Background: A randomized, controlled clinical trial is the optimal method to evaluate the effect of an experimental therapy. However a single arm trial can be used when randomization is infeasible or unethical. POSITIVE is a prospective, single arm, international study aimed at young (age 18-42) women with endocrine responsive (ER+) breast cancer (BC) who desire pregnancy. It will assess whether temporary interruption of adjuvant endocrine therapy (for up to 2 yrs) after 18-30 months of use is safe in terms of risk of recurrence. We describe methods to estimate a historical control rate for POSITIVE using data from the SOFT/TEXT Phase 3 trials. **Methods:** The primary endpoint of POSITIVE is breast cancer recurrence (BCR) at 3 yrs. In this analysis, we first identified a cohort of SOFT/TEXT pts meeting POSITIVE eligibility criteria. Method I uses the SOFT/TEXT cohort to calculate 3 yr annualized hazard rates by a piecewise exponential model and 3 yr BCR rate by Kaplan-Meier (KM) estimate. Method II uses the SOFT/TEXT cohort to group-match SOFT/TEXT pts to POSITIVE pts; sample sets of SOFT/TEXT pts were randomly drawn with replacement 5000 times to obtain sets having baseline characteristics well-balanced with POSITIVE pts. The mean 3 yr annualized hazard rates and 3 yr KM BCR rates, and their 2.5th and 97.5th percentiles, were estimates (95% CI) for the control group. **Results:** 149 POSITIVE pts were included; 1499 SOFT/TEXT pts met the eligibility criteria. POSITIVE pts were younger, had fewer positive nodes, and fewer received chemotherapy. Method II refines Method I to adjust for the imbalanced characteristics and provides more precise estimates of the annualized BCR hazard rates and 3 yr BCR rates (Table). Clinical trial information: NCT02308085. **Conclusions:** The methods used only baseline characteristics of the POSITIVE study and in addition to final analysis interpretation, have a potential role for trial monitoring. The methods should, and will, be applied using data from other sources (e.g. ABCSG-12, ASCO CancerLinQ) to assure a consistent, robust estimate of an historical control rate across different cohorts.

	Annualized BCR hazard rate	95% CI	3 yr BCR rate	95% CI
Method I	3.4%	2.8%, 4.0%	9.5%	7.9%, 11.1%
Method II	3.1%	2.6%, 3.7%	8.7%	7.2%, 10.3%

553 Poster Session (Board #45), Sat, 8:00 AM-11:30 AM

Evaluation of the OncoMasTR prognostic signature in postmenopausal women with primary ER-positive breast cancer. *First Author: Ivana Sestak, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom*

Background: The assessment of distant recurrence (DR) risk in patients with early estrogen receptor (ER) positive breast cancer receiving adjuvant endocrine therapy is essential in making decisions on additional treatment. OncoMasTR (OM) is a continuous risk prediction model that provides a quantitative assessment of the likelihood of DR in patients with ER-positive breast cancer. The aim of this study was to assess the prognostic performance of OM in predicting DR for postmenopausal patients treated with anastrozole or tamoxifen. **Methods:** OM incorporates three genes and was developed in an endocrine treated population. OMclinical incorporates clinical parameters into the molecular OM. OM was evaluated for 648 ER-positive, HER2-negative patients with 0 to 3 involved lymph nodes in the TransATAC cohort. DR was the primary endpoint. Cox regression models were used to assess the prognostic performance. OM was evaluated for the overall time period and secondarily for late DR (years 5-10), and in node-negative and node-positive patients separately. **Results:** OM and OMclinical were highly prognostic for the prediction of DR in years 0-10 among all patients ($LR\chi^2$= 25.43 and $LR\chi^2$= 48.73, respectively, $P < 0.001$). OM/OMclinical provided significant additional prognostic value beyond standard clinicopathological variables. In women with node-negative disease, OM identified 37.8% of women as low risk with a 10-year DR risk of 3.5% (1.6-7.7), which was significantly lower compared to those categorised as high risk (10-year DR risk: 16.4% (12.4-21.5); HR = 4.8 (2.0-11.2)). Similar risk stratification and 10-year DR risks were observed for OMclinical in women with node-negative disease (HR = 6.5 (2.6-16.3)). Little prognostic information was provided for node-positive patients. OM and OMclinical were also highly prognostic for the prediction of late DR ($LR\chi^2$= 12.84 and $LR\chi^2$= 25.61, respectively, $P < 0.001$). **Conclusions:** OM and OMclinical were highly prognostic for early and late DR in women with early-stage (particularly node-negative) ER-positive breast cancer receiving 5 years of endocrine therapy and merit further evaluation as risk stratifiers to identify women who can safely forego chemotherapy.

554 Poster Session (Board #46), Sat, 8:00 AM-11:30 AM

Balancing the risks versus benefits of trastuzumab: A call to action for oncologists, cardiologists, and cardio-oncologists. *First Author: Moira Katherine Rushton, University of Ottawa - Post Graduate Medical Education, Ottawa, ON, Canada*

Background: One year of adjuvant trastuzumab (T) is standard for early stage (I-III) HER2 + breast cancer (BC) patients (pts). Cardiac imaging is recommended every 3 months during treatment to monitor for cardiotoxicity (CTx) without evidence this practice improves pt care. Up to 30% of pts will experience transient, asymptomatic, drops in left ventricular ejection fraction (LVEF) on T, which may lead to early termination of T. Our objective was to evaluate the impact of routine CI on disease free (DFS) and overall survival (OS) in early stage HER2+ BC. **Methods:** Retrospective population-based cohort study of early stage BC pts treated with adjuvant T in Ontario, Canada, 2007–2016. Patient-level data was sourced through the Institute for Clinical Evaluative Sciences, which captures all patients in Ontario. The cohort was divided into three arms; A: 17-18 cycles T, no CTx; B: no CTx, ≤16 cycles T, stopped within 30 days of last cardiac imaging; C: developed CTx. CTx was defined as new diagnosis heart failure (HF), cardiomyopathy (CM) or pulmonary edema within 90 days of last cycle of T. Primary outcome: DFS; secondary outcomes: OS, cancer-specific, and cardiovascular mortality. Survival analysis was performed using Cox and subdistribution hazard models. **Results:** 4820 pts met inclusion criteria; 4018, 442 and 360 in arms A, B, and C respectively. Median cycles of T were 18, 13 and 14 in arm A, B and C. 5-year DFS was significantly worse in arms B (70.3%; 95% CI 63.5-74.7) and C (74.9%; 69.5-79.5) vs. 93.2% (92.3-94.0) arm A; HR for DFS were 2.96 (2.35-3.72) and 2.41 (1.87–3.12) respectively. 5-year OS was significantly worse in arms B (75.4%) and C (80.1%) vs. arm A (95.2%); HR for OS 3.99 (3.10–5.14) and 2.98 (2.24–3.95) respectively. All p-values were < 0.05. **Conclusions:** BC pts in Ontario who did not complete adjuvant T had significantly worse DFS and OS. A significant population stopped T shortly after cardiac imaging, without developing CTx, likely due to detection of asymptomatic drops in LVEF. These findings support the need to consider strategies to continue cancer therapy in pts with abnormal cardiac imaging, including concurrent optimization of cardiac function and cardiac risk factors.

555 Poster Session (Board #47), Sat, 8:00 AM-11:30 AM

Comparison of outcomes for AJCC 8th Anatomic and Prognostic staging in contemporary triple negative breast cancer (TNBC) multisite registry. *First Author: Rajvi H. Shah, University of Kansas Medical Center, Westwood, KS*

Background: Eighth edition of the AJCC TNM staging system incorporates biological prognostic factors along with the traditional anatomical factors and currently Prognostic (P) stage must be used for reporting of all cancer patients in the US. Comparison of patient distribution between P and Anatomic staging and outcomes associated with the P stages in a contemporary TNBC population are not known. **Methods:** 574 patients with stage I-III TNBC were enrolled in an IRB approved multisite prospective registry between 2011 and 2017. Patients were followed for recurrence and survival. AJCC 8th edition Anatomic (A) Stage and clinical Prognostic (P) stage groups were applied to all patients. Recurrence free survival (RFS) (STEEP criterion) was estimated according to the Kaplan-Meier method and compared among groups by log-rank test. **Results:** Median age was 53 years (23-85). 96% of patients received neo/adjuvant chemotherapy. 82% (468/574) of patients were upstaged on P compared to A staging. Significantly lower numbers of patients were categorized within P stage II (36%) compared to A stage II (51%) (p = 0.001). Conversely, higher number of patients were categorized within P stage III (29%) compared to A stage III (14%) (p = 0.0001), with largest relative increase in stage IIIC (3% to 13%). Table 1 provides 5 years RFS for all A and P stages. Compared to A stage IIIAB, P stage IIIAB was associated with better RFS (HR = 0.42 [0.21-0.86]; p = 0.013), whereas P and A stages IIIC had similar RFS. This suggests appropriate upstaging of TNBC patients to IIIC on P staging. **Conclusions:** 82% of TNBC patients are upstaged on P staging compared to A staging. Knowledge of outcomes associated with various P stages can guide prognostic counselling for TNBC patients who plan to undergo standard local and systemic treatment.

	Stage			5 year RFS (Est)	
N = 574	**Anatomic**	**Prognostic**	**P value**	**Anatomic**	**Prognostic**
Stage I	200 (35%)	199 (35%)	NS	86%	87%
IA	197 (34%)	3 (1%)	0.001	86%	100%
IB	3 (1%)	196 (34%)		67%	87%
Stage II	293 (51%)	207 (36%)	0.001	85%	86%
IIA	205 (35%)	80 (14%)	0.0001	87%	91%
IIB	88 (15%)	127 (22%)		80%	83%
Stage III	81 (14%)	168 (29%)	0.0001	57%	70%
IIIAB	66 (12%)	94 (16%)	0.0001	59%	83%
IIIC	15 (3%)	74 (13%)		55%	54%

556 Poster Session (Board #48), Sat, 8:00 AM-11:30 AM

Role of cardiac reserve as a tool to unmask cardiotoxicity following anthracycline therapy and whether exercise training can attenuate cardiotoxicity. *First Author: Steve Fraser, Deakin University, Burwood, Australia*

Background: Anthracycline-based chemotherapy (AC) is associated with an increased risk of cardiac damage and long-term heart failure. However, diagnosis of cardiac damage is infrequent, while long-term heart failure risk is substantial. Thus, we sought to evaluate whether exercise cardiac reserve may be a more sensitive marker of cardiac toxicity than standard measures of cardiac function and if exercise training maintained cardiac function and exercise capacity during AC. **Methods:** 28 BC patients undergoing AC were recruited into a non-randomised trial and allocated to exercise training (ET) (46.7±9.0 yrs, n = 14) or usual care (UC; 53.2±8.9 years, n = 14), respectively. Tests including echocardiography (left ventricular ejection fraction [LVEF] and global longitudinal strain [GLS]), cardiopulmonary exercise test (peak oxygen uptake, VO_2peak), and exercise cardiac magnetic resonance imaging (exCMR, cardiac reserve) were performed prior to and after completion of AC. The ET group completed a twice weekly supervised aerobic and resistance exercise program at a moderate-vigorous intensity. **Results:** There was a small statistically significant reduction resting in LVEF in both UC and ET, whereas GLS was unchanged (Table 1). VO_2peak fell by 15% in the UC, while ET significantly attenuated the decline in fitness (~4%). Cardiac reserve was reduced following AC (Visit×Exercise P= 0.05), which was not attenuated by exercise training (Visit×Exercise×Group P= 0.06). Exercise training had no effect on resting measures of LV function (Table 1). Clinical trial information: ACTRN12616001602415. **Conclusions:** AC treatment caused profound reductions in peak oxygen uptake and impaired cardiac reserve. Resting measures of cardiac function did not account for the large reduction in VO_2peak which was attenuated by exercise training.

Effect of AC and ET on resting measures of cardiac function, biomarkers and peak oxygen uptake.

	Usual Care		Exercise Training			
	Pre	Post	Pre	Post	Visit	Group × Visit
LVEF, %	62.8 ± 4.9	59.1 ± 4.1	64.1 ± 5.0	60.6 ± 5.4	0.003	0.95
GLS, %	-20.4 ± 2.1	19.5 ± 2.0	19.7 ± 2.0	19.6 ± 2.0	0.17	0.28
VO_2 peak, ml/kg/min	22.0 ±5.9	18.8 ± 5.9	27.4 ± 5.7	26.3 ± 5.3	< 0.001	0.024

557 Poster Session (Board #49), Sat, 8:00 AM-11:30 AM

CA15-3/MUC1 in CCTG MA-32 (NCT01101438): A phase III RCT of the effect of metformin vs. placebo on invasive disease free and overall survival in early stage breast cancer (BC). *First Author: Ryan JO Dowling, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The diabetes drug metformin may improve BC outcomes through enhanced obesity-related physiology or direct anti-tumor effects. We studied the effect of metformin on CA15-3 (the soluble moiety of the MUC1 protein), a marker associated with BC prognosis that also has mitogenic and metabolic effects that favor tumorigenesis. **Methods:** 3,256 women with T1-3, N0-3, M0 BC who had completed standard therapy (ongoing hormone therapy permitted) provided fasting blood (stored at -80C) at baseline and 6 months. CA15-3 and insulin were measured by Roche ECLIA; leptin, and hs-CRP by Luminex Milliplex MAP and Roche ITA. Spearman coefficients were calculated and comparisons analyzed using Wilcoxon signed rank test and multivariable linear regression models. Tests were two-sided. **Results:** Mean age was 52.3 and BMI 28.6 kg/m^2. Tumor and treatment characteristics were balanced between arms (overall: T2/3 in 59.8%, N +ve in 52.9%, grade 1/2/3 in 9.1%/35.3%/54.4%, ER+ in 69.6%, HER2+ in 17.1%; 50.4% underwent mastectomy, 74.0% received radiation, 89.2% chemotherapy, 17% trastuzumab, and 64.4% hormones). Baseline values and 6 month changes are shown below. In multi-variable analyses (including age, BMI, tumor characteristics, treatment), metformin (vs placebo) led to a greater relative reduction in CA15-3 (-5.81%; 95% CI: -3.94% to -7.64%, p < 0.0001). CA15-3 change at 6 months significantly correlated with change in BMI (r=0.10, p<0.0001), glucose (r=0.05, p=0.011) and hsCRP (r=0.05, p=0.022). **Conclusions:** Metformin significantly lowered CA15-3; change in CA15-3 was associated with improved obesity-associated physiology and BMI, consistent with hypothesized beneficial actions of metformin. Clinical trial information: NCT01101438.

	Baseline		6 Months		Change	
Variable	**Metformin**	**Placebo**	**Metformin**	**Placebo**	**Metformin**	**Placebo**
CA15-3 (U/ml)	17.8	18.0	16.5	18.9*	-1.2.	0.8*
BMI (kg/m^2)	28.8	28.5	28.1	28.7*	-0.58	0.21*
Insulin (pM)	83.4	81.0	74.1	85.5*	-7.4	5.3*
Glucose (mM)	5.2	5.2	5.1	5.2*	-0.09	0.06*
Leptin (ng/ml)	19.3	18.9	18.2	20.9*	-1.2	2.2*
hs-CRP (ug/ml)	3.1	2.7	3.4	3.3*	0.52	0.57*

Mean values. *significant difference between metformin and placebo, p < 0.05

559 Poster Session (Board #51), Sat, 8:00 AM-11:30 AM

Association of clinical/pathological parameters with axillary involvement in early breast cancer in patients with limited sentinel node involvement (< 3 LK) after neoadjuvant chemotherapy (NACT). *First Author: Hans-Christian Kolberg, Marienhospital Bottrop, Klinik für Gynäkologie und Geburtshilfe, Bottrop, Germany*

Background: The association between pathological complete remission (pCR) in the breast and clinical/pathological parameters is well established, whereas the association of clinical/pathological parameters and residual axillary involvement after NACT is still not sufficiently defined. We used data from the SENTINA trial to analyze this association in a patient population with limited sentinel lymph node (SLN) involvement. **Methods:** Patients were included if before NACT they presented with a clinically negative axilla but showed involvement of SLNs prior to NACT (Arm B). Analysis was restricted to patients with < 3 involved SLNs before NACT. All patients received SLNB and axillary dissection after NACT. Univariate and multivariate analyses were carried out to evaluate the association between clinical/pathological parameters and axillary involvement after NACT. **Results:** Arm B of the SENTINA study contained 360 patients, 265 of which were evaluable with respect to the above parameters. After NACT 66/265 (24.9%) patients had involved SLNs or non-SLNs after NACT; 71/265 (26.8%) achieved a pCR in the breast. We observed a significant association between pCR in the breast and ER negativity (p < 0.0001), PR negativity (p < 0.0001) and triple negative (TN) status (p = 0.001). However, no statistically significant association between residual axillary involvement after NACT and clinical/pathological parameters ER (p = 0.381), PR (p = 0.52), HER2 (p = 0.771), TN status (p = 0.937), grade (G) 1 (p = 0.081), G 2 (p = 0.335), G 3 (p = 0.747), age (p = 0.789), tumor size before NACT (p = 0.761) and pCR in the breast (p = 0.136) could be demonstrated. **Conclusions:** Our analysis demonstrates that patients enrolled in the SENTINA trial with clinically negative axilla but limited SLN involvement show positive axillary nodes in 24.9% of cases after NACT. We found no association between residual axillary involvement after NACT and clinical/pathological parameters. We could not identify a subset of patients in this cohort for whom axillary surgery after NACT could be safely omitted.

560 Poster Session (Board #52), Sat, 8:00 AM-11:30 AM

Hypofractionated whole breast IMRT and brachytherapy boost after conservative surgery for breast cancer: Early results of a prospective non-randomised trial. *First Author: Ines Guix, IMOR Foundation, Medical Institute for Radiotherapy and Oncology, Barcelona, Spain*

Background: To report the early results obtained in a prospective group of patients (pts) treated with whole breast IMRT radiotherapy plus brachy. boost to tumor bed after conservative surgery (CS), given either with hypofractionated or normofractionated radiotherapy. **Methods:** Between 10/2008 and 06/2016, 1,277 pts with < 4cm, N0-2 breast cancers treated with CS entered the study. Pts were offered to be treated either with IMRT hypofr. whole breast and lymph areas (if needed) radiotherapy 42.6 Gy (266cGyx16) plus a 7 Gy brachy. boost, (hypofractionated group) or IMRT normofr. 50 Gy (200cGyx25) to the whole breast and lymph areas (if needed) plus 16 Gy brachy. boost (200cGyx8) (normofractionated group). Treatment assignation was done according to the pts preference or, if none, were randomly assigned to have both groups uniformly balanced. Systemic therapy was given as needed. During treatment and follow-up special attention was taken to early and late side-effects, breast fibrosis, arm lymphedema, skin reaction, patient satisfaction and local, regional and distant disease control. **Results:** A total of 638 pts were included in the hypofractionated group and 639 in the normofractionated group. All pts completed treatment. Pts were evaluated in a weekly basis during treatment and every 3 months for the first 2 years of follow-up and in a yearly basis after. Photographs were taken at each visit. SOMA-LENT scales were used in every visit. For quality of life EORTC QLQ-C30 plus the BR-15 module were used. No patient had adverse side-effect that required treatment ending in any group. In the hypofract. group, there were 10 local recurrence, 11 distant metastases and 6 death due to the disease. In the normofract. group there were 12 local recurrences, 9 distant metastases and 7 patients died due to the disease. **Conclusions:** Hypofractionated IMRT to the whole breast followed by a 1 fraction HDR breast implant was a safe and effective method of treatment for early breast cancer treated with conservative surgery, even in those patients N+ in which the supraclavicular fossa was included in the treatment fields. Patient satisfaction was greater in the hypofractionated group.

561 Poster Session (Board #53), Sat, 8:00 AM-11:30 AM

Results from a pilot of an innovative 4R Cancer Care Delivery Model in early breast cancer: Impact on timing and sequencing of guideline recommended care. *First Author: Christine B. Weldon, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Under the "NCI ASCO Teams" Project, we proposed a 4R Model of teamwork and patient self-management (Trosman JOP '16). 4R = Right Info / Care / Patient / Time. It enables patient and care team to manage timing / sequencing of interdependent care with an innovative multimodality personalized 4R Care Project Plan. We piloted 4R at 3 centers (academic, community, safety net) and assessed impact on timing / sequencing of guideline based care. **Methods:** 4R Plans were administered to breast cancer patients stage 0-III Sept '17 – Aug '17. Clinical data for 185 patients who received 4R (4R cohort) were compared with a historical control cohort of comparable patients who received care pre-4R, Jun '16 – May '17. We used simple frequencies and Fisher's exact test in analyses. **Results:** We improved timing / sequencing of 7 guideline recommended metrics (Table). Significant improvements were shown for care lacking in the control cohort. 4R improved rate of patients receiving genetic test results and fertility in a timely manner. Neoadjuvant therapy rate doubled, but low sample size precluded statistical conclusions. However, timing / sequencing of care needed prior to neoadjuvant therapy (eg fertility, flu shot) were significantly improved. **Conclusions:** The 4R model significantly improved timing / sequencing of guideline recommended care in early breast cancer. An ongoing 4R pilot at 12 additional cancer centers across the U.S. is continuing to accrue patients and focusing on other guideline-recommended metrics.

Metric	Guideline	% 4R cohort N = 185	% Control cohort N = 162	P value
Patient Goal of Care discussion documented in medical record	NAM '13, NCCN PAL-4	98	2	.0001
Distress Screening w/in 30 days of diagnosis	ASCO '14, NCCN DIS-A	95	11	.0001
Dental referral before therapy	ADA '08	74	0	.0001
Complete dental work before therapy	ADA '08	49	NA	-
Referral to Primary Care before treatment	NCCN OAO-D	72	16	.0001
Referral to genetics	NCCN BR/OV-1	36	7	.0001
Genetic results prior to surgery	NCCN BR/OV-1	84	64	NS
Flu shot before therapy	NCCN INF-7	34	0	.0001
Fertility consult & services before treatment, < 50 years old	NCCN BINV-C	24	14	NS
Neoadjuvant Therapy	NCCN BINV-11	15	7	NS

NS = not significant

562 Poster Session (Board #54), Sat, 8:00 AM-11:30 AM

Prospective phase II multicenter trial of ablation after breast lumpectomy added to treat (ABLATE) breast cancer without radiation. *First Author: V. Suzanne Klimberg, University of Arkansas for Medical Sciences, Little Rock, AR*

Background: Background:A plethora of studies have failed to define a group of patients that can forgo radiation to complete BCS without a significant increase in recurrence rate. This has resulted in overtreatment with radiation of an estimated 85% of patients with favorable breast cancers. RFA added to standard BCS (eRFA) may not only reduce the need for re-excision for close or focally positive margins but may obviate the need for whole breast irradiation in favorable breast cancer patients. **Methods:** In an IRB-approved risk-adjusted protocol, 267 T0-2, No breast cancer patients from 7 different sites were screened for a Phase II multicenter protocol of BCS followed by cavitary RFA (eRFA) without adjuvant radiation and followed for margins, recurrence, breast pain, cosmesis and QOL. **Results:** 242 patients were accrued to the study with a median follow-up of 36 months. Re-excision for positive margins was $< 5\%$. The in breast recurrence rate was 2.5%. In this risk adjusted model XRT was added when SLNB was positive. 20% of cohort received XRT. Breast pain @ 6 months was 19% with RFA+XRT Versus 1.7% with RFA alone($p < 0.05$). Cosmesis was good or excellent in $> 90\%$ of patients. QOL did not change after eRFA. **Conclusions:** eRFA may be a new paradigm for treating favorable patients that desire lumpectomy who either cannot or do not want radiation. A majority of the patients avoided re-excision, WBI and/or mastectomy. Treatment in lieu of XRT is safe and effective and may increase definitive treatment compliance for patients as it is complete at the time of surgery. Clinical trial information: 01153035.

563 Poster Session (Board #55), Sat, 8:00 AM-11:30 AM

At surgery for a core needle biopsy diagnosis of ductal carcinoma in situ with microinvasion: Is sentinel lymph node biopsy required? *First Author: Meghan Rose Flanagan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Surgical excision upstages approximately 20% of patients with a core needle biopsy (CNB) diagnosis of ductal carcinoma in situ (DCIS) to invasive cancer, a rate insufficient to recommend *routine* sentinel lymph node biopsy (SLNB) at the initial procedure. The rate of upstaging for patients with a CNB diagnosis of DCIS with suspected or definite microinvasion (DCISM) is unknown, as is the role of SLNB. **Methods:** We identified consecutive patients with a CNB diagnosis of DCISM, suspected or definite, who underwent surgical excision between 2007 and 2017. The extent of DCISM was stratified as suspicious focus (n = 106), single focus (n = 187), multiple foci in a single biopsy (n = 69) or multiple foci in multiple biopsies (n = 24) (Table). SLNB was performed in 77%, 94%, 96% and 100%, respectively. CNB strata were correlated with imaging characteristics and final pathology in the breast and SLN. **Results:** Across CNB strata there were no clear differences in imaging characteristics. Although there was a trend toward higher final T and N stage with increasing extent of DCISM, the median extent of invasive cancer on final pathology was 0.2 cm for all strata. Among patients with CNB suspicious for DCISM, 28% were upstaged to T1a or greater but the SLNB was positive in only 1 patient (1%). In the definite DCISM strata, 37-46% were upstaged to T1a or greater, and 1-12% were at least pN1. **Conclusions:** In patients with suspicion of DCISM on CNB, 28% were upstaged to invasive cancer but the frequency of SLN metastasis is low, suggesting that SLNB may be deferred to final pathology in this setting. For patients with definite DCISM on CNB, the frequency of clinically significant lymph node metastasis supports SLNB at initial surgery.

	Focus suspicious (N = 106) N (%)	Single focus (N = 187) N (%)	Multiple foci (N = 69) N (%)	Multiple biopsies (N = 24) N (%)	P value
Final pathology					0.01
No cancer	2 (1.9)	5 (2.7)	0 (0.0)	0 (0.0)	
In situ only	53 (50.0)	60 (32.1)	12 (22.9)	5 (20.8)	
Microinvasive	21 (19.8)	53 (28.3)	22 (31.4)	9 (37.5)	
Invasive	30 (28.3)	69 (36.9)	32 (45.7)	10 (41.7)	
pN[a]					0.02
N0	81 (98.8)	161 (92.5)	62 (93.9)	20 (83.4)	
N1	1 (1.2)	12 (6.9)	3 (4.6)	3 (12.5)	
N2 or N3	0 (0.0)	1 (0.6)	1 (1.5)	1 (4.2)	

[a]Total is among 351 women with SLNB

565 Poster Session (Board #57), Sat, 8:00 AM-11:30 AM

Comparison of breast conservative therapy to mastectomy in male breast cancer: A NCDB analysis. *First Author: Sarah Bateni, University of California Davis Medical Center, Sacramento, CA*

Background: Current treatment guidelines for male breast cancer (MBC) are largely based on clinical trials limited to female participants. With limited MBC research, it remains unclear if breast conservative therapy (BCT) is equivalent to mastectomy in MBC. Therefore, the purpose of this study was to compare survival among MBC patients for BCT vs. mastectomy using a large national database. **Methods:** We performed a retrospective analysis of 11,406 MBC patients with stage I-III disease from the National Cancer Database (NCDB) years 2004-2015, excluding Paget's, T4/inflammatory, and multicentric disease. Patients were grouped according to surgical and radiation therapy (i.e. BCT, lumpectomy alone, mastectomy alone, and mastectomy with radiation). After performing standard parametric and nonparametric univariate analyses, cox proportional hazards multivariate regression analysis was performed to compare overall survival by treatment group controlling for demographic and clinicopathologic group differences. **Results:** The majority of MBC patients underwent mastectomy alone (n = 6,326, 55%), with the remaining 19% (n = 2,162) undergoing mastectomy with radiation, 18% (n = 2,085) undergoing BCT, and 7% (n = 833) undergoing lumpectomy alone. Compared with mastectomy alone and mastectomy with radiotherapy, BCT was associated with younger age (62 vs. 66 vs. 63 years old, $p < 0.01$), smaller tumors (median 1.5 cm IQR 0.9-2.0 vs. 2.0 cm IQR 1.4-2.6 vs. 2.5 cm IQR 1.8-3.5, $p < 0.001$), and lower nodal disease rates (21% vs. 31% vs. 81%, $p < 0.001$). In the multivariate model, BCT was associated with greater survival compared to mastectomy alone (HR 1.69, 95%CI 1.44-1.98, $p < 0.001$), mastectomy with radiation (HR 1.52, 95%CI 1.27-1.83, $p < 0.001$), and lumpectomy alone (HR 1.91, 1.56-2.33, $p < 0.001$). Increased age, T stage, N stage, histological grade, and triple negative hormone receptor/HER2 status were associated with poorer survival ($p < 0.05$). **Conclusions:** Although mastectomy is more common among MBC, BCT is associated with greater survival. These findings support the use of BCT as a viable treatment approach in MBC and consideration of greater adoption among surgeons and oncologists.

566 Poster Session (Board #58), Sat, 8:00 AM-11:30 AM

Prediction of pathologic complete response by image-guided biopsy before surgery in breast cancer with complete clinical response to neoadjuvant chemotherapy: A prospective feasibility trial. *First Author: Han-Byoel Lee, Department of Surgery, Seoul National University College of Medicine, Seoul, Korea, Republic of (South)*

Background: Patients who attain a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) have a favorable long-term outcome. In patients with pCR, it is suggested that the role of surgical excision may be limited to pathological confirmation, and thus may be omitted when pCR can be correctly predicted. The purpose of this study was to evaluate how accurately pCR can be predicted using MRI and image-guided biopsy. **Methods:** We prospectively enrolled 40 patients (mean age 47.1) between September 2016 and January 2018 who were suggested to have pCR on preoperative MRI. Lesion size ≤0.5cm or lesion-to-background parenchymal signal enhancement (SER) ratio ≤1.6 on MRI was defined as complete clinical response. Multiple core needle biopsy(CNB) (14G) or vacuum-assisted biopsy(VAB) (10G) was alternatively performed for the tumor bed around a clip marker placed during the course of NAC. Standard surgical excision was performed after biopsy. Matched biopsy and surgical specimens were compared for pCR assessment. **Results:** Pathologic complete response was confirmed in 27 (67.5%) surgical specimens, including 14/19 (73.7%) of HR-/HER2- and 6/8 (75%) of HR-/HER2+ patients. Preoperative biopsy had an accuracy of 90% (95% CI: 76-97%), negative predictive value of 87.1% (95% CI: 75-94%), and a false-negative rate of 30.8% (95% CI: 14-70%). Among four patients whose biopsy was not accurate in predicting pCR, two tumors were predicted to be > 0.5cm on MRI and two had less than five cores biopsied. Obtaining at least five cores in patients with ≤0.5cm lesion on MRI resulted in an accuracy of 97.1% (33/34), negative predictive value of 96.2% (25/26), and a false negative rate of 10%. There was no difference in accuracy in between multiple CNB and VAB. Breast pCR did not correlate with nodal status in 11.1% (3/27). **Conclusions:** Image-guided CNB or VAB can accurately identify patients with breast pCR in selected patients using preoperative MRI findings. This information will be used in a prospective clinical trial evaluating clinical safety of omitting breast surgery in patients with a breast pCR as determined by image-guided biopsy. Clinical trial information: NCT03273426.

567 Poster Session (Board #59), Sat, 8:00 AM-11:30 AM

Post neoadjuvant chemotherapy vacuum assisted biopsy in breast cancer: Can it determine pathologic complete response before surgery? *First Author: Marios Konstantinos Tasoulis, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: Neoadjuvant chemotherapy (NAC) is increasingly used in phenotype appropriate early operable breast cancer. Pathologic complete response (pCR) rates of up to 60% have been reported, suggesting that a proportion of patients may require less or even no surgery. In our practice, image-guided vacuum assisted biopsy (VAB) has been used after completion of NAC to assess residual disease and facilitate risk-adaptive surgery. The aim of this analysis was to investigate if post-NAC VAB could reliably identify exceptional responders who may not require surgical intervention. **Methods:** Retrospective cohort study of breast cancer patients treated with NAC, who had partial/complete imaging response and underwent post-NAC VAB to aid surgical planning, between 01/2013 and 01/2018. pCR was defined as no residual disease in the breast (ypT0). Diagnostic accuracy of VAB was calculated using final surgical pathology as the reference standard. Simple descriptive statistics and nonparametric analyses were performed. **Results:** 53 patients underwent post-NAC VAB. The overall pCR rate was 41.5% [53.8% for HER2 positive, 72.7% for triple negative (TN) phenotypes]. The post-NAC VAB false negative rate (FNR) was 19.4% (95% CI: 5.5-34.5) and the negative predictive value (NPV) was 76.9% (95% CI: 60.7-93.1) with an overall accuracy of 84.9% (95% CI: 75.3-94.5). Subgroup analysis showed that post-NAC VAB performed best in the TN group (n = 11) [FNR: 0%, NPV: 100%, overall accuracy: 90.9% (95% CI: 73.9-100)]. No significant associations were identified between tumor and technique characteristics and diagnostic performance of VAB. **Conclusions:** Our data suggest that post-NAC VAB may reliably predict pCR in patients with TN breast cancer. However, its diagnostic accuracy was not maintained across all phenotypes. Refinements and standardization in patient selection and VAB technique and more prospective trials are warranted to further explore the role of post-NAC VAB in supporting minimal or no surgery trials.

568 Poster Session (Board #60), Sat, 8:00 AM-11:30 AM

Neo-/adjuvant phase III trial to compare intense dose-dense (idd) treatment with EnPC to tailored dose-dense (dt) therapy with dtEC-dtD for patients with high-risk early breast cancer: Results on pathological complete response (pCR) for patients treated within the neoadjuvant setting. *First Author: Volker Moebus, Department of Gynecology and Obstetrics, Klinikum Frankfurt Höchst, Academic Hospital of the Goethe University Frankfurt, Frankfurt, Germany*

Background: GAIN-2 compares the effectiveness and safety of a predefined idd regimen (EnPC) vs. a dd regimen with modification of single doses depending on individual hematological and non-hematological toxicities (dtEC-dtD) as neo-/adjuvant treatment for patients with high risk breast cancer (BC) (NCT01690702). **Methods:** Patients with high risk BC (HER2+; triple negative BC (TNBC); luminal B-like: ER and/or PgR+, HER2-, Ki67 > 20%, N+; luminal A-like: ≥4 N+) were randomized to receive either iddEnPC (epirubicin 150mg/m^2 q2w, nab-Paclitaxel 330mg/m^2 q2w, cyclophosphamide 2000mg/m^2 q2w for 3 cycles each) or dtEC-dtD (epirubicin 60-100mg/m^2 and cyclophosphamide 450-1200mg/m^2 q2w for 4 cycles followed by docetaxel 60-100mg/m^2 q2w for 4 cycles). The primary objective of the trial is to compare the invasive disease-free survival (iDFS) between the two arms. pCR rates in the breast per arm (ypT0) in the neoadjuvant cohort will be reported. **Results:** In total the GAIN-2 trial accrued 2887 patients. From 08/2016 to 07/2017 598 patients have been randomized in the neoadjuvant setting (EnPC n = 298; dtEC-dtD n = 300). Median age was 49 [range 20-69] years. Overall, 2.3% had bilateral tumors, 38.0% cT1, 52.7% cT2 and 9.3% cT3/4, 55.4% cN+; 62.9% G3; 88.0% had Ki67 > 20%; 17.6% had hormone-receptor (HR)-positive/HER2-, 1.7% luminal A ≥4 N+, 31.9% HR+/ HER2+, 13.7% HR-/HER2+ and 35.1% TNBC. In the modified intention-to-treat population (EnPC n = 291; dtEC-dtD n = 293) the pCR rates for iddEnPC vs dtEC-dtD were 53.6% vs 45.1% (corrected continuity Chi-Square p = 0.047). Overall, 34.8% of the patients had at least 1 severe adverse event (EnPC 38.3% vs dtEC-dtD 31.3%). **Conclusion:** The GAIN-2 trials shows a statistically significant difference in terms of pCR rates within the breast for patients with high-risk BC receiving iddEnPC compared to dtEC-dtD as neoadjuvant chemotherapy. Further analyses are ongoing. Clinical trial information: NCT01690702.

569 Poster Session (Board #61), Sat, 8:00 AM-11:30 AM

Investigating denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules: 2x2 factorial design (GeparX)—An iterim safety analysis. *First Author: Sherko Kummel, Kliniken Essen Mitte, Essen, Germany*

Background: The GeparX study aims to investigate whether denosumab, an antibody targeting RANKL, increases the pCR rate when added to an anthracycline/taxane containing neoadjuvant chemotherapy (NACT) in patients (pts) with primary breast cancer (BC). **Methods:** GeparX enrolles pts with primary BC cT1c-cT4d, after central assessment of HER2, HR, TILs, Ki67. 778 pts will be randomized to NACT+/-denosumab (120mg s.c. q4w for 6 cycles), stratified by lymphocyte predominant BC (LPBC, ≤50% vs > 50%), subtype (HER2-/HR+ vs triple negative (TNBC) vs HER2+), and epirubicin/cyclophosphamide schedule (EC, q2w vs q3w). Secondarily, pts are randomized to different nab-paclitaxel schedules (nP): nP 125mg/m² weekly or nP 125mg/m² day 1,8 q22 followed by EC. Pts with TNBC receive carboplatin (AUC 2) and with HER2+ BC ABP 980 (trastuzumab biosimilar)+ pertuzumab. Co-primary objectives compare the pCR (ypT0 ypN0) rates of NACT+/-denosumab and the pCR rates between nP 125 weekly and nP 125 d1,8 q22. Secondary objectives are toxicity; compliance amongst others. An interim safety analysis is planned after the first 200 pts have completed nP treatment. **Results:** A total of 202 pts randomized to denosumab and the nP treatment (101 pts with weekly and 101 pts with nP d1,8 q22) were included in the interim analysis. Overall, median age was 50 years [range 23-76]; 38.6% of pts were cN+ and 5% had LPBC, 102 pts (50.5%) had HER2-/HR+ BC; 82 (40.6%) had TNBC and 18 pts (8.9%) HER2+ BC. Overall, 13.5% with and 13.1% w/o denosumab discontinued nP. 21.0 % of pts with nP weekly vs 5.3% with nP d1,8 q22 discontinued nP mainly due to AEs (17.0% vs 3.2%). During nP treatment 24 SAEs with nP weekly vs 25 SAEs with nP d1,8 q22 were reported. 17 (16.7%) SAEs were reported in the HER2-/HR+ cohort, 29 (35.4%) for the TNBC (with carboplatin) and 3 (16.7%) in the HER2+ cohort (dual-blockade, no carboplatin). **Conclusions:** The addition of denosumab to NACT does not increase toxicity. Weekly nP resulted in a higher rate of treatment discontinuations mainly due to non-serious AEs. The addition of carboplatin resulted in a higher rate of SAEs. Clinical trial information: NCT02682693.

570 Poster Session (Board #62), Sat, 8:00 AM-11:30 AM

A RB-1 loss of function gene-signature (RBsig) as a tool to predict response to neoadjuvant chemotherapy (CT) plus anti-HER2 agents (H): A substudy of the NeoALTTO trial (BIG 1-06). *First Author: Emanuela Risi, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Prato, Italy*

Background: CT added to H is the treatment of choice in HER2+ early breast cancer (BC) patients (pts). However HER2+ tumors are clinically and biologically heterogeneous and treatment response varies significantly by hormone receptor (HR) status and molecular subtype. Predictive biomarkers are needed in this context. We have previously shown that RBsig expression correlates with pathological complete response (pCR) rate following CT +/− H in ER+/HER2+ BC pts within a metadataset of 10 neoadjuvant clinical trials. The present study assessed whether RBsig is predictive of response to neoadjuvant CT in combination with H, within the NeoALTTO trial. **Methods:** We collected RNA-sequencing data from pre-treatment biopsies derived from NeoALTTO, a trial randomizing pts with HER2+ early BC to receive lapatinib, trastuzumab or both together with weekly paclitaxel. RBsig expression was computed retrospectively and correlated with pCR using receiving-operating characteristic (ROC) curves.The RBsig was dichotomized as High/Low in correspondence to the 25th percentile. The distribution of RBsig expression was evaluated within PAM50 molecular subtypes. Reported p-values resulted from Fisher exact test. **Results:** Of 455 NeoALTTO pts, 245 had available RNA-sequencing data (HR+ n = 129 HR− n = 116). Overall, pCR rate was significantly higher in pts with RBsig High tumors, than those with RBsig Low (36% vs 18% respectively p = 0.01). The area under the ROC curve (AUC) was 0.60 (95% CI 0.52-0.67). A remarkably low pCR rate of 11% was seen in HR+/ RBsig Low pts vs 28% in HR+/RBsig High. HER2-enriched (HER2e) tumors were the predominant molecular subtype in both HR+ (n = 65) and HR− (n = 89) subsets. RBsig could further stratify HER2e tumors, with RBsig High and Low showing a pCR rate of 44% and 21% respectively (p = 0.02).The pCR rate of HR+/ HER2e/ RBsig High pts was 37% vs 7% for HR+/ HER2e/ RBsig Low (p = 0.04). The ROC curve AUC was 0.65 (95% CI 0.50-0.79). **Conclusions:** RBsig Low expression identifies a subset of HER2+ pts less likely to respond to CT + H. This is particularly notable in HER2e tumors thus indicating RBsig may add significant information to molecular subtypes.

571 Poster Session (Board #63), Sat, 8:00 AM-11:30 AM

Prognostic implications of residual disease (RD) tumor-infiltrating lymphocytes (TIL) in triple negative breast cancer (TNBC) after neo-adjuvant chemotherapy (NAC). *First Author: Stephen James Luen, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: For primary TNBCs treated with NAC, higher pre-treatment TILs correlate with increased pathological complete response (pCR) rates, better recurrence-free survival (RFS) and overall survival (OS). We evaluated the prognostic value of RD TILs to pathological stage and Residual Cancer Burden (RCB) in predicting survival post NAC. **Methods:** We combined individual patient data from 4 TNBC patient series treated with NAC who did not achieve pCR. TILs were evaluated on the RD using our previously published method on H&E stained slides. TILs were investigated for associations with yp stage, RCB, RFS and OS using Cox models with stromal TILs as a continuous variable, stratified by series. The likelihood ratio (LR) test was used to evaluate added prognostic value of TILs to standard yp stage and RCB class. **Results:** In total 376 RD samples were evaluable for TILs. After 6 years median follow-up we observed 193 RFS events and 165 deaths. The median age was 50 years (range 24-83). 62% received combination anthracycline/taxane chemotherapy, and 27% anthracycline alone. For RD stage, 32% were yp node positive; RCB class I/II/III was 11%/50%/39% respectively. The median RD TIL level was 20% (IQR 10-40). TIL levels were significantly lower with increasing yp stage ($P < 0.01$), but did not differ significantly by RCB class ($P = 0.84$). Higher RD TILs were significantly associated with improved RFS (HR per 10% increment 0.86; 95%CI 0.79-0.92; $P < 0.01$) and OS (HR 0.87; 95%CI 0.80-0.94; $P < 0.01$), but were only significant for RFS in multivariate analysis after adjusting for yp stage ($P = 0.03$). RCB class was significant for RFS and OS (both $P < 0.01$). RD TILs added significant prognostic value to RCB class for both RFS and OS (both LR $P < 0.01$). The positive prognostic effect of RD TILs was of greater magnitude in the lower RCB classes I/II vs. III for both RFS and OS (both interaction $P < 0.01$). **Conclusions:** TIL levels in TNBC RD are significantly associated with improved RFS and OS and add further prognostic information to RCB class. The positive prognostic influence of TILs is significantly greater in patients with less RD burden. This data may help refine NAC clinical trial endpoints.

572 Poster Session (Board #64), Sat, 8:00 AM-11:30 AM

Impact of PIK3CA mutation status on immune marker response and pCR in the WSG-ADAPT HER2+/HR+ phase II trial. *First Author: Nadia Harbeck, Brustzentrum der Universität München (LMU), Munich, Germany*

Background: The ADAPT HER2+/HR+ phase II trial (NCT01745965) compared for the first time 12 wks. neoadjuvant T-DM1 (+/- endocrine therapy (ET)) with trastuzumab (T)+ET; pCR (ypT0/is ypN0) was > 40% in T-DM1 arms and 15% in T+ET. High CD8 at baseline or cycle 2, as well as increased CD8 expression on treatment, were associated with favorable pCR. In HER2+ mBC, T-DM1 was reported effective in both mutated and wildtype (WT) PIK3CA tumors. **Methods:** This pre-planned translational analysis aimed to identify potential early predictors for response to neoadjuvant therapy (containing T-DM1 or T) in HER2+/HR+ EBC. PIK3CA mutations were assessed by high-throughput microfluidics qPCR (MUT-MAP 13-gene panel). Immune markers, focusing here on CD8 in tumor center, were assessed by IHC in core biopsies at baseline and cycle 2. CD8 positivity was coded as percentage of positively stained cells; CD8 change was defined as cycle 2 minus baseline value. Associations between pCR and PIK3CA mutation status (mutated vs. WT) or with other variables were characterized by Fisher's exact test and T-statistics. **Results:** In 190 patients, PIK3CA mutation status was assessed in baseline biopsies (177/190) or surgical samples (or both). Results were identical in all 8 repeated assays (baseline & surgery). Prevalence of PIK3CA mutations was 31/190 (16.3%). pCR was 37.4% in WT vs 16.7% in PIK3CA mutated tumors (p = .035). Distributions of nodal status, grade, and Ki67 were independent of PIK3CA mutation status, but T1 tumors were less prevalent (25.8% vs. 47.2%) for PIK3CA mutations (p = .03); the unfavorable impact of PIK3CA mutations on pCR was strong within the T2+ patient subgroup (9.1% vs 33.8%; p = .017). While CD8 protein expression generally increased following 3 weeks of therapy, and larger positive CD8 responses were themselves associated with pCR (particularly in the T-DM1 containing arms (p = .009)), CD8 changes in PIK3CA mutated tumors were small and lower than in WT (p = .020). **Conclusions:** PIK3CA mutations were associated both directly (lower pCR) and indirectly (stagnation of CD8 change) with poorer response to neoadjuvant therapy in HER2+/HR+ EBC. Poor response in PIK3CA mutated cases occurs despite excellent overall pCR with T-DM1. Clinical trial information: NCT01817452.

573 Poster Session (Board #65), Sat, 8:00 AM-11:30 AM

Impact of 12 weeks nab-paclitaxel + carboplatin or gemcitabine followed by anthracycline administration according to pCR in triple-negative early breast cancer: Survival results of WSG-ADAPT-TN phase II trial. *First Author: Oleg Gluz, Breast Center Niederrhein and University Clinics Cologne, Moenchengladbach, Germany*

Background: Optimal chemotherapy in TNBC EBC is unclear. ADAPT TN demonstrated higher pCR (46% vs. 29%) and better safety for only 12 weeks nab-paclitaxel/carboplatin vs nab-paclitaxel/gemcitabine (JNCI 2017). **Methods:** Patients with centrally confirmed TNBC (ER/PR < 1%, HER2-, cT1c-cT4c, cN0/+) were randomized to neoadjuvant A: 4x nab-paclitaxel 125 mg/m^2/gemcitabine 1000 mg/m^2 d1,8 q3w vs. B: 4x nab-paclitaxel 125 mg/m^2/carboplatin AUC2 day 1/8 3-weekly (q3w). Primary endpoint was pCR (ypT0/is/ypN0) after 12 weeks of therapy. Event-free (EFS) – defined as time from registration to any invasive relapse, secondary malignancy or death of any cause – and overall survival (OS) were secondary endpoints. Adjuvant anthracycline-based chemotherapy (4xEC) was optional in patients with pCR. Here, we report the per-protocol interim survival analysis recommended by the DSMB after a median follow-up of 3 years. **Results:** 336 patients were enrolled (48 centers, arms A/B: n = 182/154). Median age was 50 years. At baseline, about 63% had cT2-4c tumors, 26.2% were clinically node-positive. After 36 months median FU, 68 EFS events (A/B: 37/29) and 37 deaths (A/B: 24/13) were observed. pCR (vs. non-pCR) is highly prognostic for EFS (3y EFS: 92% vs. 71%, p < 0.001) and OS (3y OS: 99.1% vs. 81.6%, p < 0.001). Despite the strong impact of carboplatin on pCR, 3y EFS was similar in (77.6% vs. 80.8%) in both arms; OS was numerically higher in Arm B (84.7% vs. 92.2%, p = 0.09). Final analysis regarding anthracycline use and its survival impact will be presented at the meeting. **Conclusions:** 12w nab-paclitaxel/carboplatin is a tolerable and effective neoadjuvant option in early stage TNBC. In ADAPT TN, the strong impact of carboplatin vs. gemcitabine on pCR seems to be "mitigated" regarding survival by subsequent adjuvant anthracycline/cyclophosphamide therapy. Our findings provide first prospective evidence supporting individualized chemotherapy regimens in early TNBC. Clinical trial information: NCT01815242.

574 Poster Session (Board #66), Sat, 8:00 AM-11:30 AM

Signatures of mutational processes and response to neoadjuvant chemotherapy in breast cancer: A genome-based investigation in the neoadjuvant GeparSepto trial. *First Author: Carsten Denkert, Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany*

Background: Different mutational processes act over the evolutionary history of a malignant tumor, driven by e.g. abnormal DNA editing, mutagens or age-related DNA alterations. Many of these processes generate defined combinations of mutation types, which have been described as mutational signatures. The clinical relevance of mutational signatures has not been studied to a great extent. We investigate the hypothesis that the individual patterns of mutational signatures determine the clinical behavior of breast cancer (BC) , in particular response to neoadjuvant chemotherapy. **Methods:** In the GeparSepto study (NCT01583426) women with primary invasive BC were randomized to either nab-paclitaxel or solvent-based paclitaxel followed by EC. Pretherapeutic FFPE core biopsies of HER2-neg BC were used for whole genome/exome sequencing (n = 405). Mutational signatures were identified as described by Alexandrov et al. (Cell Rep. 3, 2013). **Results:** 24 of the the 30 mutational signatures were present in at least 10% of the 405 tumors , the most predominant were Sig1 (age-related, 94.8%), Sig13 (APOBEC-related, 87.7%), Sig6 (MMR-def.-related, 69.9%), Sig3 (BRCA-related, 61.5%), Sig28 (60.7%), and Sig16 (60.2%). The signatures 3, 4, 11, 13, 17, 21, and 24 were increased and signatures 10, 16, 28, and 29 decreased in TNBC compared to luminal BC. A significant correlation with the number of stromal tumor-infiltrating lymphocytes was observed for signatures 3, 4, 13, 23, and 24, an association with increased Ki67 was observed for Sig 3, 4, 6, 11, 12, 13, 16, 23, and 24. Tumors with signatures 3, 11 and 13 had a significantly increased response rate to neoadjuvant chemotherapy, this was also observed in the subgroups of TNBC (sign 11) and luminal BC (sign 3, 9, 13). **Conclusions:** Whole-exome sequencing in breast cancer FFPE core biopsies from clinical cohorts can be used to identify mutational signatures. The pattern of these signatures, in particular the presence of BRCA-related (Sig3) and APOBEC-related (Sig13) reflect the clinical behavior of breast cancer and might be used to identify tumors with an increased response rate to neoadjuvant chemotherapy.

575 Poster Session (Board #67), Sat, 8:00 AM-11:30 AM

Does the sequence of anthracycline and taxane matter? The NeoSAMBA trial. *First Author: Jose Bines, Instituto Nacional de Câncer, Rio De Janeiro, Brazil*

Background: Taxanes usually follow anthracyclines in breast cancer neo/adjuvant treatment, likely due to its later introduction in clinical practice. However, there is no biological rationale that justifies this current standard-of-care. We compared an anthracycline-based regimen followed by a taxane (FAC-T) neoadjuvant chemotherapy with the reverse sequence (T-FAC) (NCT01270373). **Methods:** In this randomized, open-label, single center phase 2 trial, women with locally advanced (LABC) HER2 negative breast cancer, stratified by hormone receptor, were randomized to 3 cycles of fluorouracil, doxorubicin and cyclophosphamide followed by 3 cycles of docetaxel vs. docetaxel followed by fluorouracil, doxorubicin and cyclophosphamide. Surgery, radiotherapy and adjuvant hormonal therapy were given as per local guidelines. The primary endpoint was pathological complete response (pCR) and secondary endpoints included disease-free (DFS) and overall survival (OS). The expected baseline pCR was 15%. With 53 patients per arm, we had a 90% probability of selecting a schedule that had a true benefit of 25%. A 10% drop-out was anticipated. **Results:** Between September 2010 and November 2012, we randomly allocated 118 patients: 60 received FAC-T and 58 T-FAC. The median follow-up was 53.8 months (95% CI 51.9- 55.7). The median age was 50 years. Ninety-four patients (70.7%) had stage III tumors and 31 (26.3%) had triple negative disease. pCR was higher in triple negative patients: 21.4% vs 1.2%. Treatment sequence did not improve pCR of all patients operated (114): 3 (5.2%) and 4 (7.3%) in the FAC-T and T-FAC arms, respectively. Taxane-first when compared to anthracycline-first sequencing showed a 5y DFS of 78% and 45% (HR 0.31, 95% CI 0.16–0.59) and a 5y OS of 88% and 65% (HR 0.28, 95% CI 0.12–0.66), respectively. The relative dose intensity was similar between both arms. No unexpected toxicity was reported. **Conclusions:** We showed for the first time an improvement in DFS and OS with taxane-first when compared to anthracycline-first sequencing chemotherapy in HER2 negative LABC. Tumor and blood samples were collected for translational analyses at three time points. Clinical trial information: NCT01270373.

576 Poster Session (Board #68), Sat, 8:00 AM-11:30 AM

Breast Cancer Index (BCI) and prediction of pathological complete response (pCR) to neoadjuvant chemotherapy in estrogen receptor positive (ER+) breast cancer. *First Author: Laura Spring, Brigham and Women's Hospital, Brookline, MA*

Background: Although endocrine therapy is the mainstay of management of ER+ tumors, optimal neoadjuvant strategy for ER+ breast cancer is unclear, and improved selection of patients for neoadjuvant chemotherapy (NACT) vs neoadjuvant endocrine therapy are critical ongoing questions. BCI is a gene expression signature that stratifies patients for risk of overall (0-10y) and late (post-5y) distant recurrence and the likelihood of benefit from extended endocrine therapy. Given BCI's proliferation (MGI) and estrogen-related (HoxB13/IL17BR) activities, this study investigated its ability to predict pCR in ER+ breast cancer patients treated with NACT. **Methods:** BCI analysis was performed on pre-treatment core biopsies from patients with ER+ breast cancer treated with NACT at Massachusetts General Hospital (n = 84) and Institut Gustave Roussy (n = 101). pCR and overall survival were collected from charts by investigators blinded to the BCI results. Multivariate logistic regression and Cox proportional hazards regression were used to evaluate the association of BCI risk categories with pCR and overall survival. **Results:** Patients (N = 185; 100% ER+/HER2-, 56% N+, 65% T2, 49% grade 2) were treated with NACT, mostly anthracycline/taxane-based regimens, and 10 (5.4%) achieved pCR. BCI was significantly associated with pCR, with no pCR observed in the low risk group (P = 0.0003). BCI was the only significant predictor of pCR in multivariate analysis including tumor size, tumor grade, PR status, and nodal status (OR = 14.0 [95% CI 1.19 – 263.5], P = 0.05). BCI was also a significant predictor of overall survival in these patients following NACT (P = 0.008). **Conclusions:** Pre-treatment BCI significantly predicted response to neoadjuvant chemotherapy in ER+ breast cancer patients. Results of this study suggest potential clinical utility of BCI in stratifying ER+ patients with chemo-sensitive disease, while considering alternative treatment strategies such as neoadjuvant endocrine therapy for women who may not respond adequately to NACT and potentially avoid toxicity associated with NACT.

577 Poster Session (Board #69), Sat, 8:00 AM-11:30 AM

Association between adaptive immune signature and outcome in HER2-positive breast cancer treated with trastuzumab and lapatinib in the NCCTG-N9831 (Alliance) and NeoALTTO trials. *First Author: Saranya Chumsri, Mayo Clinic, Jacksonville, FL*

Background: Trastuzumab (H) acts in part through adaptive immune system, whereas lapatinib (L) acts through inhibition of HER2 signaling. Previous studies showed that enrichment of immune-related genes was associated with improved outcome. However, the role of immune system in response to L or LH is not fully understood. **Methods:** NanoString was used to quantify mRNA in 1,378 samples from N9831 trial: Arm A chemotherapy alone, arm B sequential H, and arm C concurrent H. Enrichment analysis was performed on genes with significant HR to generate a signature. RNA-seq data was analyzed from 193 samples from NeoALLTO trial: Arm A L, arm B H, and arm C LH. Cox models for RFS and EFS were analyzed. **Results:** In N9831, enrichment of the 17 gene adaptive immune signature (AIS) was found to be significantly associated with improved RFS in arm C (HR 0.71, 95%CI 0.56-0.90; p = 0.005). Further validation was performed in arm A and B with similar associations observed in arm B (HR 0.76, 95%CI 0.62-0.92; p = 0.006) and arm A (HR 0.84, 95%CI 0.72-0.99; p = 0.04). Enrichment of this signature was significantly associated with higher sTIL ($p < 0.0001$), ER negativity (p = 0.047), and larger tumor size ($p < 0.0001$) but not lymph node status or tumor grade. In NeoALTTO, 134 out of 244 (54.9%) patients were considered deficient AIS (dAIS). NeoALTTO patients with dAIS had significantly lower pathologic complete response (pCR) rate, compared to patients with enriched AIS (eAIS). In arm B, pCR was observed in 43% with eAIS compared to 8% with dAIS (OR = 9.12, 2.25-54.42, p = 0.0004). pCR was observed in 17% with dAIS in arm A and in 52% in arm C . Among dAIS patients, 6 year-EFS was longer in L (68%, 95%CI 0.55-0.85) or combination HL (73%, 95%CI 0.60-0.88), compared to H alone, (63%, 95%CI 0.49-0.80). **Conclusions:** Patients with dAIS had poor outcome despite receiving H likely due to inability to mount proper immune response. However, these patients appear to benefit from L and the combination of LH. Further studies are needed to validate this signature to identify patients who will benefit from dual anti-HER2 therapy. Clinical trial information: NCT00898898 and NCT00553358.

	%pCR		%6-yr EFS	
	dAIS	eAIS	dAIS	eAIS
L	17%	21%	68%	65%
H	8%	43%	63%	74%
LH	52%	44%	73%	85%

578 Poster Session (Board #70), Sat, 8:00 AM-11:30 AM

Immune profiling of pre- and post-treatment breast cancer tissues from the S0800 randomized neoadjuvant trial of weekly nab-paclitaxel with or without bevacizumab and dose dense doxorubicin and cyclophosphamide. *First Author: Xiaotong Li, Yale University, New Haven, CT*

Background: We examined changes in the tumor immune microenvironment during neoadjuvant chemotherapy by comparing immune gene mRNA expression, tumor infiltrating lymphocyte (TIL) count and PD-L1 protein expression in pre- and post-treatment tissues. **Methods:** Paired pre- and post- treatment tumor samples from 60 patients were profiled using the Nanostring Immune Oncology 360 platform to measure the expression of 770 immune-related genes that also allowed us to test 14 immune cell type and 27 previously published prognostic and immuno therapy response predictive gene signatures. All samples were also assessed for TIL counts and PD-L1 protein expression by immunohistochemistry. Gene expression levels were compared by paired t-test with Bonferroni correction. TIL count, PD-L1 protein expression and immune gene signatures were compared using Wilcoxon signed-rank test. Baseline immune markers were correlated with pathologic complete response (pCR) using estrogen receptor (ER) and treatment adjusted logistic regression. **Results:** TIL counts were significantly lower in post- compared to pre-treatment samples (17% vs 7%, p = 0.013) but stromal PD-L1 protein expression was not significantly different. At baseline, higher TIL count and PD-L1 expression were associated with pCR. High expression of a mast cell metagene was associated with residual disease (RD). No individual genes or VEGF gene signature were associated with benefit from bevacizumab. In patients with RD (n = 45), genes involved with tissue repair and inflammation (DUSP1, EGR1, IL6, ATF3, CD36, CXCL2, CD69, NGFR, KLF2, THBD, DAB2) showed significantly higher expression after therapy while most other immune markers decreased. The T effector, T-reg, MHC-I, MHC-II, IFNgamma, STAT-1 and M1 macrophage gene signatures were all significantly lower in post- versus pre-treatment samples and only the IL8/VEGFR and T-helper gene signatures showed higher expression after therapy. **Conclusions:** High mast cell gene expression is associated with lower pCR rate. TIL counts and most immune parameters decrease after neoadjuvant chemotherapy.

579 Poster Session (Board #71), Sat, 8:00 AM-11:30 AM

Integrative cluster classification to predict pathological complete response to neoadjuvant chemotherapy in early breast cancer. *First Author: Emilio Alba, Hospital Clínico Universitario Virgen de la Victoria. GEICAM Spanish Breast Cancer Group., Malaga, Spain*

Background: Integrative Clustering (IntClust) is a breast cancer (BC) classification of 10 different subgroups with distinctive molecular profiles and clinical outcomes (Curtis et al., Nature 2012). We implemented an IntClust classifier based on Copy Number Alterations (CNAs) and explored its prognostic role in a cohort of pre- and post-treatment (ttm) tumors from the neoadjuvant trials GEICAM/2006-03 (NCT00432172) and GEICAM/2006-14 (NCT00841828). **Methods:** GEICAM/2006-03 HER2-negative pts were selectively treated according to clinical subtypes: triple negative (TN) pts with standard taxane/anthracycline-based chemotherapy (TA-CT) +/- carboplatin, and luminal A patients were randomised to TA-CT vs. hormonotherapy; GEICAM/2006-14 HER2+ pts received TA-CT + anti-HER2 therapy. Shallow-whole genome Illumina sequencing DNA data from 204 paraffin-BC (100 pre- and 104 post-ttm tumors) were used to identify CNAs and grouped samples in the 10–IntClust classification. A functional clustering by grouping IntClust 1-2-6-9 as Luminal poor prognosis (LPP), IntClust 3-4-7-8 as Luminal good prognosis (LGP), IntClust 10 (Basal-like) and IntClust 5 (HER2+) were defined. Fisher test was used to analyze IntClust distribution. Logistic regression analyses were performed to explore the association of IntClust groups with outcome (pCR in breast and axila). **Results:** The comparative analysis for IntClust groups in pre- vs post-ttm samples showed significantly different distribution (p = 0.01), with an enrichment of the LGP group (32% vs 55%) in the residual samples after neoadjuvant ttm, due to an increase in IntClusters 3 and 4 (both of them characterized by a low-genomic instability), and a decrease in the rest of the groups. Logistic regression analysis showed that IntClust classification in pre-ttm tumors were significant associated with pCR independently to histological grade, Ki67 and clinical subtype (p = 0.0015) **Conclusions:** Our data suggest an association between IntClust classification and clinical outcome in terms of pCR after neoadjuvant therapy in early BC. In our study, residual tumors after ttm were predominantly Luminal-like phenotypes with low genomic instability Clinical trial information: GEICAM/2006-03 NCT00432172. GEICAM/2006-14 NCT00841828.

580 Poster Session (Board #72), Sat, 8:00 AM-11:30 AM

Intrinsic subtypes of HER2-positive breast cancer and their associations with pathologic complete response (pCR) and outcomes: Findings from NSABP B-41, a randomized neoadjuvant trial. *First Author: Sandra M. Swain, NSABP/NRG Oncology, and Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC*

Background: NSABP B-41, randomly assigned 529 patients with HER2 positive breast cancer to receive neoadjuvant trastuzumab, lapatinib, or the combination, with weekly paclitaxel following doxorubicin and cyclophosphamide x 4. No significant difference in pCR was found among three arms (Robidoux 2013), but overall survival was significantly increased for patients who obtained a pCR (Robidoux 2016). This study evaluated outcomes in B-41 based on intrinsic subtype. **Methods:** H&E slides were reviewed by study pathologist for areas of invasive carcinoma having > 10% tumor cells. RNA was isolated and hybridized to the "RUO-PAM50" CodeSet (NanoString Technologies). Intrinsic PAM50 subtype was determined for each sample. Contingence-table analyses were used to compare pCR breast and nodes (ypT0/is ypN0) among intrinsic subtypes and Kaplan-Meier estimates and Cox models were used to compare event-free survival and overall survival among subtypes. **Results:** Core biopsy samples from 276 patients, prior to therapy, were evaluated. Intrinsic subtype was determined in 271: 197 (73%) were HER2 enriched (E) (97 ER negative and 100 ER positive), 26 (10%) basal-like, 23 (8%) luminal A, and 25 (9%) luminal B. pCR was 61% in HER2-E (69% in ER negative and 53% in ER positive) and 26% in others (basal-like, luminal A/B) (p < 0.001). In HER2-E, patients on trastuzumab-based arms had higher pCR than those on the lapatinib arm (67% vs 49%, p = 0.02). Patients with basal-like tumors had higher pCR than those with luminal A/B tumors (38.5% vs 13% & 24%) but their long-term prognosis is poor, compared with other three subtypes: five-year EFS = 0.724 [0.506, 0.858] (p = 0.28) and five-year OS = 0.808 [0.598, 0.915] (p = 0.005). In HER2-E, EFS and OS were no different between the three arms. **Conclusions:** HER2-E subtype is a good marker for predicting benefit from HER2 targeted therapies, particularly if trastuzumab-based. Whether tumors with other subtypes are suitable for HER2 targeted therapies needs further investigation. Survival outcomes are limited by the small number of events and would benefit from meta-analysis with other similar studies. Clinical trial information: NCT00486668.

581 Poster Session (Board #73), Sat, 8:00 AM-11:30 AM

Care 001: Multicenter randomized open label phase II trial of neoadjuvant trastuzumabemtansine (T-DM1) in combination with lapatinib and nab-paclitaxel compared with paclitaxel, trastuzumab and pertuzumab in HER 2 neu over-expressed breast cancer patients (TEAL study). *First Author: Tejal Amar Patel, Methodist Cancer Center, Houston, TX*

Background: Based on data from our phase I study of trastuzumab-emtansine (T-DM1), Lapatinib (L) and Nab Paclitaxel (Nab-P), a multicenter randomized open label phase II neoadjuvant study was conducted comparing this regimen to the standard of care (SOC) Paclitaxel (Pac), Trastuzumab (T), and Pertuzumab (P) in patients with HER2 over-expressed breast cancer. **Methods:** Patients in the experimental arm received T-DM1 3.0 mg/kg Q3W, L 750mg oral daily and Nab-P 80 mg/m^2 weekly (QW) X 12 weeks. Patients in SOC arm received Pac 80mg/m^2 QW, T 2mg/kg QW, and P 420mg Q3W X 12 weeks. The primary objective was to evaluate the proportion of patients with residual cancer burden (RCB) 0 or 1. Key secondary objectives included correlative assessments of PIK3CA mutations, PTEN expression, and HER2 subtypes, all of which are ongoing. **Results:** Thirty of the 33 enrolled patients were evaluable. Patient demographics were.The proportion of patients with RCB 0 & I was significantly higher in the T-DM1, L and Nab-P arm than in the SOC arm (100% vs. 62.5%, p 0.0035). Importantly, the RCB 0 & 1 in the ER positive subset of patients was 100% compared with 25% in SOC (p 0.0035). Common adverse events included elevated liver function tests, fatigue, diarrhea and neuropathy. **Conclusions:** TDM1 plus L and Nab-P therapy was well tolerated with noteworthy responses in all patients, and especially in the ER positive subset, a group which has historically had lower response rates to neoadjuvant anti-HER2-directed therapy. Further evaluation of this regimen is warranted. Clinical trial information: NCT02073487.

Efficacy.

	Experimental	SOC	P-value
RCB 0 - and I	14 (100)	10 (62.5)	0.0035
ER Negative	6 (100)	8 (100)	
ER Positive	8 (100)	2 (25)	
RCB II and III	0	6 (37.50)	

582 Poster Session (Board #74), Sat, 8:00 AM-11:30 AM

Predicting neo-adjuvant chemotherapy response from pre-treatment breast MRI using machine learning and HER2 status. *First Author: Nathaniel Braman, Case Western Reserve University, Cleveland, OH*

Background: Many breast cancer patients receiving neo-adjuvant chemotherapy (NAC) will ultimately fail to achieve pathological complete response (pCR). A pre-treatment clinical marker of pCR could guide NAC without requiring potentially ineffective initial treatment periods. Advances in medical image analysis, such as deep learning (pattern recognition using neural networks) and radiomics (computer-extracted quantitative image features), demonstrate significant potential for non-invasive assessment of NAC outcome. We present a machine learning (ML) approach for pre-NAC response prediction fusing deep learning, radiomics, and clinical variables. **Methods:** 166 patients with pre-treatment contrast-enhanced MRI from the ISPY1-TRIAL and surgically-confirmed NAC response outcome (ypT0N0, 49 pCR, 117 non-pCR) following anthracycline-cyclophosphamide chemotherapy with or without taxane were retrospectively analyzed. Patients were divided randomly into training (n = 133) and testing (n = 33) cohorts, with proportionate distribution of pCR between cohorts. Multinomial logistic regression integrated DL, radiomics, and HER2 status was assessed by area under the receiver operating characteristic curve (AUC), sensitivity, and specificity within the testing set. Deep learning: A six-layer convolutional neural network was trained to predict response using 65 pixel square patches centered within a tumor. Radiomics: From a pool of 215 radiomic intra-tumoral heterogeneity features, the 8 best-performing features were identified algorithmically and used to train a linear discriminant analysis classifier within the training set. **Results:** A ML only approach strongly predicted response (AUC = .84) in the testing set. Integrating clinical HER2 status into the combined imaging model yielded optimal pre-treatment response prediction (AUC = .93), with 75% sensitivity and 92% specificity. **Conclusions:** Further validation of an approach fusing deep learning, radiomic analysis, and clinical information could potentially provide a means of pre-NAC response prediction from MRI.

	AUC	Sensitivity	Specificity
HER2 Status	.69	63%	76%
ML only	.84	63%	84%
ML+HER2 Status	.93	75%	92%

583 Poster Session (Board #75), Sat, 8:00 AM-11:30 AM

Efficacy analyses of central laboratory pCR results from the LILAC study comparing the biosimilar ABP 980 and trastuzumab. *First Author: Hans-Christian Kolberg, Marienhospital Bottrop, Klinik für Gynäkologie und Geburtshilfe, Bottrop, Germany*

Background: The phase 3 LILAC Study compared ABP 980 with trastuzumab (TRAS) on pathologic complete response (pCR) in women with HER2+ early breast cancer. The primary efficacy results, based on local laboratory evaluation of tumor samples, have been reported previously. Here we report the results of pCR analysis based on central laboratory evaluation of tumor samples. **Methods:** After run-in anthracycline-based chemotherapy, patients were randomized 1:1 to ABP 980 or TRAS plus paclitaxel Q3W x 4 or Q1W x 12. The co-primary endpoints were risk difference (RD) and risk ratio (RR) of pCR adjusted for baseline covariates in breast tissue and axillary lymph nodes. Clinical similarity was supported by the central pathology evaluation as the 2-sided 90% CIs were within the equivalence margin for RD (-13% to 13%) and RR (0.759 to 1.318). Representative samples of tumor material were sent to the central laboratory for evaluation. Samples were determined to be adequate for evaluation based on the presence of tumor bed and integrity of nuclear detail. Each sample was evaluated by 2 independent central pathologists, who were blinded to patients' treatment and to each other's assessment. If discordance between the 2 pathologists was found, the case was sent to a third blinded pathologist to determine the outcome. **Results:** 725 patients were randomized; 696 (ABP 980: n = 358; TRAS: n = 338) were included in the pCR evaluable population. pCR was achieved in 48.0% for ABP 980 and 40.5% for TRAS, based on local review. RD of pCR was 7.3% (90% CI: 1.2%, 13.4%); RR was 1.19 (90% CI: 1.033, 1.366). The upper limit of the CIs slightly exceeded the equivalence margin. Based on central review, pCR was achieved in 47.8% for ABP 980 and 41.8% for TRAS. RD was 5.8% (90% CI: -0.5, 12.0%); RR was 1.14 (90% CI: 0.993, 1.312). Both RR and RD were contained within the equivalence margin. **Conclusions:** Results based on central evaluations support clinical equivalence of ABP 980 and TRAS. All sensitivity analyses based on central pathology evaluation were within the prespecified equivalence margins. This study demonstrates the feasibility of including central laboratory review of pCR rates in a large multicenter, multinational study. Clinical trial information: NCT01901146.

584 Poster Session (Board #76), Sat, 8:00 AM-11:30 AM

Impact of residual nodal disease burden on sentinel node mapping and accuracy of intraoperative frozen section in node positive (cN1) breast cancer patients treated with neoadjuvant chemotherapy (NAC). *First Author: Alison Laws, University of Calgary, Calgary, AB, Canada*

Background: Recent trials have demonstrated the feasibility of SLN biopsy in cN1 patients who become cN0 after NAC. We sought to evaluate success of SLN mapping and accuracy of intraop frozen section (FS) by residual nodal disease burden. **Methods:** cT1-3 cN1 patients receiving NAC and surgery (1/2016 to 5/2017) were identified from a prospective database. Pts who converted to cN0 and had SLN biopsy with dual-tracer were included. Adequate mapping (defined as ≥3 SLN) and false negative rate (FNR) of intraop FS were assessed by residual nodal disease burden (ypN0, ypNmi+ITC, ypN1-3). **Results:** Among 137 cT1-3 cN1 pts, 76 met inclusion criteria. Median age 45 yrs [27-82]; median tumor size 4.3cm [0.8-15.0]. 32 (42%) pts were ER+HER2-, 24 (32%) HER2+ and 20 (26%) ER-HER2-. Adequate mapping was achieved in 50 (66%) pts; 14 (18%) failed to map and 12 (16%) had < 3 SLN identified. Adequate mapping was not associated with residual node burden (table, p = 0.21). Among 48 pts with adequate mapping and FS, 16 were ypN+ on FS and 28 were ypN+ on final pathology; FNR of 12/28 (43%). Smaller residual node burden was associated with false negative FS (table, p = 0.005). 28/76 (37%) pts achieved axillary pCR, of whom 20 (71%) had ≥3 negative SLN and were spared ALND. Of 36 pts with successful mapping and positive SLN, 22 (61%) underwent ALND, of whom 8 (36%) had additional nodal disease; the remaining 14 (39%) had axillary radiation. **Conclusions:** Among pre-NAC cN1 pts, SLN biopsy was technically adequate in 66%. Of these, 40% achieved axillary pCR and avoided ALND. The FNR of intraop FS was 43%. Residual nodal disease burden was not associated with adequate mapping; micrometastases and ITCs were associated with higher likelihood of false negative FS. Preoperative counseling for SLN biopsy should include realistic assessment of the limitations of SLN mapping and intraop FS and the potential need for ALND.

	Volume of residual nodal disease in 76 patients with attempted SLN biopsy			
	ypN0 (n = 28, 37%)	ypNmi / ITCs (n = 11, 14%)	ypN1-3 (n = 37, 49%)	p-value
Adequate SLN mapping*	20/28 (71%)	9/11 (82%)	21/37 (57%)	0.21
FNR of FS in pts with ≥3 SLN	–	8/9 (89%)	5/20 (25%)	0.005

*≥3 SLN

585 Poster Session (Board #77), Sat, 8:00 AM-11:30 AM

Immune profiling of BRCA-mutated breast cancers. *First Author: Jeremy Meyer Force, Duke University Medical Center, Durham, NC*

Background: Increased tumor infiltrating lymphocytes (TILs) are predictive and prognostic for improved outcomes in breast cancers. Increased tumor mutational burden can be immune activating. BRCA-mutated (BRCA+) breast cancers may have increased tumor mutational burden compared to BRCA wildtype (BRCA-). Immune system responses to BRCA+ breast cancers have not been well described. The primary aim of our study was to assess tumor infiltrating immune cells in early stage breast cancers with and without germline BRCA mutations. **Methods:** Here we report TILs and genomic profiling from our full study cohort. Assuming the %TILs in the BRCA- group was 20% we determined 124 early stage breast cancers with and without BRCA mutations was needed to detect a 20% difference in TILs between cohorts to attain 80% power with a one-side alpha of 0.05. We identified 124 early stage untreated breast cancers with BRCA mutations (n = 62) and without (n = 62). Our BRCA- control group were matched by hormone receptor (HR) status followed by age then stage. TILs were measured on pretreatment H&E slides. A NanoString BC360 panel was applied to RNA isolated from 80 breast cancers (BRCA+ = 39; BRCA- = 41). **Results:** Compared to BRCA- early stage breast cancers, median TILs were increased in the BRCA+ cohort (median 5 vs 10, p = 0.007). BRCA+/HR- samples did not have more TILs compared to BRCA-/HR- (median 10 vs 15, p = 0.10). BRCA+/HR+ had increased TILs compared to BRCA-/HR+ (median 1 vs 5, p = 0.005). An 18 gene RNA tumor immune score (TIS) moderately correlated with TILs (R^2 = 0.339, p < 0.001), was increased in BRCA+ cancers (p = 0.29), but was primarily elevated in those with a basal-like phenotype (p < 0.001). **Conclusions:** Early stage BRCA+ breast cancers have increased TILs compared to BRCA-. TILs are significantly more abundant in BRCA+/HR+ breast cancers, which might be explained by an increased basal-like phenotype. TIS moderately correlates with TILs. TIS is increased in BRCA+ breast cancers, but reaches significance in the basal-like phenotype. Many BRCA+/HR+ cancers with luminal phenotypes had increased TILs and elevated TIS. To guide development of immunomodulating therapies in BRCA+ cancers, further immune analyses should be investigated in hereditary breast cancers and compared to sporadic cancers.

586 Poster Session (Board #78), Sat, 8:00 AM-11:30 AM

Durvalumab (MEDI4736) concurrent with nab-paclitaxel and dose dense doxorubicin cyclophosphamide (ddAC) as neoadjuvant therapy for triple negative breast cancer (TNBC). *First Author: Lajos Pusztai, Yale Cancer Center, New Haven, CT*

Background: The goal of this Phase I/II trial is to assess the safety and efficacy of concurrent administration of durvalumab with weekly nab-paclitaxel (100 mg/m2) x 12 followed by dd AC x 4 as neoadjuvant therapy for stage I-III TNBC. The primary efficacy endpoint is pathologic complete response (ypT0 ypN0, pCR). **Methods:** The Phase I portion of the trial assessed two dose levels of durvalumab; 3 mg/kg and 10 mg/kg iv every 2 weeks in combination with chemotherapy, dose limiting toxicities (DLT) were evaluated over the entire 20 weeks of therapy. The Phase II portion follows Simon's two step design, with early stopping for futility if < 7 patients achieve pCR among the first 22. **Results:** No DLT were encountered during the Phase I portion of the trial; the 10 mg/kg was recommended as the phase II dose. Thirty-two patients are enrolled in the trial 14 are still receiving therapy, 16 have completed treatment and underwent surgery and 1 patient withdraw consent. Nine patients (56%, 95% CI: 32%-78%) achieved pCR, 2 of the 4 patients at the 3 mg/kg dose level and 7 of the 12 at the 10 mg/kg dose. Eight patients (25%) experienced grade 3 adverse events including 3 patients with neutropenia (1 neutropenic fever), and one patient each with fatigue, dyspnea, line infection, transaminitis, hypertension/skin rash. No perioperative adverse events were seen. **Conclusions:** Concomitant administration of durvalumab with weekly nab-paclitaxel and sequential ddAC neoadjuvant chemotherapy is safe and the pCR rates appear to be higher than what is expected with chemotherapy alone. Clinical trial information: NCT02489448.

587 Poster Session (Board #79), Sat, 8:00 AM-11:30 AM

The impact of chemotherapy sequence on survival in node-positive invasive lobular carcinoma. *First Author: Nina Prabha Tamirisa, Duke University Medical Center, Durham, NC*

Background: Breast cancer patients with invasive lobular carcinoma (ILC) have lower rates of downstaging after neoadjuvant chemotherapy (NACT) than those with invasive ductal carcinoma; however, similar criteria – including lymph node involvement – are used to determine administration of NACT in both subtypes. We sought to determine the impact of chemotherapy sequence on survival among node-positive (cN+) ILC patients receiving systemic therapy. **Methods:** We identified cN1-3 ILC patients in the National Cancer Data Base (2004-2014) who received chemotherapy and divided them into neoadjuvant and adjuvant cohorts. Unadjusted overall survival (OS) was estimated using the Kaplan-Meier method, and differences between groups were tested using the log-rank test. Cox proportional hazards modeling was used to estimate the effect of chemotherapy timing on OS after adjustment for known covariates. **Results:** 75.7% (n = 17,957) of patients with cN+ ILC (n = 23,736) received chemotherapy; 7,609 (42.3%, median age 54, IQR 47-63) received NACT and 10,348 (57.6%, median age 58, IQR 49-66) received adjuvant chemotherapy. In both cohorts, most patients had grade 2 (NACT 50.1% vs adjuvant 54.2%), ER+ (NACT 86.6% vs adjuvant 92.3%), HER2- (NACT 80.6% vs adjuvant 87.6%) disease. NACT patients had higher rates of cT4 disease vs adjuvant patients (17.4% vs 2.3%, $p < 0.001$). Unadjusted 5-year OS was worse for NACT patients vs those receiving adjuvant chemotherapy (73.6% vs 83.1%, log-rank $p < 0.001$). In multivariate analysis, NACT continued to be associated with worse OS (HR 1.33, 95% CI 1.21-1.46). Improved OS was associated with age < 50 (HR 0.82, 95% CI 0.75-0.91), receipt of endocrine therapy (HR 0.60, 95% CI 0.53-0.68), and receipt of radiation therapy (HR 0.81, 95% CI 0.73-0.90). Worse OS was associated with ER- status (HR 1.22, 95% CI 1.03-1.44), PR- status (HR 1.55, 95% CI 1.39-1.72), cT4 stage (HR 2.09, 95% CI 1.76-2.47), and receipt of mastectomy (HR 1.30, 95% CI 1.15-1.45). **Conclusions:** Among node-positive ILC patients, receipt of NACT is associated with worse survival compared with receipt of adjuvant chemotherapy. These findings suggest that use of NACT in node-positive ILC may be of limited benefit and should be used judiciously.

588 Poster Session (Board #80), Sat, 8:00 AM-11:30 AM

Incidence of PI3K pathway aberrations and their impact on response to neoadjuvant chemotherapy (NACT) in triple-negative breast cancer (TNBC) subtypes. *First Author: Reva K Basho, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: TNBC cell lines characterized as mesenchymal (M) and luminal androgen receptor (LAR) commonly have aberrations in the PI3K pathway. However, the incidence in human tumors and impact on response to therapy is less clear. **Methods:** Pre-treatment biopsies were collected from TNBC patients (pts) prior to NACT. Tumors were categorized into 5 groups using the Pietenpol criteria (Lehmann JCI 2011): basal-like (BL) comprised of BL-1 and BL-2, M comprised of M and mesenchymal stem-like, immunomodulatory (IM), LAR, or unspecified (UNS). Using RNAseq data, variants were identified in 16 PI3K pathway genes: *AKT1*, *AKT2*, *AKT3*, *CRKL*, *IRS2*, *MTOR*, *PIK3CA*, *PIK3CG*, *PIK3R1*, *PTEN*, *RICTOR*, *RPTOR*, *RNF43*, *TSC1*, *TSC2*. **Results:** Data was available in 63 pts (N = 4 stage I; N = 41 stage II; N = 18 stage III). There was no significant association between stage and subtype. 67 PI3K pathway variants were identified in 39 (62%) tumors. The incidence of mutated tumors and their differential response to NACT defined by residual cancer burden (RCB) in each subtype is presented in the table. There was no significant association between subtype and incidence of mutated tumors (P = 0.10). However, there were more mutated tumors in the LAR compared to non-LAR subsets (100% vs 57%); the majority of LAR tumors (5/7) had a variant in the *PIK3R1* gene. The incidence of mutated tumors in the M vs non-M subsets was similar (57% vs 63%). Pts with mutated tumors did not have a significantly worse response to NACT overall (46% vs 54%; P = 0.61) or within the M subset (25% vs 50%; P = 0.58). **Conclusions:** In this cohort of TNBC pts, the incidence of PI3K pathway aberrations was higher than previously reported, likely due to the comprehensive genes evaluated. There was no significant difference in incidence of aberrations across subtypes, and PI3K pathway aberration was not associated with altered response to NACT. Larger cohorts are needed to clarify the impact of PI3K pathway aberrations in TNBC subtypes.

Subtype	N	PI3K Mutated Tumors N (%)	RCB 0-I if PI3K Wild Type N (%)	RCB 0-I if PI3K Mutated N (%)
All	63	39 (62)	13 (54)	18 (46)
BL	20	11 (55)	5 (56)	6 (55)
M	14	8 (57)	3 (50)	2 (25)
IM	12	9 (75)	2 (67)	6 (67)
LAR	7	7 (100)	-	2 (29)
UNS	10	4 (41)	3 (50)	2 (50)

589 Poster Session (Board #81), Sat, 8:00 AM-11:30 AM

Ki67 to predict RCB0/I after neoadjuvant chemotherapy and endocrine therapy in HER2- breast cancer patients from ABCSG 34. *First Author: Christian F. Singer, Department of Gynecology and Obstetrics, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*

Background: Achievement of complete or near complete pCR (RCB0/I) after neoadjuvant systemic therapy is associated with improved DFS. We have evaluated the utility of Ki67 measurements in predicting RCB0/I in women with early breast cancer who were treated with neoadjuvant endocrine (NET) therapy or chemotherapy (NACT). **Methods:** This translational study was carried out within a prospectively randomized phase-II trial in 400 patients with HER2- eBC (ABCSG 34): 89 postmenopausal women with ER+++, or ER++ and Ki67 $< 14\%$, and G1/2/X tumors received 24 weeks of letrozole (NET). 311 postmenopausal patients with ER-, or ER+ and Ki67 $\geq 14\%$, or with G3 tumors, or premenopausal patients, received 8 cycles of anthracycline/taxane-based NACT. Ki67 was measured in the whole specimen area at baseline, after 12 weeks of therapy, and at surgery after 24 weeks, and was correlated with Residual Cancer Burden (RCB) and pCR. **Results:** Median Ki67 profoundly decreased after 12 weeks of NET and NACT, and there was no significant further decrease at 24 weeks. NACT-treated patients with a $\geq 30\%$ decrease at week 12 were more likely to achieve RCB0/I (OR 2.778 [95%CI 1.25-6.19], $p = 0.0124$), while no such effect was found in NET-treated patients. NACT-treated tumors with baseline Ki67$\geq 50\%$ were markedly more likely (OR 3.568 [95%CI 2.08-6.11], $p < 0.0001$) to achieve RCB0/I and pCR (OR 5.797 [2.88-11.66], $p < 0.0001$) when compared to tumors with Ki67 $< 50\%$. Conversely, NET-treated patients with baseline Ki67$\geq 20\%$ were less likely (OR of 0.268 [95%CI 0.08-0.85], $p < 0.0247$) to achieve RCB0/I. 76/153 patients with Ki67$\geq 50\%$ vs 26/120 with Ki67 $< 50\%$ experienced RCB0/I in response to NACT (NPV: 78.3%; PPV: 49.7%). 5/47 patients with Ki67$\geq 20\%$ vs 12/39 with Ki67 $< 20\%$ experienced RCB0/I in response to NET (NPV: 89.4%; PPV: 30.8%). **Conclusions:** Maximal Ki67 suppression was achieved after 12 weeks of neoadjuvant therapy, and a decrease of $\geq 30\%$ under NACT predicted excellent response (RCB 0/1). Baseline Ki67 values were *per se* already highly predictive in a clinically meaningful manner: NACT-treated tumors with a Ki67 of $\geq 50\%$ had a 1:1 chance to achieve RCB0/I, while NET-treated tumors with a Ki67 of $\geq 20\%$ achieved RCB0/I in only 1 out of 9 cases. Clinical trial information: 2011-004822-85.

590 Poster Session (Board #82), Sat, 8:00 AM-11:30 AM

Pathological complete response in basal subtype tumors to predict improved distant metastasis free survival in the NBRST trial. *First Author: Pat W. Whitworth, Nashville Breast Center, Nashville, TN*

Background: In the multi-institutional NBRST study (NCT01479101), conducted from June 2011 to December 2014, 20% of ER+/HER2- patients were classified as Basal subtype by the 80-gene functional subtype signature (80-GS). 3-year event-driven follow-up (FU) is now available. **Methods:** The 70-gene risk of recurrence signature (70-GS) and 80-GS results were combined to classify patients (Pts) into four molecular subtypes: Basal, HER2, Luminal-B (high risk Luminal), and Luminal-A (low risk Luminal). The rate of pathological complete response (pCR) was previously assessed following neoadjuvant therapy. Here we evaluated FU for these Pts to determine if pCR was predictive of positive outcome using distant metastasis free interval (DMFI) as an endpoint. **Results:** Of 706 NBRST Pts currently reporting FU, 35% were Basal, 16% HER2, 34% Luminal-B, and 15% Luminal-A. Overall 26% of Pts had a pCR, with notable differences by subtype: 34% in Basal, 67% in HER2, 9% in Luminal-B, and 5% pCR in Luminal-A patients. FU from diagnosis ranged from 0.3-70.8 months (median 34 months). Sixty-nine percent of Pts received some adjuvant therapy: 51% endocrine therapy (AET), 10% chemotherapy (ACT), and 16% received adjuvant targeted therapy (53% with AET/ACT). There were 94 DMFI events at last FU: 81 in Pts who did not have a pCR, 13 in Pts who did have a pCR. 80-GS basal subtype Pts who achieved a pCR exhibited better 3-yr probability of DMFI, compared to those who did not. **Conclusions:** NBRST's event-driven FU supports the I-SPY2 TRIAL's findings that a pCR predicts better distant metastasis free outcomes. The results in this population further show that 80-GS basal subtype patients with pCR have substantially better outcome at 3 years, compared to those who do not have pCR. 70-GS low risk Luminal Pts showed minimal impact with neoadjuvant chemotherapy. Clinical trial information: NCT01479101.

	pCR		no pCR		Hazard Ratio	
Subtype	events/total Pts	%DMFI at 3yrs	events/total Pts	%DMFI at 3yrs	Ratio (95%CI)	P value
Basal	7/83	94% (88-100%)	52/163	68% (60-76%)	0.13 (0.048-0.36)	< 0.001
HER2	3/77	96% (91-100%)	4/38	91% (81-100%)	0.37 (0.08-1.68)	0.20
Luminal-B	3/21	95% (87-100%)	22/216	91% (86-95%)	1.17 (0.35 -3.94)	0.81
Luminal-A	0/5	100%	3/103	96% (92-100%)	0 (NA)	0.61

591 Poster Session (Board #83), Sat, 8:00 AM-11:30 AM

Pharmacokinetics of CT-P6 and reference trastuzumab by clinical factors in patients with HER2 positive early-stage breast cancer (EBC). *First Author: Justin Stebbing, NIHR Research Professor, Imperial College, London, United Kingdom*

Background: CT-P6 is a proposed biosimilar to reference trastuzumab, Herceptin (H) (Genentech, S San Francisco, CA, USA). A randomized phase III trial showed efficacy equivalence and comparable pharmacokinetics (PK) and safety between CT-P6 and H (NCT02162667). Clinical factors have been shown to affect trastuzumab parameters. We compared known factors that may affect the PK of CT-P6 and H in HER2 positive EBC patients. **Methods:** A total of 549 patients were randomized to receive CT-P6 (n = 271) or H (n = 278) with combination chemotherapy in the neoadjuvant setting. CT-P6 or H was administered at 8 mg/kg (Cycle 1 only) followed by 6mg/kg every 3 weeks. The primary endpoint was pathological complete response (pCR). Key PK parameters for CT-P6 and H were assessed during the neoadjuvant period in terms of C_{trough} and C_{max}. C_{trough} at steady state (predose of cycle 8, $C_{troughSS}$) was analyzed by age, race, weight, and pathological response. **Results:** The serum concentration gradually increased and steady state was reached at cycle 7 (predose of cycle 8). There was no statistically significant difference between CT-P6 and H in any of the subgroups analyzed. Clinical trial information: NCT02162667. **Conclusions:** The serum $C_{troughSS}$ level of trastuzumab was comparable between CT-P6 and H groups in all subgroups analyzed. These data support the PK similarity between CT-P6 and H independently of age, race, weight or pCR assessment method.

Statistical analysis of geometric mean $C_{troughSS}$ (μg/ml) for trastuzumab (ANOVA) by subgroup.

Subgroup	CT-P6	H	Ratio of Geometric Means (95% CI)
Age			
< 65	54.33	55.35	98.16 (90.86,106.05)
≥65	58.72	59.36	98.92 (81.44,120.15)
Race			
Asian	47.28	48.39	97.70 (79.87,119.51)
Non-Asian	56.79	57.55	98.67 (91.58,106.31)
Weight			
< 70kg	52.70	51.28	102.78 (92.67,114.00)
≥70kg	57.41	60.92	94.25 (85.58,103.80)
Total Pathological Response (breast and lymph nodes)			
pCR (ypT0/is ypN0)	54.30	57.57	94.32 (85.45,104.11)
No pCR	55.23	54.33	101.66 (91.64,112.76)
Breast Pathological Response			
pCR (ypT0/is)	55.00	56.40	97.51 (88.57,107.36)
No pCR	54.63	55.31	98.76 (88.64,110.03)
Breast Pathological Response (GBG criteria)			
pCR (ypT0 ypN0)	54.52	58.58	93.08 (83.35,103.95)
No pCR	54.99	54.16	101.53 (92.40,111.56)

592 Poster Session (Board #84), Sat, 8:00 AM-11:30 AM

Dynamic genomic instability modulation by neoadjuvant therapy in early breast cancer (GEICAM/2006-03_2006-14). *First Author: Emilio Alba, Hospital Clínico Universitario Virgen de la Victoria. GEICAM Spanish Breast Cancer Group., Malaga, Spain*

Background: Genomic instability (GI) drives tumor development, generates selective clonal competence and enhances cancer aggressiveness. Copy Number Alterations (CNAs) data from a cohort of pre- and post-treatment (ttm) breast cancer (BC) tumors from patients (pts) in neoadjuvant trials GEICAM/2006-03 (NCT00432172) and GEICAM/2006-14 (NCT00841828) were used to obtain a GI Index for each sample. We analyzed the variation of GI index induced by therapy and their associations with tumor phenotype. **Methods:** GEICAM/2006-03 HER2-negative pts were selectively treated according to clinical subtypes: triple negative (TN) pts were treated with standard taxane/anthracycline-based chemotherapy (TA-CT) +/- carboplatin, while luminal patients were randomized to TA-CT vs. hormonotherapy; GEICAM/2006-14 HER2+ pts received TA-CT plus anti-HER2 therapy. Shallow-whole genome Illumina sequencing DNA data from 204 paraffin-BC (100 pre- and 104 post-ttm tumors) were segmented to obtain CNAs. The area under the segmentation curve (sum of segmented mean normalized by CNAs number) was calculated for each sample as index of GI. Differences between GI indexes in pre- and post-ttm samples were analyzed using Wilcoxon test. **Results:** A significant reduction in GI index was observed after ttm compared to pre-therapy samples (p = 5.1e-07), which was confirmed in a subset of pre/post-therapy paired tumors (N = 39, p = 0.0034). Luminal (61%) tumors revealed a significant decrease in GI index, both in overall population (median GI index: 0.141 pre-ttm vs 0.068 post-ttm, p = 1e-09) and in paired samples (0.126 vs 0.072, p = 0.00013). Similarly, HER2+ (9%) tumors showed a trend towards GI reduction (0.143 vs 0.079, p = 0.085). In contrast, TN (30%) cases presented an increasing trend in GI index in the residual tumor (0.132 pre- vs 0.17 post-ttm, p = 0.68). **Conclusions:** Our data suggest that GI could be a direct target of neoadjuvant therapy in BC. Treatment seems selectively eliminate tumor cells with higher genomic aberrations in luminal and HER2+ BC, resulting in a reduction of GI index in the residuals tumors. In contrast, according to previous publications, we suggest that GI could be a mechanism of adaptative CT resistance in TNBC. Clinical trial information: GEICAM/2006-03 NCT00432172. GEICAM/2006-14 NCT00841828.

593 Poster Session (Board #85), Sat, 8:00 AM-11:30 AM

Impact of metaplastic histology (MpBC) in triple-negative breast cancer (TNBC) patients (pts) receiving neoadjuvant systemic therapy (NAST). *First Author: Clinton Yam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MpBCs are aggressive cancers, often TNBC, and considered chemo-resistant, such that some providers avoid NAST. Using data from an IRB approved prospective trial, we compared characteristics and outcomes between MpBC and non-metaplastic (non-MpBC) TNBC pts receiving NAST. **Methods:** Per protocol, pts began a planned 4 cycles of Adriamycin-based chemo (AC). Volumetric change by ultrasound (vUS) was performed after 2 (optional) and 4 cycles of AC and evaluated as a predictor of response in MpBC pts. Pts with chemo-insensitive disease during/after AC were enrolled in targeted therapy trials (TT) as the 2nd phase of NAST. Sensitive disease received taxane-based therapy (T). Residual Cancer Burden (RCB) was assessed after surgery. Differences between MpBC and non-MpBC were analyzed by Fisher's exact, Wilcoxon rank sum and Student's t tests as appropriate. **Results:** 170 pts (21 MpBC, 149 non-MpBC) were evaluable for RCB including 2 pt deaths during AC (counted as RCB II-III). Despite lower rates of nodal positivity, [p = 0.002] and lower grade [p = 0.009], MpBC pts had higher rates of progression (PD) on AC (24 vs 8%; p = 0.041) and RCB II-III status after NAST [67 vs 42%; p = 0.036] (Table). Of the MpBCs with RCB 0-I (n = 7, 33%), 6 received AC-T and 1 had TT. 14 MpBC pts underwent vUS after 2 cycles of AC. Among these 14 pts, 21% had PD on vUS after 2 cycles of AC. Notably, pts with ≥60% volumetric reduction in the primary tumor (n = 4) had significantly higher RCB 0-I rates than those with < 60% (n = 10) [100 vs 10%, p = 0.005]. **Conclusions:** This is the largest prospective series of NAST outcomes in MpBC. A clinically acceptable RCB 0-I rate of 33% and the opportunity to participate in neoadjuvant and adjuvant trials supports the use of NAST in MpBC. MpBC pts should be monitored closely for PD while receiving NAST.

	MpBC (n = 21)	Non-MpBC (n = 149)	p-value
Median age (range)	56 (34-74)	54 (27-78)	0.64
Mean tumor size - cm (SD)	4.2 (3.4)	3.4 (1.9)	0.08
		n (%)	
Node			
Neg	18 (86)	74 (50)	**0.002**
Pos	3 (14)	75 (50)	
Grade			
1	1 (5)	0	**0.009**
2	5 (24)	14 (9)	
3	15 (71)	135 (91)	
Progression on AC			
No	16 (76)	137 (92)	**0.041**
Yes	5 (24)	12 (8)	
Targeted Trial			
No	13 (62)	115 (77)	0.17
Yes	8 (38)	34 (23)	
Outcome			
RCB 0-I	7 (33)	87 (58)	**0.036**
RCB II-III	14 (67)	62 (42)	

594 **Poster Session (Board #86), Sat, 8:00 AM-11:30 AM**

Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic markers in patients with HER2pos operable breast cancer treated with neo-adjuvant trastuzumab-containing chemotherapy. *First Author: Deirdre Kelly, Department of Medical Oncology, St Vincents University Hospital Dublin Ireland, Cork, Ireland*

Background: Inflammation plays an important role in cancer development and proliferation.Host systemic markers of inflammation including the neutrophil-to-lymphocyte ratio (NLR) have been associated with a poor prognosis in solid tumours. The objectives of our study were to evaluate NLR and platelets-to-lymphocytes ratio (PLR) in patients (pts) with operable HER2pos breast cancer (BrCa) treated with neo-adjuvant trastuzumab (T)-containing chemotherapy (NACT) and to correlate NLR and PLR with Disease Free Survival (DFS) and Overall Survival (OS). **Methods:** This was a retrospective, single-center analysis of a prospectively accrued Institutional database (The One-Thousand HER2pos Patients project) of non-metastatic operable HER2pos BrCa pts who received NACT. Pts with confirmed supraclavicular/internal mammary nodes were excluded. NLR and PLR were calculated at baseline prior to HER2 therapy (Tx) initiation. All patients underwent curative surgery (Sx) following T-containing NACT. **Results:** 156 female patients were included. Pts characteristics: median age 55.6(27-78) yrs, median time from diagnosis to initiation of HER2 Tx 4(1-18)weeks, ER positive 93(60%), cytology-proven positive lymph nodes at diagnosis 41 (26%). NACT was: TCH 116(74%), Docetaxel/Cyclophosphamide/T or single-agent taxane/T 20(13%), AC-TH/FEC-TH 7(4%), other regimens 13 (8%). Median follow up is 4.3(11-1)yrs. Pts with NLR $<$ 2.5 at baseline had significantly better PFS (HR 0.29 p = 0.03)and OS (HR 0.14 p = 0.07) compared to pts with NLR $>$ 2.5. Baseline PLR $<$ 150 was associated with superior OS (HR 0.15 p = 0.08) compared to PLR $>$ 150. No statistically significant association was observed between PLR and PFS. (HR 0.35 p = 0.07) **Conclusions:** This study represents one of the largest real-world datasets looking at NLR and PLR as prognostic markers in NACT for HER2pos BrCa. Baseline NLR $>$ 2.5 and PLR $>$ 150 are inexpensive and readily available prognostic markers of adverse outcome and may play a clinically significant role in refinement of risk estimates within disease stages and subgroups and treatment de-escalation.

595 **Poster Session (Board #87), Sat, 8:00 AM-11:30 AM**

Platinum-based neoadjuvant chemotherapy (NACT) in triple-negative breast cancer (TNBC): A systematic review and meta-analysis of randomized controlled trials (RCTs). *First Author: Francesca Poggio, Department of Medical Oncology, Institut Jules Bordet, L'Université Libre de Bruxelles (U.L.B.), Bruxelles, Belgium*

Background: The role of platinum-based NACT in TNBC is highly controversial and its use is not endorsed by current guidelines in unselected TNBC patients. Our meta-analysis aimed to better evaluate the activity, efficacy and safety of platinum-based NACT in TNBC. **Methods:** A systematic search of MEDLINE, Web of Knowledge and conference proceedings up to October 31th 2017 was performed to identify RCTs evaluating platinum-based vs. platinum-free NACT in TNBC patients. Summary risk estimates (odds ratio [OR] and hazard ratio [HR] with 95% confidence intervals [CI]) were calculated for the effect of platinum-based vs. platinum-free NACT in terms of pathological complete response (pCR: ypT0/is pN0), event-free survival (EFS), overall survival (OS), and grade 3-4 adverse events (AEs: neutropenia, anemia, thrombocytopenia and neuropathy). Pooled analyses were performed using the fixed- and random-effect models. This study is registered in the PROSPERO website (CRD42018080042). **Results:** Nine RCTs (n = 2,107 patients) were included. Overall, platinum-based NACT significantly increased pCR rates from 35.7% to 52.1% (OR 1.99, 95% CI 1.51-2.62). The result did not change and remained significant when considering only the 7 RCTs using anthracycline-and taxane-based NACT in both arms (54.1% vs. 38.7%; OR 1.88, 95% CI 1.34-2.63) or the 3 RCTs using the same standard regimen of weekly paclitaxel ($\pm$ platinum) followed by anthracycline and cyclophosphamide in both arms (54.9% vs. 33.3%; OR 2.53, 95% CI 1.37-4.66). Two RCTs (n = 748) reported on survival outcomes. A non-significant trend for improved EFS favoring platinum-based NACT (HR 0.72, 95% CI 0.49-1.06) was observed, with no difference in OS (HR 0.86, 95% CI 0.46-1.63). Platinum-based NACT was associated with a significantly higher risk of grade 3-4 hematological AEs and no increased risk of grade 3-4 neuropathy. **Conclusions:** Platinum-based NACT significantly improved pCR with a trend towards improved EFS at the cost of higher risk of hematological toxicities in TNBC. Our findings question the current recommendation to limit the use of platinum-based NACT only to *BRCA*-mutated breast cancer patients.

TPS596 **Poster Session (Board #88a), Sat, 8:00 AM-11:30 AM**

POSITIVE (IBCSG 48-14/BIG 8-13/A221405): Evaluating outcomes after interrupting endocrine therapy (ET) for women with endocrine responsive (ER+) early breast cancer (BC) who desire pregnancy. *First Author: Ann H. Partridge, Dana-Farber Cancer Institute, Boston, MA*

Background: Retrospective evidence suggests that pregnancy after BC does not negatively impact disease outcomes in pts with ER+ BC and is safe for the offspring. Young BC pts are often diagnosed before completing family planning, and cannot wait 5-10 yrs to complete ET before attempting pregnancy. Thus, prospectively evaluating the safety of temporary interruption of ET to allow conception is an unmet, patient-oriented, medical need. **Methods:** Young pts with ER+ early BC who desire pregnancy interrupt ET for approximately 2 yrs to attempt pregnancy [treatment wash-out (3 mos), and, ideally, conception (~3-6 mos), delivery (~9 mos), breast feeding if feasible (~6 mos)]. Pts are advised to resume ET as soon as child-bearing is completed to finish 5-10 yrs ET. Major eligibility requirements: pt wishes to become pregnant; histologically-proven stage I-III ER+ BC; age $\geq$ 18 and $\leq$ 42 yrs; prior adjuvant ET for $\geq$18 mos but $\leq$30 mos; premenopausal status at BC diagnosis. With 500 pts enrolled and followed for a median of 3 yrs, the statistical design is based on the 95% CI for the 3 yr BC recurrence rate; interim monitoring assumes a 2% BC recurrence risk/yr with continuous ET and high chance to stop early if the BC risk exceeds 4%/yr with ET interruption. Translational research will evaluate aspects related to fertility, pregnancy and BC biology. The Psycho-oncological Companion Study (POCS) explores psychological distress, fertility concerns and decisional conflicts (mandatory in the US and open to interested centers elsewhere), with a target accrual of 200. More than 170 participating centers in 20 countries: USA/Alliance, Canada/CCTG, Switzerland/SAKK, Italy, Belgium, Spain/SOLTI/GEICAM, Slovenia, Japan/JBCRG, Norway/NBCG, Netherlands/BOOG, Ireland/CTI, Portugal/SOLTI, Australia, Israel, Greece/HORG, Hungary, South Korea, Serbia, Austria/ABCSG and France. Eligible sites can open POSITIVE through NCTN (Alliance) or IBCSG, and referral to participating centers of eligible pts on ET who are interested in having a pregnancy after BC is strongly encouraged. Current Accrual (13 Feb 2018): 205 main study; 114 POCS. Clinical trial information: NCT02308085.

TPS597 **Poster Session (Board #88b), Sat, 8:00 AM-11:30 AM**

ABC trial (A011502): Randomized phase III double blinded placebo controlled trial of aspirin as adjuvant therapy for breast cancer. *First Author: Wendy Y. Chen, Dana-Farber Cancer Institute, Boston, MA*

Background: In-vitro and in-vivo evidence suggest that aspirin may have an anti-tumor effect. Epidemiologic studies have reported improved breast cancer survival among regular aspirin users compared to non-users. Pooled data from randomized trials of aspirin for cardiovascular disease have also reported a decreased risk of metastatic cancer with aspirin use. However, the exact benefits and risks for breast cancer survivors need to be confirmed in a randomized trial. Even if the clinical effect were modest, the global impact would be substantial since aspirin is inexpensive and widely available. **Methods:** Primary objective is to compare the effect of 300 mg daily aspirin vs placebo upon invasive disease-free survival (iDFS) in high risk HER2 negative breast cancer patients. Secondary objectives include effects on overall survival, cardiovascular disease, toxicity, and adherence. A biospecimen repository will be created for correlative analyses including tumor collection at baseline and blood and urine samples and questionnaires assessing lifestyle factors associated with inflammation (pain, sleep, stress, depression) at baseline and 2 years. Study design: Subjects will be randomized 1:1 to aspirin 300 mg vs placebo daily for 5 years in a double-blind fashion. Stratification factors include hormone receptor (HR) status (positive vs negative), body mass index ($<$ or $\geq$ 30 kg/m2), and stage. Subjects will be followed every 6 months while on study drug, then annually for 10 years. Accrual goal is 2936 patients to reach 381 iDFS events with 80% power to detect HR 0.75 assuming 5-year iDFS on placebo of 77%. Eligibility: Patients aged 18-70 diagnosed with a primary invasive HER2 negative breast cancer in the past year. If HR positive, tumors need to be node positive. If HR negative, tumor can be node positive or node negative with tumor size $>$ 2 cm. Patients who currently use any anticoagulant or those with a prior history of GI bleeding, atrial fibrillation, or myocardial infarction will be excluded. Regular aspirin users need to stop 30 days prior to enrollment. Study is actively enrolling. Updated accrual numbers will be given at the time of presentation. Clinical trial information: NCT02927249.

TPS598 Poster Session (Board #89a), Sat, 8:00 AM-11:30 AM

The Breast Cancer Weight Loss (BWEL) trial: Randomized phase III trial evaluating the role of weight loss in adjuvant treatment of overweight and obese women with early-stage breast cancer (Alliance A011401). *First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA*

Background: Obesity is a growing health problem in the Unites States and around the world. Excess body weight has been linked to both an increased risk of developing breast cancer and poor prognosis in women diagnosed with early stage disease. A recent meta-analysis of 82 studies demonstrated that risk of breast cancer mortality was increased by 35% in women who were obese at the time of breast cancer diagnosis compared to women who were of normal weight. The Breast cancer Weight Loss (BWEL) study will evaluate the effect of weight loss after breast cancer diagnosis on risk of cancer recurrence. **Methods:** BWEL is a Phase III randomized trial evaluating the impact of a telephone-based weight loss intervention vs control on invasive disease-free survival (iDFS) in 3136 overweight and obese women with Stage II-III breast cancer. Eligibility criteria include diagnosis of hormone receptor positive or triple negative breast cancer within the preceding 12 months, body mass index of $\geq$27kg/m^2, and completion of surgery, chemotherapy, and radiation (if administered). Participants are randomized to a 2-year telephone- and mail-based weight loss intervention, adapted from the Diabetes Prevention Program, plus a health education program or to a health education alone control group. The study has 85% power, using a one-sided Type I error rate of 0.025, to detect a hazard ratio of 0.80 between groups. This equates to a 4.1% absolute reduction in iDFS events in the intervention group vs. controls. Secondary aims will evaluate the impact of the weight loss intervention upon overall survival, weight and body composition, and patient-reported outcomes. Fasting blood is collected serially over time, and tissue samples of malignant and benign breast tissue are collected at baseline to provide insight into the biologic mechanisms linking obesity and breast cancer. BWEL opened in September 2016. To date, 1015 patients have been randomized and more than 1100 sites in the US and Canada have activated the trial. Support: U10CA180821, U10CA180882, U10CA180820, U10CA180868, U10CA077202. Clinical trial information: NCT02750826.

TPS599 Poster Session (Board #89b), Sat, 8:00 AM-11:30 AM

Comparison of operative to monitoring and endocrine therapy for low-risk DCIS (COMET study). *First Author: Thomas Lynch, Duke University, Durham, NC*

Background: Approximately 50,000 women in the U.S. are diagnosed with ductal carcinoma *in situ* (DCIS) each year. Without treatment, it is estimated that only 20-30% of DCIS will lead to invasive breast cancer. However, over 97% of women are currently treated with guideline-concordant care (GCC) including surgery and/or radiation. An alternative to GCC is active surveillance (AS) which focuses on early detection of invasion rather than "treatment" of DCIS. The COMET study will compare risks and benefits of AS versus GCC in the setting of a Phase III pragmatic prospective randomized clinical trial. The study is funded by the Patient-Centered Outcomes Research Institute (PCORI). **Methods:** The primary objective is to assess whether the 2-, 5-, and 7-year ipsilateral invasive breast cancer rate for AS is non-inferior to that for GCC. Secondary objectives include determining whether AS is non-inferior to GCC for 2-year mastectomy rate; breast conservation rate; contralateral breast cancer rate; overall and breast cancer-specific survival. Patient reported outcomes (PROs) will enable comparison of health-related quality of life and psychosocial outcomes between GCC and AS groups at baseline, 6-months and years 1-5. Eligibility criteria include: age $>$ 40 at diagnosis; pathologic confirmation of grade I/II DCIS without invasion by two pathologists; ER and/or PR $\geq$ 10%; HER2-negative (0, 1+, or 2+ if testing performed). Following randomization to either GCC or AS, patients who decline participation will still be eligible to participate in the non-randomized cohort of the study. The planned accrual goal is 1200 randomized patients across 100 Alliance for Clinical Trials in Oncology sites, with a projected drop-out rate of 30%, for a total of approximately 900 patients treated according to randomized arm, analyzed in an intent-to-treat analysis. Sample size of n = 446 per group will have 80% power to detect the specified non-inferiority margin. The COMET trial opened in the U.S. in June 2017. To date, 50 sites have activated the trial. Comparable studies are taking place in UK (LORIS Trial) and Europe (EORTC LORD Trial); data from all three trials will be analyzed in a planned combined analysis. Clinical trial information: NCT02926911.

TPS600 Poster Session (Board #90a), Sat, 8:00 AM-11:30 AM

POSNOC: Positive Sentinel Node—Adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy. *First Author: Amit Goyal, Royal Derby Hospital, Derby, United Kingdom*

Background: Role of additional axillary treatment (AxT) (axillary lymph node dissection (ALND) or axillary radiotherapy (ART)) in women with macrometastases and undergoing systemic therapy remains unclear. Z11 included both micro and macrometastases (around 40% micrometastases) and showed that ALND may be omitted in women with $\leq$2 positive nodes undergoing breast conserving surgery (BCS) and receiving whole breast RT. Paradoxically, MA20, demonstrated improved DFS following the addition of regional RT. 51.8% (949/1832) had 1 or 2 positive nodes. 98.9% (1812/1832) had T1/T2 tumors. A post Z11 survey shows that most US oncologists treat the undissected axilla in women with macrometastases with ART rather than omitting AxT. Therefore, a confirmatory study is needed to clarify the role of additional AxT in women with $\leq$2 macrometastases undergoing BCS and other subgroups that were not included in Z11 e.g. mastectomy, extranodal invasion and sentinel node biopsy (SNB) before NACT. **Methods:** Primary objective is to assess whether for women with $\leq$2 macrometastases at SNB, systemic therapy alone is non inferior to systemic therapy plus AxT in terms of axillary recurrence at 5 years. Secondary objectives are arm morbidity assessed by LBCQ and QuickDASH questionnaires; QoL assessed by FACT B+4 questionnaire; anxiety assessed by STAI; locoregional recurrence; distant metastasis; time to axillary recurrence; axillary recurrence free survival; DFS; OS; contralateral breast cancer; non breast malignancy; economic evaluation. Eligibility criteria are: $\geq$18 y, uni or multifocal invasive cancer, T1/T2, 1 or 2 macrometastases, with or without extranodal invasion. Target sample size is 1900 with a projected drop out and non compliance with treatment allocation rate of 10%. Primary analysis will be per protocol. Following pre specified subgroup analyses shall be performed: number of macrometastases, age (50, $\geq$50), type of breast surgery, ER status, tumour grade (1 or 2, 3), SN assessment technique (OSNA, non OSNA), extranodal invasion. POSNOC opened to recruitment in July 2014. To date 960 women have been recruited at 82 sites in the UK and 18 sites in Australia and New Zealand. Clinical trial information: NCT02401685.

TPS601 Poster Session (Board #90b), Sat, 8:00 AM-11:30 AM

NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence-free interval (IBCR-FI) in patients (pts) with positive axillary (PAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC). *First Author: Eleftherios P. Mamounas, NSABP/NRG Oncology, and Orlando Health UF Cancer Center, Orlando, FL*

Background: This phase III post-NC trial evaluates if CWRNRT post-Mx or whole breast irradiation (WBI) with RNRT after BCS significantly reduces the IBCR-FI rate in pts with PAx nodes that are negative after NC. Secondary aims are OS, LRR-FI, DR-FI, DFS-DCIS, second primary cancer, and comparison of RT effect on cosmesis in reconstructed Mx pts. Correlative science examines RT effect by tumor subtype, molecular outcome predictors for residual disease pts, and predictors for the degree of reduction in locoregional recurrence. **Methods:** Clinical T1-3, N1 IBC PAx nodes (FNA or core needle biopsy) pts complete $\geq$8 weeks of NC (anthracycline and/or taxane). HER2+ pts receive anti-HER2 therapy. Following NC, BCS or Mx, sentinel node biopsy ($\geq$2 nodes) and/or Ax dissection with histologically negative nodes is performed. ER/PR and HER-2neu status before NC is required. Pts receive appropriate adjuvant systemic therapy. Radiation credentialing with a facility questionnaire/case benchmark is required. Random assignment for Mx pts is to no CWRNRT or CWRNRT and for BCS pts to WBI or WBI+RNRT. Statistics: 1636 pts to be enrolled over 5 yrs (definitive analysis at 7.5 yrs). Study is powered at 80% to test that RT reduces the annual hazard rate of events for IBCR-FI by 35% for an absolute risk reduction of 4.6% (5-yr cumulative rate). Intent-to-treat analysis with 3 interim analyses (43, 86, and 129 events) and a 4th/final analysis at 172 events. Pt-reported outcomes focusing on RT effect will be provided by 736 pts before random assignment and at 3, 6, 12, and 24 mos. Accrual as of 1-23-18 is 848 (51.83%). Contacts: Protocol: CTSU member website https://www.ctsu.org. Questions: NRG Oncology Pgh Clin Coord Dpt: 1-800-477-7227 or ccd@nsabp.org. Pt entry: OPEN at https://open.ctsu.org or the OPEN tab on CTSU member website. Support: U10 CA-2166; -180868, -180822; 189867; Elekta Clinical trial information: NCT01872975.

TPS602 **Poster Session (Board #91a), Sat, 8:00 AM-11:30 AM**

KEYNOTE-522: Phase III study of pembrolizumab (pembro) + chemotherapy (chemo) vs placebo + chemo as neoadjuvant therapy followed by pembro vs placebo as adjuvant therapy for triple-negative breast cancer (TNBC). *First Author: Peter Schmid, Barts Cancer Institute, Centre for Experimental Cancer Medicine, London, United Kingdom*

Background: Recently presented data from the I-SPY 2 trial showed that pembrolizumab, a humanized, anti–PD-1 monoclonal antibody, significantly increased the pathologic complete response (pCR) rate in early-stage TNBC, when combined with neoadjuvant chemotherapy (Nanda et al. ASCO 2017. Abs 506). KEYNOTE-522 (NCT03036488) is a phase III study of pembro+ chemo vs placebo+chemo as neoadjuvant treatment, followed by pembro vs placebo as adjuvant treatment in pts with TNBC. **Methods:** Approximately 855 pts with TNBC, defined as combined primary tumor (T) and regional lymph node (N) staging per AJCC (investigator-assessed: T1c N1-2, T2-4 N0-2), will be randomly assigned to 1 of 2 arms. Stratification will be by tumor nodal status (positive vs negative), size (T1/T2 vs T3/T4), and carboplatin regimen choice (Q3W vs QW). In arm 1, pts will receive 4 cycles of pembro 200 mg Q3W+paclitaxel (80 mg/m^2 QW on d 1, 8, 15)+carboplatin (AUC 5 Q3W on d 1 or AUC 1.5 QW on d 1, 8, 15) and then 4 cycles of pembro+[doxorubicin (60 mg/m^2 Q3W on d 1) or epirubicin (90 mg/m^2 Q3W on d1)]+cyclophosphamide (600 mg/m^2 Q3W on d 1) as neoadjuvant therapy. In arm 2, placebo will replace pembro. Definitive surgery will be 3-6 wk after the last cycle, then pts will receive 9 cycles of pembro (200 mg Q3W) or placebo as adjuvant therapy. All cycles = 21d; treatment is up to 17 cycles or until disease progression/unacceptable toxicity. Primary end points are pCR rate using ypT0/Tis ypN0 and EFS. Secondary end points include safety, OS, and pCR rate by ypT0 ypN0, and ypT0/Tis in all pts; and OS, EFS, and pCR rate by ypT0/Tis ypN0, ypT0 ypN0, and ypT0/Tis in pts with PD-L1+ tumors (combined positive score, CPS$\geq$1). Eligible pts are aged $\geq$18 y with previously untreated, locally advanced, nonmetastatic TNBC. Pts with inflammatory breast cancer or bilateral or multifocal primary tumors are allowed. Adequate organ function and ECOG PS 0-1 are required. Pts with a history of invasive malignancy that was diagnosed and/or treated within the last 5 y are excluded. Clinical trial information: NCT03036488.

TPS603 **Poster Session (Board #91b), Sat, 8:00 AM-11:30 AM**

NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in Patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. *First Author: Charles E. Geyer, NSABP/ NRG Oncology and Virginia Commonwealth University Massey Cancer Center, Richmond, VA*

Background: TNBC is associated with higher percentages of pathological complete response (pCR) to neoadjuvant chemotherapy (NAC), and women with a pCR have a favorable prognosis. However, Liedtke (2008) and Loibl (2017) found that women with residual disease have a substantially higher risk of recurrence than women with other subtypes of breast cancer. Additionally, Adams (2017) and Schmid (2017) found that therapeutic blockade of PD-L1 binding by atezolizumab has resulted in relevant antitumor efficacy. **Methods:** Design This is a phase III, double blind, placebo-control trial evaluating neoadjuvant atezolizumab with NAC followed by adjuvant atezolizumab in TNBC. Pts are stratified by region (North America; Europe), tumor size (1.1-3.0cm; $>$ 3.0cm), AC/EC schedule (q2w; q3w), and nodal status (positive; negative), then randomized 1:1 to receive atezolizumab/placebo 1200 mg IV every 3 wks concurrently with both sequential regimens of weekly paclitaxel 80 mg/m2 IV for 12 doses with every 3-wk carboplatin AUC of 5 IV for 4 doses followed by AC/EC every 2-3 wks (per investigator discretion) for 4 cycles. Following surgery, pts resume atezolizumab/placebo 1200 mg IV every 3 wks as adjuvant therapy for 6 months. Radiotherapy based on local standards is co-administered with atezolizumab/placebo. Eligibility criteria Centrally-confirmed ER-neg, PR-neg, HER2-neg invasive breast cancer by ASCO/CAP guidelines. Primary tumor must be stage T2 or T3 if cN0 or cN1 with negative biopsy or T1c, T2, or T3 if cN1 with positive biopsy or cN2 or cN3. LVEF $>$ 55% and no significant cardiac history. Statistical methods Co-primary endpoints are event-free survival (EFS) and pCR breast/nodes. Secondary endpoints include pCR breast, overall survival, distant disease-free survival, safety and toxicity. Trial is an academic collaboration between NSABP and GBG with support from Genentech/Roche. NCT03281954 Support: Genentech/Roche Clinical trial information: NCT03281954.

TPS604 **Poster Session (Board #92a), Sat, 8:00 AM-11:30 AM**

NRG Oncology BR005: Phase II trial assessing accuracy of tumor bed biopsies (Bx) in predicting pathologic response in patients (Pts) with clinical/radiological complete response (CR) after neoadjuvant chemotherapy (NCT) in order to explore the feasibility of breast-conserving treatment (BCT) without surgery. *First Author: Mark Basik, NRG Oncology, and The Jewish General Hospital, Montreal, QC, Canada*

Background: The increased use of neoadjuvant chemotherapy (NCT) has enabled higher rates of breast-conserving surgery (BCS) as well as provided prognostic information for women with breast cancer. High pathological complete response (pCR) rates question the requirement for surgery, with its attendant morbidity. In order to avoid surgery, the ability to predict pCR prior to it must be very high. Trimodality imaging alone is inadequate to predict pCR prior to surgery. We hypothesize that performing core needle biopsy (bx) of the tumor bed in addition to trimodality imaging in pts having had a clinical complete response (cCR) will increase the ability to predict pCR. Utilizing predetermined imaging response criteria of complete or near-complete response coupled with a stereotactic core needle bx of the tumor bed, BR-005 aims to determine the predictive value of imaging followed by tumor bed bx for pCR and demonstrate its reproducibility across a multi-institutional setting. **Methods:** 175 pts with operable focal or multifocal (T1-T3), stage II/IIIA invasive ductal carcinoma [all receptor subtypes]) will be entered. Pts must have completed a minimum of 8 wks of standard *neoadjuvant* chemotherapy and achieved a complete or near-complete radiologic tumor response on breast imaging with mammogram, ultrasound, and MRI, and undergo BCS. Following cCR and prior to surgery, pts will undergo a stereotactic-vacuum-assisted breast bx with clip placement. The primary endpoint is the proportion of pts with post-NCT neg image-directed bx who have a pCR. Residual cancer burden (RCB) scores and core bx pathology will be collected along with trimodality imaging data. Evaluation after 135 pts will allow for the possibility of early termination of the study. Results will provide the first step towards a paradigm change in the treatment of breast cancer, enabling a study to assess the criteria for successful avoidance of surgery in pts with high response rates to NCT. Accrual as of 1/19/2018: 13. Support U10CA180868, -180822, UG1CA189867 Clinical trial information: NCT03188393.

TPS605 **Poster Session (Board #92b), Sat, 8:00 AM-11:30 AM**

PARTNER: Randomised, phase II/III trial to evaluate the safety and efficacy of the addition of olaparib to platinum-based neoadjuvant chemotherapy in triple negative and/or germline BRCA mutated breast cancer patients. *First Author: Jean Abraham, University of Cambridge, Department of Oncology & NIHR Cambridge Biomedical Research Centre & Cambridge University Hospitals NHS Foundation Trust, Cambridge Breast Cancer Research Unit, Cambridge, United Kingdom*

Background: No specific targeted therapies are available for triple negative breast cancer (TNBC), an aggressive and diverse subgroup. The basal TNBC subgroup show some phenotypic and molecular similarities with germline BRCA mutated BC (gBRCA). In gBRCA patients, and potentially other homologous recombination deficiencies, these already compromised pathways may allow PARP inhibitors to work more effectively. PARTNER was designed to establish if the addition of olaparib to neoadjuvant platinum-based chemotherapy for basal TNBC and/or gBRCA BC is safe and improves efficacy (pathological complete response (pCR)). **Methods:** Trial design: 3-Stage open label randomised Phase II/III trial of neoadjuvant CP: Carboplatin AUC5 with weekly Paclitaxel 80mg/m2 +/- olaparib 150mgBD for 12 days x 4 cycles, followed by clinicians' choice of anthracycline regimen x 3 cycles. Basal-TNBC and / or gBRCAm patients are eligible for inclusion. Tumour infiltrating lymphocytes and basal profile are assessed at baseline. *Stage 1 and 2:* Patients are randomised (1:1:1) to CP: CP + olaparib from day (D) –2: or CP + olaparib from D 3. *Stage 3:* Patients are randomised (1:1) to either control arm or to the research arm selected in stage 2. Primary endpoints: *Stage 1* – Safety; *Stage 2* - Schedule selection criteria by pCR rate and completion rate of olaparib protocol treatment. 53 patients in each research arm will be evaluated within a "pick the winner" design. Null hypothesis of pCR $\leq$35% versus alternative hypothesis of pCR $\geq$55% will be tested with 90% power and 5% one sided significance level in each of the research arms. *Stage 3* - Efficacy: anticipated pCR ~45-55% for all trial patients and ~50-60% for gBRCA patients. The trial is powered to detect an absolute improvement of 15% (all patients) and 20% (gBRCA patients) by adding olaparib to chemotherapy (enriched design). Enrichment design is applied with overall significance level 0.05(α) = 0.025(αall) + 0.025 (αgBRCA) and 80% power. Current enrolment: 133 of planned 527 patients. *Stage 1* accrual is complete. *Stage 2* began in August 2017. 19 sites open and 12 more in active set-up. Clinical trial information: NCT03150576.

1000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): Results from MONALEESA-3. *First Author: Dennis J. Slamon, UCLA Medical Center, Santa Monica, CA*

Background: First-line RIB + letrozole significantly prolonged progression-free survival (PFS) in postmenopausal women with HR+, HER2– ABC. Here we report results from MONALEESA-3 (NCT02422615), a Phase 3 randomized, double-blind, placebo-controlled study of RIB + FUL in pts with HR+, HER2− ABC who received no or up to 1 line of prior endocrine therapy (ET) for ABC. **Methods:** Postmenopausal women with HR+, HER2– ABC were randomized 2:1 (stratified by presence of liver and/or lung metastases and prior ET) to RIB (600 mg/day; 3-weeks-on/1-week-off) + FUL (500 mg) or placebo (PBO) + FUL. Primary objective: investigator-assessed PFS. Secondary objectives included overall survival, overall response rate (ORR), clinical benefit rate (CBR), and safety. **Results:** 726 pts were enrolled. Baseline pt characteristics were balanced between arms. Median duration from randomization to data cut-off: 20.4 months. The primary objective was met: PFS was significantly improved in the RIB arm vs the PBO arm (hazard ratio: 0.593; 95% confidence interval [CI]: 0.480–0.732; $p = 4.10\times10^{-7}$); median PFS: 20.5 months; 95% CI: 18.5–23.5 vs 12.8 months; 95% CI: 10.9–16.3. Blinded independent review committee data supported primary efficacy results. Consistent PFS benefit was observed in pts with no (hazard ratio: 0.577; 95% CI: 0.415–0.802) and up to 1 line of prior ET for ABC (hazard ratio: 0.565; 95% CI: 0.428–0.744). In pts with measurable disease at baseline, ORR was 41% vs 29% (RIB vs PBO arm; p = 0.003); CBR was 69% vs 60% (p = 0.015). Common all-grade (G) adverse events (AEs; ≥30% of pts; RIB vs PBO arm) were neutropenia (70% vs 2%), nausea (45% vs 28%), and fatigue (31% vs 33%). In the RIB vs PBO arms, G3/4 neutropenia occurred in 47%/7% vs 0%/0% of pts, G3/4 increased ALT in 7%/2% vs < 1%/0%, and G3/4 increased AST in 5%/1% vs 1%/0%. Post-baseline QTcF > 480 ms (RIB vs PBO arm) occurred in 6% vs 3% of pts. **Conclusions:** RIB + FUL vs PBO + FUL significantly prolonged PFS and demonstrated a manageable safety profile in postmenopausal pts with HR+, HER2– ABC who received no or up to 1 line of prior ET for advanced disease. RIB + FUL may, therefore, be a treatment option for this pt population. Clinical trial information: NCT02422615.

1001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Genetic landscape of resistance to CDK4/6 inhibition in circulating tumor DNA (ctDNA) analysis of the PALOMA3 trial of palbociclib and fulvestrant versus placebo and fulvestrant. *First Author: Nicholas C. Turner, Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: CDK4/6 inhibition combined with endocrine therapy is now a standard of care for advanced estrogen receptor (ER) positive breast cancer. Mechanisms of resistance to CDK4/6 inhibitors have been described in pre-clinical models, although there is limited evidence from clinical samples. We investigated the mechanisms of resistance to CDK4/6 inhibitor in the PALOMA3 trial using ctDNA analysis. **Methods:** The PALOMA3 phase III trial randomized 521 patients with endocrine pre-treated disease to palbociclib and fulvestrant (P+F) versus placebo and fulvestrant (F). Using driver mutation targeted sequencing we conducted a longitudinal ctDNA analysis in 193 pairs of baseline and end of treatment (EOT) plasma samples, supplemented with exome ctDNA sequencing in 16 paired samples of high tumor purity from patients treated with P + F. **Results:** Paired ctDNA analysis was performed on P+F (n = 125) and F alone (n = 68), with the ctDNA cohort representative of the overall study. *RB1* mutations emerged at EOT on P+F in a small minority of patients (6/125, 4.8%, p = 0.041), with no *RB1* mutations emerging at EOT on F alone. New driver mutations emerged in both *PIK3CA* (p = 0.00018) and *ESR1* at EOT, in particular the *ESR1* Y537S mutation (p = 0.006), with no difference in frequency between P+F and F groups. Evolution of driver gene mutations was uncommon in patients progressing early on P+F, but common in patients progressing late on treatment. Paired exome analysis in 16 patients on P+F demonstrated that clonal evolution was frequent during P+F therapy, with copy number profiles remaining consistent before and after treatment. **Conclusions:** Breast cancer driver mutation landscapes are largely similar after treatment with P+F and with F alone, with acquired *PIK3CA* and *ESR1* Y537S mutations that likely contribute to fulvestrant resistance. Acquired *RB1* mutations are selected infrequently by P + F. These findings may inform future treatment strategies to address resistance to palbociclib and fulvestrant.

1002 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Abemaciclib for pre/perimenopausal women with HR+, HER2- advanced breast cancer. *First Author: Patrick Neven, University Hospitals Leuven, Leuven, Belgium*

Background: Abemaciclib is a selective inhibitor of CDK4 & 6 that is dosed on a continuous schedule and is approved for the treatment of HR+, HER2- advanced breast cancer (ABC) as monotherapy and in combination with fulvestrant (F). In the intent-to-treat (ITT) population in the MONARCH 2 study, abemaciclib in combination with F demonstrated improved progression-free survival (PFS) and objective response rate (ORR) compared to placebo (P) + F (16.4 vs 9.3 months; hazard ratio [HR] .553; 95% CI: .449, .681; p < .0000001; ORR in measurable disease 48.1% vs 21.3%; p < .001). Here, we compare the efficacy and safety of abemaciclib + F vs P + F in the pre/peri-menopausal subgroup. **Methods:** MONARCH 2 was a Phase 3 randomized, double-blind, placebo-controlled study of abemaciclib + F vs P + F in pts with HR+, HER2- ABC that progressed on ET. Key eligibility criteria were: pre/peri- and post-menopausal women with HR+, HER2- ABC (pre/peri-menopausal pts received a GnRH agonist); ECOG PS ≤ 1; progression on (neo) adjuvant ET, ≤12 months from end of adjuvant ET, or on first line ET for metastatic disease; ≤1 line of ET; no prior chemotherapy for metastatic disease. Pts received orally administered abemaciclib 150 mg twice daily + 500 mg F (per label) or P + F. Primary objective was investigator-assessed PFS. Secondary objectives included ORR, clinical benefit rate, disease control rate, duration of response, safety and tolerability. **Results:** 114 pre/peri-menopausal pts were randomized 2:1 to abemaciclib + F (N = 72) and P + F (N = 42) arms. 57 PFS events were observed. Median PFS was not reached for the abemaciclib + F arm and was 10.5 months for the P + F arm (HR, .446; 95% CI: .264, .754; p = .002). In pts with measurable disease (n = 79, 69.3%), ORR was significantly higher in the abemaciclib + F arm: 60.8% (3.9% complete response [CR]) vs 28.6% (0% CR; p = .006). The most frequent adverse events (any grade) for abemaciclib + F vs P + F were diarrhea (87.3% vs 23.8%), neutropenia (59.2% vs 7.1%) and leukopenia (43.7% vs 4.8%). **Conclusions:** Abemaciclib + F in combination with a GnRH agonist significantly improved PFS and ORR, and had a generally tolerable safety profile in pre/peri-menopausal women with HR+, HER2- ABC. Clinical trial information: NCT02107703.

1003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase III multicenter, randomized study of utidelone plus capecitabine versus capecitabine alone for heavily pretreated, anthracycline- and taxane-refractory metastatic breast cancer. *First Author: Binghe Xu, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Utidelone, a genetically engineered epothilone analog, showed excellent efficacy in phase II and III trials in terms of PFS as a primary end point and ORR as a secondary end point. In this multi-center phase III trial, we sought to determine whether utidelone plus capecitabine (CAP) could improve overall survival (OS) compared with CAP alone in patients with metastatic breast cancer (MBC) previously treated with anthracycline and taxanes. **Methods:** A total of 405 patients with MBC previously treated with anthracycline and taxanes were randomly assigned with a 2:1 ratio to either utidelone (30mg/m^2/d intravenously on d1-d5) plus CAP (1,000 mg/m^2 orally bid on d1-d14) or CAP alone (1,250 mg/m^2 orally bid on d1-d14) given every three weeks. Kaplan-Meier methods were used to estimate the median OS , 2-year survival rate and corresponding 95% confidence intervals (CI) in the intention-to-treat (ITT) population between the two groups by means of two-sided log-rank tests. Survival HR (two-sided 95% CI) is computed using Cox proportional hazards model for the comparisons. **Results:** By March 9, 2018, 281 patients had died with 180 (66.7%) in the combination group and 101 (74.8%) in the CAP alone. In the ITT population, median OS was 14.75 months (95%CI 13.08-16.69) with combination group and 12.22 months (95%CI 11.14-14.26) with CAP alone. OS was significantly improved for the combination group vs CAP alone (HR 0·63, 95% CI 0·45—0·88 ; p = 0·0047). The 2-year survival rate was 39.0% (95% CI 33.2%, 45.1%) vs 26.6% (19.4%, 35.0%), which was significantly improved by 12.4% (1.9%- 22.4% ; p = 0.015) for utidelone plus CAP. Peripheral neuropathy was the only grade 3 adverse event associated with utidelone that occurred at a prominent rate (25%), but was manageable and reversible, in the combination arm. Notably, utidelone caused very mild myelosuppression and no liver toxicities. This is the first study to show a significant OS benefit of an epothilone, and utidelone is the first microtubule inhibitor to demonstrate non-significant myelosuppression with a superior safety profile compared with ixabepilone. **Conclusions:** Utidelone plus CAP significantly improved OS in this heavily pretreated population with no significant increase in myelosuppression and most other adverse events compared to CAP alone. Clinical trial information: NCT02253459.

1004 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Efficacy of sacituzumab govitecan (anti-Trop-2-SN-38 antibody-drug conjugate) for treatment-refractory hormone-receptor positive (HR+)/HER2- metastatic breast cancer (mBC). *First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Sacituzumab govitecan is a novel antibody-drug conjugate consisting of SN-38, the active metabolite of irinotecan, conjugated to a humanized mAb targeting Trop-2 (trophoblastic antigen-2), which is highly expressed in many epithelial cancers. A phase I/II basket trial (NCT01631552) investigated its activity in patients (pts) with advanced cancers, and we previously reported on pts with triple-negative mBC. Results in HR+/ HER2 negative (as per ASCO/CAP guidelines) mBC pts who had ≥ 1 prior hormonal therapy are presented here. **Methods:** Pts received sacituzumab govitecan at a dose of 10 mg/kg on days 1 & 8 of a 21-day cycle until progression or unacceptable toxicity. Eligibility included ≥ 1 prior line of standard therapy for metastatic disease, measurable disease by CT or MRI. Efficacy was assessed locally by RECIST 1.1. Adverse events (AE) were evaluated according to CTCAE v4.0, **Results:** Fifty-four pts with HR+/HER2- mBC (all female; median age 54 yrs, range 33-79) were accrued between 2/2015 and 6/2017. For metastatic disease, all pts received at least 2 prior treatments, with a median of 3 prior hormonal agents and 2 prior chemotherapy regimens. Prior treatments in any setting included taxane (93%), anthracycline (69%) and CDK 4/6 inhibitors (69%). 16 pts have died, 27 are in long-term follow-up and 11 still on treatment. The median number of doses was 11 (range 1-74). Treatment was generally well tolerated, with no treatment-related deaths. Based on currently available AE data, grade ≥ 3 toxicity (≥10%) included neutropenia and leukopenia; there was 1 case each of grade ≥ 3 diarrhea and febrile neutropenia. As of 12/31/2017 data cutoff, the overall response rate (ORR) was 31% (17 PRs/54) by local assessment, and the clinical benefit rate (CBR: PR+SD > 6 months) was 48%. For pts who received CDK inhibitors, ORR was 24% (9 PRs/37). Maturing durability of response and progression-free survival to be presented at the meeting. **Conclusions:** Sacituzumab govitecan as a single agent induced objective responses in heavily pre-treated HR+/HER2neg mBC, and was well tolerated with a safety profile consistent with previous reports. Clinical trial information: NCT01631552.

1005 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Everolimus (EVE) + exemestane (EXE) vs EVE alone or capecitabine (CAP) for estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC): BOLERO-6, an open-label phase 2 study. *First Author: Guy Heinrich Maria Jerusalem, CHU Sart Tilman Liège and Liège University, Liège, Belgium*

Background: BOLERO-6 (NCT01783444) was designed to estimate the clinical benefit of EVE + EXE vs EVE alone or CAP for ER+ HER2– ABC that progressed on nonsteroidal aromatase inhibitors. **Methods:** Patients were randomized 1:1:1 to EVE 10 mg/day + EXE 25 mg/day, EVE alone or CAP 1250 mg/m^2 twice-daily. The primary objective was to estimate the hazard ratio (HR) of progression-free survival (PFS) for EVE + EXE vs EVE. The key secondary objective was to estimate the HR of PFS for EVE + EXE vs CAP. Other secondary objectives were overall survival (OS) and safety. This was not a confirmatory study and no statistical comparisons were planned **Results:** 309 patients received EVE + EXE (n=104), EVE (n=103) or CAP (n=102). Baseline characteristics were generally consistent; however vs the EVE + EXE arm, patients in the CAP arm were younger (68% vs 63% were aged <65 years), more had bone-only lesions (24% vs 13%), were Caucasian (89% vs 75%) or fully active (56% vs 52%) and fewer had visceral disease (62% vs 66%) or ≥3 metastatic sites (44% vs 50%). Median follow-up from randomization to data cut-off (June 1, 2017) was 37.6 months. The estimated HR of PFS for EVE + EXE vs EVE was 0.74 (90% CI 0.57–0.97). The estimated HR of PFS for EVE + EXE vs CAP was 1.26 (90% CI 0.96–1.66) but a stratified multivariate Cox regression model adjusted on prognostic factors and baseline covariates with imbalances between arms gave a HR closer to 1 (HR 1.15; 90% CI 0.86–1.52). More patients in the CAP arm were censored for initiating new antineoplastic therapies (20% vs 9% with EVE + EXE). Median OS was 23.1 months with EVE + EXE vs 29.3 months with EVE (HR 1.27; 90% CI 0.95–1.70) and 25.6 months with CAP (HR 1.33; 90% CI 0.99–1.79). Grade 3/4 adverse events (AEs) were most common with CAP. Serious AEs were most common with EVE + EXE. **Conclusions:** The estimated HR of PFS for EVE + EXE vs EVE (0.74) is indicative of a treatment benefit. While the estimated HR of PFS for EVE + EXE vs CAP was 1.26, the CAP arm may have been favored by baseline imbalances and potential informative censoring. The safety profile of EVE + EXE was consistent with the known profile of this combination. Clinical trial information: NCT01783444.

LBA1006 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) *v* FULV in patients (pts) with estrogen receptor (ER)-positive, *PIK3CA*-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. *First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

1007 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial. *First Author: Peter Schmid, Queen Mary University of London, London, United Kingdom*

Background: The PI3K/AKT signalling pathway is frequently activated in triple-negative breast cancer (TNBC). AZD5363 is a highly-selective, oral, small molecule AKT inhibitor. The PAKT trial investigated the addition of AZD5363 to paclitaxel as 1st-line therapy for TNBC. **Methods:** This investigator-led, double-blind, placebo-controlled, randomised phase II trial, recruited women with previously untreated, metastatic TNBC at 42 sites in 6 countries. Patients were randomly assigned (1:1) to paclitaxel 90mg/m^2 (days 1, 8, & 15) with either AZD5363 (400mg BD) or placebo (days 2-5, 9-12, 16-19) every 28 days until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), PFS in the subgroup with *PIK3CA/AKT1/PTEN*-alterations, response, and safety. **Results:** Between 05/2014 and 06/2017, 140 patients were randomised to paclitaxel + AZD5363 (n = 70) or paclitaxel + placebo (n = 70). Median duration of follow-up was 18.2 months (95% CI, 13.6 to 24.0). In the ITT analysis, median PFS was 5.9 months (m) for AZD5363 compared to 4.2m for placebo (hazard ratio [HR], 0.75; 95% CI, 0.52 to 1.08; one-sided p = 0.06; two-sided p = 0.11 [predefined significance level of 0.10, one-sided]). Median OS was 19.1m for AZD5363 compared to 12.6m for placebo (HR, 0.64; 95% CI, 0.40 to 1.01; one-sided p = 0.02; two-sided p = 0.04). Results for the subgroup with *PIK3CA/AKT1/PTEN*-altered tumours will be presented. Most common grade 3 or worse adverse events were diarrhoea (12% [8/68] of AZD5363-treated patients *vs* 1% [1/70] of placebo-treated patients), infection (4% *vs* 1%), neutropenia (3% *vs* 3%), rash (4% *vs* 0) and fatigue (4% *vs* 0). **Conclusions:** The trial met its primary endpoint. Addition of AZD5363 to 1st-line paclitaxel therapy for TNBC resulted in significantly longer PFS and OS. AZD5363 warrants further investigation for the treatment of TNBC. Clinical trial information: NCT02423603.

1008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). *First Author: Rebecca Dent, National Cancer Center, Singapore*

Background: In LOTUS (NCT02162719), adding the oral AKT inhibitor IPAT to first-line PAC for mTNBC improved progression-free survival (PFS; primary endpoint) [Kim, Lancet Oncol 2017]. The stratified PFS hazard ratio (HR) in the intent-to-treat (ITT) population (n = 124) was 0.60 (95% CI 0.37–0.98; p = 0.037; median PFS 6.2 vs 4.9 months with IPAT vs PBO, respectively). In prespecified analyses of patients (pts) with *PIK3CA/AKT1/PTEN*-altered tumors, the unstratified PFS HR was 0.44 (95% CI 0.20–0.99; median 9.0 vs 4.9 months). We now report updated OS results in the ITT population after OS events in ~50% of pts. OS results in the *PIK3CA/AKT1/PTEN*-altered subgroup are immature. **Methods:** Eligible pts had measurable inoperable mTNBC previously untreated with systemic therapy. Pts were stratified by prior (neo) adjuvant therapy, chemotherapy-free interval (6–12 months vs > 12 months vs not applicable) and tumor IHC PTEN status, and randomized 1:1 to PAC 80 mg/m^2 (d1, 8, & 15) with either IPAT 400 mg or PBO (d1–21) q28d until progression or unacceptable toxicity. OS was a prespecified secondary endpoint. **Results:** The table shows results after 23 months' follow-up (data cutoff 26 July, 2017). No new safety signals were seen. **Conclusions:** The previously observed PFS improvement with IPAT was followed by a trend toward improved OS (~5-month difference in the medians) at the updated OS analysis. Post-progression therapy was similar. These findings support further evaluation of first-line IPAT + PAC for mTNBC in the ongoing IPATunity130 (NCT03337724) randomized phase 3 trial. Final OS results from LOTUS are expected in 2019. Clinical trial information: NCT02162719.

Parameter	IPAT + PAC (n = 62)	PBO + PAC (n = 62)
OS events, n (%)	33 (53)	35 (56)
Median OS, months (95% CI)	23.1 (18.6–28.1)	18.4 (15.1–29.1)
OS hazard ratio (95% CI)	Stratified: 0.62 (0.37–1.05) Unstratified: 0.77 (0.48–1.25)	
1-year OS rate, % (95% CI)	83 (73–93)	70 (58–81)
Post-progression systemic anti-cancer therapy, n (%)	47 (76)	55 (89)
Immunotherapy	7 (11)	7 (11)
Adverse event leading to treatment discontinuation, n (%)[a]		
IPAT/PBO	4 (7)	1 (2)
PAC	7 (11)	6 (10)

[a]n = 61 in IPAT + PAC arm

1009 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

The integrated genomic and immune landscapes of lethal metastatic breast cancer (MBC). *First Author: Leticia De Mattos-Arruda, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: The heterogeneous fates of MBC preclude our understanding of both resistance to therapy and escape from cancer immunoediting. Here, we performed a comprehensive molecular analysis of lethal MBC patients (pts), interrogating both the malignant and immune tumor microenvironment (TME) compartments, and T-cell receptor (TCR) repertoires, across multiple metastases (mets). **Methods:** Multi-platform profiling of mets (N = 182 mets to 22 organs, 5-36 mets/pt), primary tumors (pr) (N = 6) and ctDNA from body fluids (4.7/pt) in 10 warm autopsies of MBC pts (5 ER+/HER2-, 3 ER+/HER2+, 1 ER-/HER2+, 1 ER-/HER2-), included exome seq (N = 86), shallow whole genome seq (N = 168), RNA seq (N = 61), ultra-deep targeted seq (TS) (N = 243), TCRseq (N = 70) and IHC (N = 102). State-of-the-art bioinformatics was applied to the data. **Results:** Mutation (mut) burden landscape varied between pts (11,579 mut, median 255.41 mut/pt) and across mets within each pt (median 122 mut/met); was greater than TCGA mut burden (median 63.5 mut/pr, p = 4.927e-14). Landscape of mut and predicted neo-antigen were dominated by stem (present in all mets/pt) or clade (some mets/pt), but not private (one met/pt). TS data confirmed that all pr tumors contained the clonal ancestors of 10 pts, and characterized ctDNA bathing organs. Copy number alteration profiles were remarkably similar across mets in 9 of the 10 pts, except in a ER+/HER2- pt, whose mets shared a common ancestor (1q gain/16q loss), then early sub-clonal evolution occurred. Mets were grouped into phylogenic clades that share common genomic ancestry and accumulated previously unknown mutation signatures. Mets evolved as communities of clones as a fraction of the metastatic stem and clade mutations were sub-clonal. Immune TME was either homogeneous in a particular metastatic clade, or different across mets to a particular organ. Stem and clade clonotypes prevailed across TCR landscape within each pt. TCR repertoires revealed adaptive immune responses to co-evolve with the metastatic genomes. **Conclusions:** The genomic and immune landscapes demonstrate an unprecedented integrated view of the heterogeneous landscape of genomic aberrations, TME features and T-cell adaptive immune responses in lethal MBC.

1010 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Determinants of high tumor mutational burden (TMB) and mutational signatures in breast cancer. *First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA*

Background: High TMB correlates with high neoantigen burden, and this is thought to be predictive of response to immunotherapy. The aim of this work is to evaluate frequency, mutational patterns, and genomic profile of hypermutated breast cancer. **Methods:** We used sequencing data from publically available on cbioportal.org, including TCGA, France 2016, MSK-IMPACT, MBCProject, AACR-GENIE, and ongoing studies at our institute (The Center for Cancer Precision Medicine Metastatic Breast Cancer Study; The Young Women's Breast Cancer Study) to evaluate mutational load across breast cancers. Samples were classified as having high TMB if they had > 10 mutations (mut) per megabase (MB). **Results:** We included 3689 samples for the analysis. The median TMB was 1.55 mut/MB. TMB significantly varied according to histology (ductal > lobular, $p = 4.6 \times 10^{-13}$), tumor subtype (HR-/ HER2+ > TNBC > HR+/HER2+ > HR+/HER2-, $p < 0.05$), staging (metastatic > primary, $p = 2.2 \times 10^{-16}$) and site of metastasis (higher soft tissue, and lowest lung, $p < 0.05$). We found a total of 70 (~2%) hypermutated tumors (62.8% metastatic vs 37.2% primary samples). Mutational signature analysis of the hypermutated samples showed the presence of dominant APOBEC (77.1%), homologous recombination (HR; 2.9%), defective DNA mismatch repair (MMR; 18.6%), and POLE hypermutation (1.4%) signatures. Median TMB was higher for samples with POLE and HR signature, followed by those with MMR and APOBEC (93.1, 38.7, 14.6 and 12.4 mut/MB, respectively). Among hypermutated tumors, 8 samples had somatic mutation in the *POLE* gene, but only the case with POLE signature high had a characterized *POLE* driver mutation. In addition, 80% of hypermutated tumors with APOBEC signature had *PIK3CA* mutations *versus* 31% of hypermutated tumors with other signatures (p = 0.0005). **Conclusions:** TMB is correlated with clinical parameters including histology, receptor subtype and site of metastasis. Different mutational signatures are present in this population, including POLE, defective DNA MMR, HR and APOBEC. The potential role of these different signatures in predicting benefit to immunotherapy in hypermutated breast cancers is unclear, and warrants further investigation.

1011 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

TOPACIO/Keynote-162: Niraparib + pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC), a phase 2 trial. *First Author: Shaveta Vinayak, Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, OH*

Background: Chemotherapy is a standard of care for TNBC despite its suboptimal efficacy. ≈15–20% of TNBC have *BRCA1/2* mutations (mut); ≈75% of *BRCA1* mut BCs are TN. Single agent poly(ADP-ribose) polymerase (PARP) inhibitors have clinical activity in pts with *BRCA1/2* mutations (*BRCA*mut) BC and provide median PFS of 6 mos in pts with *BRCA*mut TNBC vs 3.5 mos for chemotherapy. Single-agent pembrolizumab (pembro), a programmed death 1 (PD–1) inhibitor, has shown objective response rates (ORR) of 5–18% in previously treated TNBC. TOPACIO (NCT02657889) is a fully enrolled study evaluating the safety and efficacy of combination treatment with selective PARP1/2 inhibitor niraparib + pembro in pts with met TNBC. **Methods:** Pts received niraparib 200 mg orally once daily + pembro 200 mg IV on day 1 of each 21-day cycle. Primary efficacy endpoint was ORR and secondary endpoints included disease control rate (DCR = CR+PR+SD [stable disease]). **Results:** As of Jan 2018, 12 of 54 enrolled TNBC pts (22%) had deleterious *BRCA*mut; 9 (17%) not tested/indeterminate results. Median age was 54 yrs, with median of 1 prior line of therapy in the met setting (range 0–3); 22 (41%) had received prior platinum in the met setting; 39 (72%) had received prior (neo)adjuvant therapy. Forty-five pts were evaluable, with ≥1 on-study scan. To date, ORR is 29% and DCR is 49%, including 3 CR (7%), 10 PR (22%), 9 SD (20%), and 23 progressive disease (PD) (51%). Ten of 13 responders have ongoing responses; 13 pts have received > 6 mos of treatment (6 *BRCA*mut, 5 *BRCA*wt, 2 *BRCA*unk); 11 pts remain on treatment. The 12 *BRCA*mut pts were 1 CR, 7 PR, 1 SD and 3 PD. Median PFS in *BRCA*mut group is 8.1 mos (95% CI 0.2–NE). ORR (any *BRCA* status) was 33% in PD-L1-pos (combined proportion score ≥1%) vs 15% in PD-L1-neg pts. Treatment-related grade ≥3 AEs occurred in 27 pts (50%); most common were thrombocytopenia (13%) & anemia (11%). Follow-up is ongoing. **Conclusions:** Preliminary activity is encouraging with durable responses observed irrespective of *BRCA*1/2 or PD-L1 status or prior platinum exposure with the highest ORR in *BRCA*mut pts. No new safety signals were identified with the combination. Clinical trial information: NCT02657889.

	ORR	DCR
TNBC overall, n = 45	29%	49%
TNBC *BRCA*mut, n = 12	67%	75%

1012 Clinical Science Symposium, Mon, 3:00 PM-4:30 PM

Adaptive phase II randomized trial of nivolumab after induction treatment in triple negative breast cancer (TONIC trial): Final response data stage I and first translational data. *First Author: Marleen Kok, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Anti-PD(L)1 can result in durable responses in patients with metastatic triple negative breast cancer (TNBC). However, only a subgroup of TNBC patients benefits from anti-PD(L)1 with response rates of 5-10% in unselected cohorts. Strategies to render the tumor micro-environment (TME) more susceptible to anti-PD(L)1 might include stimulation of anti-cancer immune responses by induction treatment with irradiation or low dose chemotherapy. **Methods:** In stage I (non-comparative Simon's two stage design) patients with metastatic TNBC who received $\leq$ 3 lines of palliative chemotherapy were randomly allocated to one of five 2-week induction treatments consisting of 1) 3x8 Gy irradiation of one metastatic lesion 2) 2x doxorubicin 15mg weekly flat dose3) cyclophosphamide 50mg daily orally 4) 2x cisplatin 40mg/m^2 weekly 5) no induction treatment. After this induction period, all patients received nivolumab until iRECIST progression. After at least 5x10 evaluable patients with paired biopsies (stage I) arms will be closed according to a 'pick the winner' concept taking into account safety, clinical responses and immunological correlates. **Results:** Stage I has been closed with 66 patients available for response evaluation. Previous treatments for metastatic disease were 0, 1 or 2+ lines in 23%, 45% and 32%, respectively. For the total group the ORR is 20% with 2 CRs and 11 PRs. In addition, two patients had SD for $>$ 24 weeks (3%), resulting in a clinical benefit rate of 23%. ORR on nivolumab after induction with irradiation, doxorubicin, cyclophosphamide and cisplatin were 8% (1/12), 35% (6/17), 8% (1/12) and 23% (3/13), respectively. In the nivolumab-only cohort the ORR was 17% (2/12). Analyses of changes in the TME, gene expression and TCR sequencing induced by irradiation, low dose chemotherapy and nivolumab will be presented at the meeting as well as the design of stage II according to the 'pick the winner' strategy. **Conclusions:** This basket trial shows that short term induction with irradiation or low dose chemotherapy before nivolumab is feasible. Final clinical and translational results of stage I will be presented at ASCO 2018. Clinical trial information: NCT02499367.

1013 Poster Discussion Session; Displayed in Poster Session (Board #94), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Final overall survival (OS) analysis of PHEREXA: A randomized phase III trial of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) in patients with HER2-positive metastatic breast cancer (MBC) who experienced disease progression during or after H-based therapy. *First Author: Ander Urruticoechea, Onkologikoa Foundation, San Sebastían and Catalan Institute of Oncology-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain*

Background: In PHEREXA (NCT01026142), adding P to H + X did not significantly improve independent review facility-assessed progression-free survival (IRF-PFS; primary endpoint) in patients with HER2-positive MBC who received a prior taxane and progressed during or after H-based therapy (hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.65–1.02; p= .0731). An 8-month increase in median OS to 36.1 months was observed with P, but due to hierarchical testing of IRF-PFS, and subsequently of OS, statistical significance could not be claimed. No new safety signals were identified. We now report the final prespecified analysis. **Methods:** Randomization arms were A: intravenous H 8 mg/kg→6 mg/kg every 3 weeks (q3w) + oral X 1250 mg/m^2 twice daily (2 weeks on, 1 week off q3w) and B: intravenous P 840 mg→420 mg q3w + intravenous H per Arm A + oral X 1000 mg/m^2 (same schedule as Arm A). Treatment was given until disease progression, unmanageable toxicity, or patient request for discontinuation. OS and investigator-assessed PFS (INV-PFS) were assessed in the intent-to-treat population (all randomly assigned patients); adverse events (AEs), in the safety population (patients who received $\geq$1 dose of study drug). Results are descriptive. **Results:** At clinical cutoff (20-Sep-17), median time on study, including follow-up, was 23 months in Arm A and 33 months in Arm B. Efficacy is shown in the table. There was a small increase in AE incidence with longer follow-up, and no new symptomatic left ventricular systemic dysfunction (0 patients in Arm A and 5 [2.2%] in Arm B). **Conclusions:** While final OS results of PHEREXA are descriptive, median OS of 37.3 months in Arm B, with a 9.1-month increase versus Arm A, shows that clinical efficacy of H + P is maintained with longer follow-up. There were no new safety signals and no evidence of late cardiac toxicity. Clinical trial information: NCT01026142.

	Arm A H + X n = 224		Arm B P + H + X n = 228
OS			
Events, n (%)	136 (60.7)		134 (58.8)
Median, months	28.1		37.2
Δ, months		9.1	
HR (95% CI)		0.76 (0.60–0.98)	
INV- PFS			
Events, n (%)	182 (81.3)		201 (88.2)
Median, months	9.0		11.8
Δ, months		2.8	
HR (95% CI)		0.83 (0.68–1.02)	

1014 Poster Discussion Session; Displayed in Poster Session (Board #95), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. *First Author: Cristina Saura, Medical Oncology Department, Breast Cancer Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: SYD985, (vic-)trastuzumab duocarmazine, is a HER2-targeting antibody-drug conjugate with a cleavable linker-duocarmycin payload that causes irreversible alkylation of the DNA in tumor cells. The dose-escalation part of a Phase I study was completed previously; we herein present preliminary efficacy data of the breast cancer expansion cohorts and safety data of all expansion cohorts (breast, gastric, urothelial and endometrial cancer). **Methods:** HER2 tumor expression was determined by a central lab and had to be immunohistochemistry (IHC) 1+ or higher; HER2-positive was defined as IHC 2+/3+/ISH+ and HER2-low as IHC 1+/2+/ISH-. Patients were treated with 1.2 mg/kg SYD985 IV every 3 weeks until disease progression or unacceptable toxicity. Tumor evaluation scans were done every 6 weeks. **Results:** Ninety-nine (99) breast cancer patients were enrolled. Of the 50 patients with HER2-positive breast cancer, the majority received 3 or more prior HER2-targeting regimens in the locally advanced or metastatic setting, including (ado-)trastuzumab emtansine in 80% of the patients. Preliminary results showed that SYD985 demonstrated an overall response rate (ORR) of 33% and a median PFS of 9.4 months. At the time of data cut-off, 8 patients (16%) received SYD985 for over one year and 5 patients (10%) continued to receive treatment. Efficacy has also been demonstrated in heavily pretreated patients with HER2-low metastatic breast cancer, including hormone-receptor positive (N = 32) and triple-negative breast cancer (N = 17). The ORRs were 27% and 40%, respectively, with several patients ongoing on SYD985. The safety profile was manageable and mainly characterized by grade 1 and 2 events. The most common adverse drug reactions were fatigue, dry eyes, conjunctivitis and increased lacrimation. Grade 3/4 adverse drug reactions most commonly reported included neutropenia (6%) and conjunctivitis (4%). **Conclusions:** SYD985 shows promising efficacy in heavily pretreated patients with breast cancer, in both HER2-positive and HER2-low tumors with or without hormone receptor expression. A Phase III study (TULIP) is currently ongoing in HER2-positive breast cancer patients. Clinical trial information: NCT02277717.

1015 Poster Discussion Session; Displayed in Poster Session (Board #96), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Clinical benefit of tucatinib after isolated brain progression: A retrospective pooled analysis of tucatinib phase 1b studies in HER2+ breast cancer. *First Author: Rashmi Krishna Murthy, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: For MBC patients with isolated brain progression, current guidelines recommend treatment with CNS-directed therapy and continuation of current systemic therapy, although there are limited data evaluating this strategy. Two Phase 1b trials of tucatinib permitted patients with HER2+ MBC to continue study treatment following CNS-directed therapy in instances of isolated brain metastases (BM) progression. **Methods:** 2 Phase 1b studies of tucatinib were pooled to identify patients with isolated brain progression (defined as new or progressive BM with stable or responding systemic disease) while on study. In patients treated for isolated brain progression, the median time to any subsequent progression or death was determined. **Results:** 117 patients were analyzed, 57 in the 004 (tucatinib + T-DM1) and 60 in the 005 (tucatinib +/- trastuzumab +/- capecitabine) trials. 25 patients (21%) with isolated BM were identified and comprised 2 groups: 14 who discontinued study and 11 who continued study treatment following CNS-directed therapy. Median time to isolated brain progression differed between these groups (12.3 months in post-progression treated vs. 6.3 months). The median time to any second event was 8.3 months in the post-progression CNS-treated patients. Patients selected for post-progression treatment had less exposure to pertuzumab, were more frequently treated with the triplet combination, had a longer time from pre-study CNS-directed therapy, had better preserved performance status, and were less likely to have new neurologic adverse events compared to patients not treated post-progression. **Conclusions:** Patients with isolated BM progression treated post-progression with CNS-directed therapy and continuation of study therapy had a median of 8.3 months to any second event, suggesting a substantial benefit for this treatment strategy. The selection of patients with post-progression treatment appears to be a composite of characteristics both at baseline and at time of brain progression. These results support the further evaluation of this approach to patients with isolated brain progression in the ongoing randomized HER2CLIMB trial. Clinical trial information: NCT01983501 and NCT02025192.

ABSTRACT WITHDRAWN

1017 Poster Discussion Session; Displayed in Poster Session (Board #98), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase II, single arm study assessing the efficacy of pembrolizumab (Pembro) plus radiotherapy (RT) in metastatic triple negative breast cancer (mTNBC). *First Author: Heather L. McArthur, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Overall response rates of 5-7% have been reported with checkpoint inhibitor monotherapy in PD-L1-unselected mTNBC as second line or subsequent therapy. RT is frequently used to enhance local control in mTNBC and has been reported to induce distant (abscopal) tumor responses when combined with immunotherapy. In this study, we evaluate the safety and efficacy of RT combined with pembro, a programmed death 1 (PD-1) inhibitor, in a phase II, single-arm, Simon two-stage, study in mTNBC. **Methods:** Eligible women had biopsy-proven mTNBC and ≥2 measurable sites of metastatic disease with at least one site requiring RT. PD-L1 expression was not required for study entry. A total RT dose of 3000 cGy was delivered in 5 daily fractions. Pembro was given intravenously at 200 mg within 3 days of the first RT fraction, then every 3 weeks +/-3 days until disease progression. The primary endpoint was overall response rate at week 13 in the non-irradiated lesions by RECIST v1.1. Secondary endpoints included safety and overall survival. Tumor biopsies were obtained at baseline and at week 7. **Results:** Of the 17 women enrolled, the median age was 52 y (range 37-73y), and the median number of prior cytotoxic therapies for metastatic disease was 3 (range 0 to 8). Of the 8 women not evaluable at 13 weeks: 5 died secondary to disease-related complications (at weeks 2, 6, 7, 8, and 9) and 3 progressed prior to week 13. Of the 9 women evaluable at week 13, 3 (33%) had a partial response, 1 (11%) had stable disease and 5 (56%) had disease progression. The stable disease response was durable for 22 weeks. The 3 partial responses represented 60%, 54%, and 34% decreases in tumor burden by RECIST v1.1 and were durable for 31, 21, and 40 weeks, respectively. Common toxicities were mild and included fatigue, myalgia and nausea. **Conclusions:** The combination of pembro and RT was well-tolerated with durable responses outside the RT field in 3/9 (33%) evaluable patients unselected for PD-L1 expression. Thus, the addition of RT to PD-1 blockade represents a promising strategy for improving response rates in pre-treated mTNBC. Clinical trial information: NCT02730130.

1018 Poster Discussion Session; Displayed in Poster Session (Board #99), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Clinical and biomarker results from phase I/II study of PI3K inhibitor BYL 719 (alpelisib) plus nab-paclitaxel in HER2-negative metastatic breast cancer. *First Author: Priyanka Sharma, University of Kansas Medical Center, Kansas City, KS*

Background: Activation of Phosphatidylinositol-3-kinase (PI3K) pathway may confer resistance to taxanes and in preclinical models concomitant inhibition of the PI3K pathway enhances efficacy of taxanes. Alpelisib is a potent oral, class I inhibitor of PI3K alpha isoforms with antitumor activity in tumors that harbor PI3KCA mutations. **Methods:** Eligible patients had HER-2 negative MBC with any number of prior chemotherapy. Phase I was 3+3 dose-escalation design with three dose levels of alpelisib (250mg, 300mg, 350mg) PO daily (D1-28) and nab-Paclitaxel (nP) 100 mg/m^2 D 1, 8, 15 every 28 days. Phase II was designed according to Simon's Minimax design. Aims were to determine 1) Recommended Phase II Dose (RPTD), 2) Objective Response Rate (ORR), 3) Progression-free survival (PFS). PIK3CA activating mutations in tumor and circulating tumor DNA (ctDNA) were assessed using next-generation sequencing. **Results:** There were no DLTs in the three dose levels of phase I (n = 10). 33 patients were treated in phase II on the RPTD (Alpelisib 350mg PO daily plus nP 100mg/m2 D1,8,15 every 28 days). Median age was 55 years; 30% had TNBC. 84% had visceral disease, 74% had received prior chemotherapy for MBC, 84% had received prior taxane. Hyperglycemia (G3:29%,G4:0%), neutropenia (G3:24%,G4: 7%), anemia (G3:12%, G4:0%), diarrhea (G3:7%, G4:0%) were the most common grade 3/4 adverse events. In 42 patients evaluable for response, ORR was 57% (24/42) (CR = 2, PR = 22) and an additional 21% demonstrated SD ≥16wks. ORR for patients treated at RPTD was 55% (18/33). Median PFS is 9 months (95% CI: 6-12). Mean duration of treatment is 8 months(2-26 months). 40%(17/42) demonstrated tissue and/or ctDNA PIK3CA mutation (ctDNA/tissue concordance = 70%). Compared to patients without PIK3CA mutation, those with PIK3CA mutation demonstrated significantly better PFS (7 vs 13 months HR = 0.39, p = 0.03). **Conclusions:** Alpelisib and nP combination shows encouraging efficacy with manageable toxicity in HER2 negative MBC. Efficacy was especially robust in patients with PIK3CA mutation (ORR = 65%, PFS = 13months). Randomized trial of this combination in PIK3CA mutation selected patients is warranted. Clinical trial information: NCT02379247.

1019 Poster Discussion Session; Displayed in Poster Session (Board #100), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The impact of circulating tumor cells (CTCs) detection in metastatic breast cancer (MBC): Implications of "*indolent*" stage IV disease (Stage IV$_{indolent}$). *First Author: Andrew A. Davis, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL*

Background: CTCs count has been validated as a prognostic biomarker in MBC. In primary breast cancer, diagnostic tools exist to select less aggressive treatments in patients with indolent disease. In the largest CTC analysis to date, we define an indolent subset of patients in MBC, Stage IV $_{indolent}$, identified using CTC counts. **Methods:** We performed a combined pooled analysis of individual patient data in two large cohorts: the European Pooled Analysis Investigators (EPAC) cohort (N = 1,944) and the MD Anderson Cancer Center (MDACC) cohort (N = 492). For all patients (N = 2,436), CTC enumeration was performed using the FDA-approved CellSearch™ (Menarini Silicon Biosystems, LLC) with baseline samples collected before starting a new treatment. Overall survival (OS) data were collected from both cohorts. Patients were stratified based on 5 CTCs/7.5 mL blood (N = 1,336 with < 5 CTC or Stage IV $_{indolent;}$ ≥5 CTC, Stage IV $_{aggressive}$). Proportional hazards regression model and stratified log rank tests were performed. **Results:** For all patients, CTC ≥5 identified patients with a worse outcome (HR 2.43, 95% CI 2.17-2.73, P < 0.0001), while the indolent CTC group had a median OS of 36.3 months (mts). Moreover, for patients with *de novo* MBC prior to treatment (N = 244), the indolent cohort demonstrated an OS greater than 5.5 years. The Stage IV $_{indolent}$ disease showed significantly longer OS across all disease subtypes compared to the aggressive cohort, HR+ (44 mts vs. 17.3 mts, P < 0.0001), TNBC (23.8 mts vs. 9.0 mts, P < 0.0001), and HER2+ (36.7 mts vs. 20.4 mts, P < 0.0001). Furthermore, Stage IV $_{indolent}$ consistently discriminated a less aggressive cohort among subtypes even in the refractory setting. **Conclusions:** CTC < 5 identifies an indolent subset of MBC, Stage IV $_{indolent}$, independent of line of treatment and molecular subtype. A CTCs-based classification of MBC has tremendous implications and practical applications including, considerations for cost-effective single-agent therapy, particularly in the first-line setting, and the availability of a validated stratification tool in prospective efficacy clinical trials.

1020 Poster Discussion Session; Displayed in Poster Session (Board #101), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Comparison of tissue genotyping (TG) vs circulating tumor DNA (ctDNA) for selection of matched therapy and impact on clinical outcomes among patients with metastatic breast cancer (MBC). *First Author: Neelima Vidula, UC San Francisco, San Francisco, CA*

Background: Oncogenic mutations are attractive targets for targeted therapies, but the clinical impact is unclear. We evaluated the impact of TG or ctDNA on the selection of matched therapy and clinical outcomes in MBC patients. **Methods:** MBC patients with TG (Next Generation Sequencing/NGS, institutional platform) or ctDNA (NGS, Guardant360) at Massachusetts General Hospital between 1/2016-12/2017 were identified. A review of records to identify tumor subtype, demographics, treatment, outcomes, and TG or ctDNA results was performed. Associations between genomic results and the selection of matched therapy targeted to an actionable mutation, progression free survival, and overall survival (OS) were determined. **Results:** Among 252 patients with ctDNA testing, 232 (92%) had detectable mutations. Of those 232 cases, 196 (84%) had actionable mutations and 86 patients with actionable mutations received matched therapy with agents including CDK 4/6, mTOR, PI3K, AKT, PARP, androgen receptor, and FGFR inhibitors, SERDs, HER2 directed therapy, and DNA damaging chemotherapy. Among 118 patients with TG, 90 (76%) had detectable mutations. Of those 90 cases, 59 (66%) were actionable and 13 patients with actionable mutations received matched therapy with agents including mTOR, PI3K, or AKT inhibitors, or SERDs. There were significantly more actionable mutations detectable by ctDNA vs TG (84.5% vs 65.6%, $p < 0.0005$) and a significantly higher proportion of patients with ctDNA vs TG received matched therapy (46.7% vs 27.7%, $p = 0.018$). On multivariate Cox regression analysis adjusted for tumor subtype in ctDNA patients, OS was significantly better for patients with matched therapy vs those with unmatched therapy (HR 0.45, 95% CI 0.25-0.80, $p = 0.007$). Additional survival analyses will be presented at the meeting. **Conclusions:** ctDNA testing resulted in higher detection and greater application of matched therapy as compared with TG. Patients who had matched therapy based on ctDNA results had better OS compared to those with unmatched therapy post-ctDNA testing. These novel findings require confirmation in additional studies.

1021 Poster Discussion Session; Displayed in Poster Session (Board #102), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Molecular alterations in the Ras-Raf-Erk (MAPK) pathway in metastatic hormone receptor positive (HR+)/HER2- breast cancer: Incidence and impact on clinical outcomes. *First Author: Arielle Medford, Massachusetts General Hospital, Boston, MA*

Background: While molecular alterations in PI3K pathway, including *PIK3CA* mutations, are common in HR+ breast cancer, molecular alterations in MAPK pathway, including *KRAS* and *BRAF* mutations, are considered rare in HR+ breast cancer. However, tumors can acquire new molecular alterations over time, and blood-based genotyping via circulating tumor DNA (ctDNA) could provide a more accurate molecular snapshot. **Methods:** This study analyzed data collected from metastatic breast cancer (MBC) patients who had genotyping (2016-2017) via a next generation sequencing-based (NGS) assay that detects ctDNA mutations (Guardant 360 panel), including alterations in MAPK pathway. Mutation profiles were also analyzed in tissue biopsies via SNaPshot-NGS, an institutional genotyping assay. Multivariate analysis was performed to evaluate the hazard ratio (HR) for the association between these mutations and time to progression (TTP), adjusting for key prognostic variables. **Results:** Among the HR+ MBC patients (N = 174), 25% (N = 44) were found to have molecular alterations in MAPK pathway in ctDNA, including mutations in *BRAF* (7.5%), *KRAS* (5.7%), *NRAS* (0.57%), *MAP2K1* (1.1%) and *NF-1* (14.4%); 14.5% had a concurrent *PIK3CA* mutation, 9.2% had a concurrent *TP53* mutation, and multiple alterations were acquired. Among patients with MAPK molecular alterations versus not, there was no significant difference in baseline characteristics, including age at metastatic diagnosis (57 vs 55; $p = 0.78$) and visceral metastases (74% vs 81%; $p = 0.87$). In multivariate analysis, patients with MBC harboring MAPK molecular alterations had worse TTP (HR: 2.08; $p = 0.02$) compared to controls. However, there was no difference among those with *PIK3CA* mutant tumors versus not (HR: 1.09; $p = 0.74$). **Conclusions:** Molecular alterations in MAPK pathway, hitherto considered rare in primary HR+ breast cancer, are not uncommon in metastatic HR+ breast cancer and are associated with worse outcomes. The study highlights the value of blood-based assays for identification of novel targets and their potential clinical utility in development of genotype driven trials for patients with MBC.

1022 Poster Discussion Session; Displayed in Poster Session (Board #103), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

First-line ribociclib (RIB) + letrozole (LET) in hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): MONALEESA-2 biomarker analyses. *First Author: Gabriel N. Hortobagyi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In MONALEESA-2, first-line RIB + LET improved investigator-assessed progression-free survival (PFS; primary endpoint) vs placebo (PBO) + LET in postmenopausal pts with HR+, HER2– ABC. Previous MONALEESA-2 biomarker analyses, involving immunohistochemistry, gene expression, and NGS of ctDNA, showed consistent RIB benefit. Here, we present additional MONALEESA-2 gene expression data. **Methods:** Tumor samples (n/N, 391/668) were evaluated for gene expression using the NanoString 230-gene nCounter® GX Human Cancer Reference panel. To assess correlations between gene expression level and PFS, pts were classified into low (L) and high (H) messenger RNA expression subgroups using a 10% cut-off for *RB1* and median expression as the cut-off for other genes. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CI). **Results:** RIB + LET improved PFS in all pt subgroups (Table). Kaplan–Meier curves will be presented. Clinical trial information: NCT01958021. **Conclusions:** Benefit of RIB was consistent across gene expression subgroups; H vs L *ESR1* and L vs H RTK expression trended towards greater RIB benefit. Genes implicated preclinically in mechanisms of resistance to CDK4/6 inhibitors require further investigation based on metastatic/liquid biopsies, and in larger clinical datasets.

		Events, n/N		
Gene(s)	**Expression level**	**RIB + LET**	**PBO + LET**	**Hazard ratio; 95% CI**
CDK pathway and breast cancer				
ESR1	L	51/101	62/95	0.74; 0.51–1.07
	H	34/96	58/99	0.39; 0.25–0.60
RB1	L	11/21	14/19	0.52; 0.23–1.16
	H	74/176	106/175	0.55; 0.41–0.74
E2F1	L	31/105	45/91	0.56; 0.35–0.89
	H	54/92	75/103	0.52; 0.37–0.75
Implicated in CDK4/6 inhibitor resistance				
CDK2	L	40/103	49/93	0.64; 0.42–0.98
	H	45/94	71/101	0.48; 0.33–0.71
CCNE1	L	32/97	51/99	0.53; 0.34–0.83
	H	53/100	69/95	0.54; 0.38–0.78
FGFR1	L	32/93	59/103	0.45; 0.29–0.69
	H	53/104	61/91	0.63; 0.43–0.91
Involved in alternative pathways				
Cell cycle control	L	32/99	47/97	0.66; 0.42–1.03
	H	53/98	73/97	0.45; 0.31–0.64
PI3K pathway	L	37/98	54/98	0.57; 0.37–0.86
	H	48/99	66/96	0.54; 0.37–0.79
MAPK pathway	L	42/99	61/97	0.55; 0.37–0.81
	H	43/98	59/97	0.56; 0.37–0.83
RTKs	L	39/103	59/93	0.41; 0.27–0.61
	H	46/94	61/101	0.74; 0.50–1.08

1023 Poster Discussion Session; Displayed in Poster Session (Board #104), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Treatment effect of palbociclib (PAL) plus endocrine therapy (ET) by prognostic and intrinsic subtype: A joint analysis of PALOMA2 and PALOMA3. *First Author: Richard S. Finn, David Geffen School of Medicine at University of California, Los Angeles, Santa Monica, CA*

Background: PAL + ET showed significant progression-free survival (PFS) benefit vs ET alone in patients (pts) with HR+/HER2- advanced breast cancer (ABC) in PALOMA2 (PAL2) and PALOMA3 (PAL3). Exploratory analyses were conducted on pts who received neo/adjuvant therapy to evaluate the effect of initial disease-free interval (DFI) in PAL3 or treatment-free interval (TFI) in PAL2 on PFS outcomes. Other analyses assessed luminal (Lum) subtype on PAL efficacy. **Methods:** Pre/postmenopausal pts whose disease has progressed after prior ET (PAL3; N = 521) and postmenopausal pts previously untreated for ABC (PAL2; N = 666) were randomized 2:1 to receive ET (fulvestrant [F] 500 mg or letrozole [L] 2.5mg/d, respectively) + PAL (125 mg/d, 3 wk on/1 wk off) or placebo (PBO). Median follow up was 14 mos (PAL3; 23Oct2015) and 37 mos (PAL2; 31May2017). DFI in PAL3 was calculated as *time between first diagnosis of BC and disease recurrence* and TFI in PAL2 as *time between end of any neo/adjuvant therapy and relapse*. Subpopulation treatment effect pattern plot (STEPP) analysis evaluated the association between DFI/TFI and PFS outcomes of PAL+ET vs PBO+ET for each study. In PAL3 and PAL2, 226 and 364 pts respectively provided FFPE tissue from recurrent or de novo disease where Lum subtype was determined. Gene expression profiling used HTG Molecular's EdgeSeq OBP to assess Lum A/B subtype. **Results:** In PAL3 and PAL2, 355 and 334 pts, respectively, received adjuvant therapy (232/347 PAL + F and 123/174 F + PBO; 219/444 PAL + L and 115/222 L + PBO). Median DFI in PAL3 was 49.2 mo in PAL + F and 52.0 mo in F + PBO; $>$ 80% of pts had DFI $>$ 2 y. Median TFI in PAL2 was 48.9 mo in PAL + L and 44.9 in L + PBO; ~70% of pts had TFI $>$ 2 y. STEPP analyses suggest no impact on PFS outcomes from baseline DFI in PAL3 and TFI in PAL2. Both Lum A and B pts benefited more from PAL +ET than PBO+ET in PAL2 (Lum A HR [95% CI], 0.546 (0.385-0.773); Lum B: 0.508 [0.335-0.768]) and PAL3 (Lum A: 0.408 [0.253-0.659]; Lum B 0.642 [0.379-1.089]). **Conclusions:** Adding PAL to ET showed a significant increase in PFS regardless of the length of initial TFI/DFI and of Lum subtype. Sponsor: Pfizer Clinical trial information: NCT01740427, NCT01942135.

1024 Poster Discussion Session; Displayed in Poster Session (Board #105), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Benefit of CDK 4/6 inhibition in less common breast cancer subsets: A U.S. Food and Drug Administration pooled analysis. *First Author: Jennifer J Gao, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Cyclin dependent kinase 4/6 inhibitors (CDKIs) are approved for 1st and 2nd line endocrine-based therapy in hormone-receptor positive, HER2-negative advanced breast cancer. There is limited clinical data on the benefit and value of adding CDKIs to endocrine therapy in less common subtypes, such as progesterone receptor negative (PR-), de novo metastatic, and lobular breast cancer, which may have differing degrees of endocrine sensitivity. **Methods:** We pooled data from 5 phase 3 randomized registration trials of CDKI with an aromatase inhibitor (AI) in the 1st or fulvestrant in the 2nd-line setting. Exploratory subset analyses focused on patients with de novo metastatic, PR-, and lobular cancer. Progression free survival (PFS) was examined in the ITT populations using Kaplan Meier plots and hazard ratios (HR) with 95% confidence intervals (CI). **Results:** We estimated median PFS differences between the CDKI and control arms (Table 1). In patients with PR- tumors (n = 490), the estimated median PFS difference with the additional CDKI to endocrine therapy was 9.1 mo (HR 0.50, 95% CI 0.40-0.64). In patients with de novo metastatic disease (n = 877), the estimated median PFS difference was 9.6 mo (HR 0.59, 0.48-0.71). In patients with lobular cancer(n = 264), the estimated median PFS difference was 6.9 mo (HR 0.58, 0.42-0.80). Analyses of studies limited to the 1st line setting with an AI and studies in the 2nd line setting with fulvestrant showed similar results. These results are considered hypothesis generating. **Conclusions:** Addition of CDKIs to endocrine-based therapy appears to confer a similar benefit in the relative risk of disease progression or death for the studied subsets of patients compared to the broad population in the labeled indication. Further research is needed to help clinicians identify which patients benefit most from addition of CDKI to endocrine therapy and which should receive CDKI in the 1st-line, 2nd-line, or both settings.

Results.

Subset	N	Median PFS (mo), CDKI	Median PFS (mo), Placebo	PFS Difference (mo)	HR (95% CI)
PR Negative	490	16.5	7.4	9.1	0.50 (0.40-0.64)
De Novo Metastatic	877	24.3	14.7	9.6	0.59 (0.48-0.71)
Lobular Histology	264	16.1	9.2	6.9	0.58 (0.42-0.80)

1025 Poster Session (Board #106), Sat, 8:00 AM-11:30 AM

PAM50 HER2-enriched/ERBB2-high (HER2-E/ERBB2H) biomarker to predict response and survival following lapatinib (L) alone or in combination with trastuzumab (T) in HER2+ T-refractory metastatic breast cancer (BC): A correlative analysis of the EGF104900 phase III trial. *First Author: Tomás Pascual, Department of Medical Oncology, Hospital Clínic of Barcelona, Barcelona, Spain*

Background: In HER2+ BC, HER2-E subtype with high ERBB2 mRNA expression (HER2-E/ERBB2H) is better associated with response following neoadjuvant L and T without chemotherapy than either variable alone (ASCO2018 submitted). Here, we evaluated the ability of this combined biomarker to predict response and survival following anti-HER2 therapy alone in T-refractory HER2+ BC. **Methods:** EGF104900 randomized 296 women with HER2+ advanced BC who experienced progression on prior T-containing regimens to receive either L alone or L+T. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR) and clinical benefit rate (CBR). The expression of 50 PAM50 genes was evaluated from FFPE tumors using an nCounter. A pre-defined HER2-E/ERBB2H definition was applied blinded from clinical data. Multivariable analyses were used to test the association of the HER2-E/ERBB2H variable with PFS, OS, ORR and CBR. Interaction tests between the biomarker and treatment were also evaluated. **Results:** 177 tumors (60%) were analyzed. Subtype distribution was 58.2% HER2-E, 15.3% Basal-like, 10.2% Luminal B, 2.3% Luminal A and 14.1% normal-like. The HER2-E/ERBB2H group represented 48% of all samples. The adjusted PFS hazard ratio (HR) of the HER2-E/ERBB2H group vs. others was 0.48 (95% CI 0.34-0.69, $P < 0.001$). Median PFS of the HER2-E/ERBB2H group was 3.5 months (2.6-54) compared to 1.2 months (1-1.7) in others. The ORR and CBR of the HER2-E/ERBB2H group were higher compared to others (ORR 16.25% vs. 3.66%; $p = 0.017$ and CBR 66.25% vs. 26.83%; $P < 0.001$). For OS, the adjusted HR for HER2-E/ERBB2H vs. others was 0.65 (0.44-0.96, $P = 0.034$). Median OS was higher in the HER2-E/ERBB2H group (14.4 months) compared to others (9.1 months). No significant interaction was observed between HER2-E/ERBB2H and treatment. **Conclusions:** HER2-E/ERBB2-high biomarker in HER2+ T-refractory advanced BC can identify patients who might be good candidates to receive anti-HER2 treatment alone without chemotherapy.

1026 Poster Session (Board #107), Sat, 8:00 AM-11:30 AM

A phase II study of cabozantinib (cabo) alone or in combination with trastuzumab (T) in patients (pts) with breast cancer brain metastases (BCBM). *First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Boston, MA*

Background: BCBM rely on VEGF pathway activation for angiogenesis and dissemination. Activation of MET leads to tumor invasion and resistance to anti-VEGF therapy. The aim of this study was to analyze the efficacy and tolerability of cabo —a small molecule inhibitor of MET and VEGFR2— alone or with T in BCBM pts. **Methods:** This is a single-arm, two-stage phase II study. Eligible pts had new or progressive measurable BCBM. The study included 3 cohorts: Cohort 1 (HER2+), Cohort 2 (HR+ HER2-) and Cohort 3 (triple negative). Pts received cabo 60 mg daily on a 21-day cycle. Cohort 1 also received standard T every 3 weeks. Pts had restaging scans every 6 weeks for 6 cycles, then every 9 weeks; a research brain MRI was performed at baseline and after 1 cycle. Primary objective was CNS objective response rate (ORR) by RECIST 1.1 in Cohort 1. Target sample size for Cohort 1 was 21 pts; if ≥ 3 pts had CNS ORR the null rate (5%) would be rejected in favor of a 30% rate of activity. Secondary objectives were CNS ORR in Cohorts 2 and 3, progression-free survival (PFS), overall survival (OS), toxicity, and changes in *f*MRI vascular parameters and plasma biomarkers. **Results:** 35 pts (Cohort 1 n = 21, Cohort 2 n = 6, Cohort 3 n = 8) were enrolled and this analysis was done with a median follow up of 7.3 months (range 0.8-30.6). Median age was 50 years (range 28-69). Pts had a median of 3 prior lines for metastatic disease (range 1-9). Prior to enrollment, 4 pts underwent craniotomy, 24 pts whole brain radiation and 11 pts stereotactic radiosurgery. Efficacy is shown in the Table. Most common grade 3/4 AE included elevations in lipase (12%), AST (9%), ALT (6%), hyponatremia (9%), thromboembolism (9%), hypertension (6%), fatigue (6%) and vomiting (6%). Ongoing studies are exploring MRI perfusion changes with cabo, and biomarkers of response. **Conclusions:** Cabo was well tolerated but had insufficient activity in heavily pretreated BCBM. Biomarker changes and their association with outcome will be presented at the meeting. Clinical trial information: NCT02260531.

	Cohort 1	Cohort 2	Cohort 3
CNS ORR	5%	17%	0%
Non-CNS ORR	0%	0%	0%
Clinical benefit rate (CR + PR + SD) at 12 weeks	43%	17%	13%
Median time on therapy (months)	4.2	0.8	2.5
Median PFS (months)	4.2	0.8	2.5
Median OS (months)	13.9	2.2	5.2

1027 Poster Session (Board #108), Sat, 8:00 AM-11:30 AM

NSABP FB-10: Phase Ib dose-escalation trial evaluating trastuzumab emtansine (T-DM1) with neratinib (N) in women with metastatic HER2+ breast cancer (MBC). *First Author: Jame Abraham, NSABP Foundation and Cleveland Clinic, Cleveland, OH*

Background: T-DM1 is an antibody-drug conjugate composed of trastuzumab and the maytansinoid antimicrotubule, DM1. T-DM1 was granted FDA approval in 2nd-line MBC after prior trastuzumab (T) and taxane. Current practice in USA is for pts to receive T and pertuzumab (P) as neoadjuvant or as 1st-line therapy. Retrospective analysis of T-DM1 after T-P suggests a lower response rate (17%) than T-DM1 after T and taxane (EMILIA 43%). This study investigates the safety and efficacy of T-DM1 + N. **Methods:** Eligible pts had prior T-P as neoadjuvant therapy or in 1st-line, measurable disease, ECOG PS ≤2, adequate hematologic, renal, and liver function. Pts with stable brain metastases (CNS) were eligible. Treatment was T-DM1 at 3.6 mg/kg iv q 3 wk and N at escalating doses of 120, 160, 200, and 240 mg/d using 3+3 design. HER2 + was required on primary tissue but was not reassessed at entry. Blood samples were required upon entry. Pharmacokinetic (PK) studies were performed on a limited number of pts. Primary diarrhea prophylaxis with intensive loperamide was mandated. **Results:** Twenty-seven T-P resistant pts were enrolled. 26 were evaluable for toxicity, and 20 were evaluable for efficacy. A dose-limiting toxicity occurred in 6 during cycle 1. The RP2D was N 160 mg/d. Treatment-related grade 3 toxicities included diarrhea (5 pts), thrombocytopenia (4), nausea (3), and ALT elevation (1). Of 20 pts evaluable after 2 cycles, 3 had CRs and 9 had PRs (ORR 64%). The duration of response ranged from 42 d to 650+ d. New CNS disease occurred in 1 (8/27 at entry). Nine pts had PK determinations during the first 24h, and 13 had steady-state neratinib level on cycle 2 d1. There was no correlation between N dose and peak or steady-state levels; responses were seen at all doses. Data from blood samples collected on d 1 for HER2 amplification by ctDNA will be presented. **Conclusions:** Full-dose T-DM1 + N at 160 mg/d was well tolerated with notable activity. Responses were seen at all dose-levels of N. Limited PK analysis did not show that peak or steady-state concentration of N was related to response. Baseline peripheral blood samples are being assessed for HER2 amplification. Support: Puma Biotechnology Clinical trial information: NCT02236000.

1028 Poster Session (Board #109), Sat, 8:00 AM-11:30 AM

An open-label, multicenter, phase Ib study to evaluate RC48-ADC in patients with HER2-positive metastatic breast cancer. *First Author: Binghe Xu, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: RC48-ADC is a novel HER2-targeting antibody–drug conjugate (ADC) that selectively delivers anticancer agent MMAE into HER2-overexpressing tumor cells. A Phase I study (NCT02881138) has preliminary demonstrated that RC48-ADC is well tolerated and has clear clinical activity in patients (pts) with metastatic breast cancer (MBC). **Methods:** This was a phase Ib, open-label, multicenter study with 3 dose cohorts (1.5, 2.0 and 2.5mg/kg , Q2W). Eligible pts (18-70 years) were assessed HER2-positive (IHC 2+/FISH +, or IHC 3+) MBC, with relapsed/refractory to prior standard treatment. **Results:** From Dec, 2016 to Jan, 2018, 30 female pts (6 IHC2+/FISH+; 24 IHC 3+) pretreated with trastuzumab/chemotherapy were enrolled for 1.5 and 2.0 mg/kg cohorts. Median age was 53 years (range: 26-62). 19 pts (63.3%) received HER2-targeting agents. 16 pts (53.3%) received three or more previous chemotherapy regimens in metastatic setting. Disease control (CR+PR+SD) was observed in 29 of 30 evaluable pts who received RECIST 1.1 assessment (96.7%), with 11 PR (ORR: 36.7%; 30-76% regression) and 18 SD (60.0%) with tumor regression. CBR (CR + PR + SD ≥6 months) was presented in 14 pts (46.7%). ORR was 26.7% and 46.7% in the 1.5mg/kg and 2.0 mg/kg cohorts, respectively; it was 57.1% in trastuzumab-naive pts and 33.3% in trastuzumab-pretreated pts (12 pts treated with≥3 prior chemotherapy). The common treatment-related adverse events (TRAEs) reported were AST elevation (50.0%), ALT elevation (43.3%), leucopenia (33.3%), neutropenia (33.3%), numbness (23.3%); most were Grade 1-2 in severity. Only 3 pts (10%) reported Grade≤2 thrombocytopenia. Grade 3 TRAEs occurred in 4 pts (13.3%), including neutropenia (10%), leucopenia (6.7%), AST elevation (3.3%), ALT elevation (3.3%). No Grade ≥4 AE was observed. Pharmacokinetic analyses showed dose-dependent exposure with 1-1.5 d half-life. **Conclusions:** RC48-ADC has showed manageable safety and encouraging efficacy profiles in pts with HER2-positive MBC. Investigation of 2.5 mg/kg expansion cohort has not yet been started. Results obtained from Phase I study will determine whether 2.5mg/kg cohort expansion is performed. Clinical trial information: NCT03052634. Clinical trial information: NCT03052634.

1029 Poster Session (Board #110), Sat, 8:00 AM-11:30 AM

A phase I study of a PD-L1 antibody (Durvalumab) in combination with trastuzumab in HER-2 positive metastatic breast cancer (MBC) progressing on prior anti HER-2 therapies (CCTG IND.229)[NCT02649686]. *First Author: Stephen K. L. Chia, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: Immune checkpoint inhibitors are active in a broad range of advanced cancers. Antibody dependent cell mediated cytotoxicity is a mechanism of action of trastuzumab. The combination of the two may enhance activity and/or overcome acquired resistance. We performed a phase I study of durvalumab and trastuzumab in HER-2 positive MBC previously treated with chemotherapy and anti HER-2 antibodies to assess safety, efficacy and correlative end-points. **Methods:** Patients with HER-2 positive MBC, PS 0-2, and previously treated with taxanes and trastuzumab were enrolled on a standard 3+3 dose escalation schedule. Dose level 1 was standard doses of durvalumab (1125 mg i.v. day 1) and trastuzumab (8 mg/kg i.v. loading then 6 mg/kg day 1) on a q3 weekly cycle. An expansion cohort at the recommended phase II dose (RP2D) performed baseline and post cycle 1 tumor biopsies. The primary endpoint of the study was to establish the RP2D. **Results:** 15 patients were accrued across 3 Canadian centres from April – December 2016, of which 14 were evaluable for response. Median age was 54 years (range 40-86), the majority had visceral disease (87%); ≥3 prior lines of chemotherapy (73%), including trastuzumab (93%), pertuzumab (60%) and TDM1 (93%) for MBC. No dose limiting toxicities were observed at dose level 1 (n = 6) or dose expansion (n = 9) during cycle 1. One patient developed ≥ grade 3 irAE (grade 4 diabetes mellitus). No responses by RECIST were seen, with 4/14 (29%) demonstrating stable disease as best response at week 6 (median duration 2.7 months). All patients had < 1% PD-L1 expression on archival tissue (7/15) or pre-study biopsy (8/15). In the dose expansion cohort, evaluable pre-treatment and on-treatment tumor biopsies (n = 5) showed minimal CD8 cell infiltration. Work on the serial ctDNA collected is ongoing. **Conclusions:** The RP2D of durvalumab and trastuzumab is standard full doses of both agents. No significant clinical activity was observed in heavily pre-treated HER-2 positive MBC patients with evidence of cytotoxic T-cell exhaustion. Clinical trial information: NCT02649686.

1030 Poster Session (Board #111), Sat, 8:00 AM-11:30 AM

An open-label, dose-escalation phase I study to evaluate RC48-ADC, a novel antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer. *First Author: Jiayu Wang, Department of Medical Oncology, National Caner Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: There is still urgent medical needs for new therapeutics in the patients with metastatic breast cancer (MBC) and other solid tumors with HER2 overexpression. RC48-ADC is an antibody-drug conjugate drug with a novel humanized anti-HER2 antibody conjugated to monomethyl auristatin E (MMAE) through a cleavable linker. Preclinical data in various animal models, including breast cancer, gastric cancer and ovarian cancer, suggested excellent antitumor efficacy. **Methods:** It was an open-label, single-center, phase I study. Eligible pts (18-65 years) were confirmed by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) as HER2-positive (IHC 2+/FISH+ or IHC 3+) MBC. A 3+3 dose-escalation was conducted with a 28-day window to evaluate dose limiting toxicity (DLT). DLT was mainly defined as Grade 4 neutropenia effectively managed with symptomatic treatment, Grade 3 neutropenia accompanied by infection and Grade 3 non-hematological toxicity. Tumor response was accessed per RECIST 1.1 every 6 weeks. **Results:** As of 29 Jan, 2018, 23 female pts with MBC were treated in 5 dose escalation cohorts (dose levels 0.5, 1.0, 1.5, 2.0, 2.5 mg/kg) once every two weeks (Q2W). Median age was 57 (32-65), and the course of disease was more than 3 years in 15 pts (65.2%). 16 pts (69.7%) were previously treated with trastuzumab. Median prior lines of therapy in metastatic setting was 3 (1-6). 14 pts (60.9%) had≥3 visceral metastatic sites of disease. MTD was not reached at doses up to 2.0 mg/kg Q2W. The most common treatment-related AEs (TRAEs) were leucopenia (43.5% Grade 1-2; 4.3% Grade 3), AST elevation (43.5% Grade 1-2; 4.3% Grade 3), followed by neutropenia (30.4%, Grade 1-2, 13% Grade 3-4), which could be readily managed. 20 pts were evaluable for response. Of 14 pts at doses≥1.5mg/kg , 8 (57.1%) achieved PR and 4 (28.6%) SD. For 11 trastuzumab-pretreated pts, ORR was 72.7%. **Conclusions:** RC48-ADC administrated with Q2W has demonstrated good tolerability and promising antitumor activity in HER2-positive pts with MBC. The MTD has not been determined and 2.5 mg/kg Q2W dose escalation is ongoing. Clinical trial information: NCT02881138. Clinical trial information: NCT02881138.

1031 Poster Session (Board #112), Sat, 8:00 AM-11:30 AM

Serum PD-L1 and outcomes in CCTG MA.31 phase 3 trial of anti-HER2 therapy in first-line HER2+ metastatic breast cancer patients (trastuzumab arm only). *First Author: Kim Leitzel, Penn State Hershey Medical Center, Hershey, PA*

Background: In MA.31 the lapatinib-taxane combination led to shorter PFS than trastuzumab-taxane in HER2+ metastatic breast cancer. We previously reported the positive prognostic utility of pretreatment serum PD-L1 in 63 trastuzumab-treated patients (ASCO 2017, #1024), and here we evaluated it in the trastuzumab arm of MA.31. **Methods:** MA.31 accrued 652 centrally and/or locally-identified HER2-positive patients; in the trastuzumab arm 186 patients had pretreatment serum available.TheELLA immunoassay platform (ProteinSimple, San Jose, CA) was used to quantitate serum PD-L1. Stratified step-wise forward Cox multivariate analysis was used for PFS and OS. **Results:** In univariate analysis for PFS, serum PD-L1 was not a significant biomarker for PFS. In univariate analysis for OS, higher serum PD-L1 was a significant biomarker for shorter OS (continuous PD-L1: HR 3.86, p = 0.044; quartiles of PD-L1: HR 1.55, p = 0.002; median cutpoint PD-L1: HR 2.16, p = 0.014). In multivariate analysis for OS [14 covariates included: age, race, ECOG status, anthracyclines, other chemo, endocrine, radio, other prior adjuvant therapy, disease status, ER status, PR status, Ki67 (log transformed), CK5, EGFR, serum PD-L1], elevated serum PD-L1 was a significant independent covariate [continuous PD-L1: HR 22.7, p = 0.001; median cutpoint PD-L1: HR 2.91, p = 0.0061 (Table)]. **Conclusions:** In the CCTG MA.31 trial, elevated pretreatment serum PD-L1was associated with a shorter OS (but not PFS) with trastuzumab treatment. Immune evasion by the tumor may decrease the effectiveness of trastuzumab therapy. Elevated serum PD-L1 may identify patients who would benefit from addition of an immune checkpoint inhibitor.

Multivariate significant independent covariates for OS (186 patients).

Covariate	p-value	Hazard Ratio	Lower 95% CI	Higher 95% CI
Prior adjuvant/metastatic endocrine therapy (yes vs no)	0.001	4.07	1.75	9.46
Performance status (0 vs 1 or 2)	0.002	0.30	0.14	0.65
Central Review ER status (continuous IHC score)	0.006	0.99	0.98	0.99
Serum PD-L1 (pretreatment) (> median vs < median)	0.006	2.91	1.36	6.25
Prior adjuvant / metastatic radiotherapy (yes vs no)	0.049	0.44	0.19	0.99

1032 Poster Session (Board #113), Sat, 8:00 AM-11:30 AM

Results from a phase I study of andecaliximab in combination with paclitaxel in patients with previously untreated metastatic breast cancer. *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Matrix metalloproteinase-9 (MMP-9) is highly expressed in several advanced cancers, including metastatic breast cancer, and confers an adverse prognosis. In a preclinical breast cancer model, inhibition of MMP-9 was demonstrated with tumor growth inhibition. Andecaliximab (ADX) is a chimeric antibody directed against MMP-9, engineered to remove T cell epitopes and reduce risk of immunogenicity. In this phase I multicohort study, we hypothesized that the combination of ADX with standard of care chemotherapy (paclitaxel) should be safe and tolerable, and demonstrate clinical activity in patients with previously untreated metastatic breast cancer. (Clinicaltrials.gov NCT# 01803282) **Methods:** We enrolled 15 eligible (13 female) patients with radiographically measurable disease and previously untreated metastatic breast cancer. The median age was 59 years (range 23-81). Patients were treated with 800 mg ADX IV every 2 weeks + paclitaxel (80mg/m^2 on days 1, 8, and 15 of a 28-day cycle). The primary endpoints of this study were safety and tolerability. Exploratory endpoints were investigator assessed objective response rate (ORR), progression free survival (PFS), and overall survival (OS). **Results:** As of September 22, 2017, the median ADX treatment duration for this study was 5.3 months. The most common adverse events were alopecia (60%), fatigue (60%), constipation (47%), neutropenia (40%), diarrhea (33%), and nausea (33%). Serious adverse events (SAEs) were reported in 33% of patients. The most common SAEs were acute kidney injury and atrial fibrillation (7% each). The median PFS was 7.4 months (90% CI 5.3-8.6 months) and the overall response rate was 53% (95%CI 30-76%) with 7% complete response rate. The median OS was not reached at the time. Study treatment continues in 27% of patients. **Conclusions:** Combination of ADX with paclitaxel was safe and effective in first-line treatment of patients with metastatic breast cancer. Updated data will be presented at the time of the meeting. Clinical trial information: NCT01803282.

1033 Poster Session (Board #114), Sat, 8:00 AM-11:30 AM

Safety and efficacy of pembrolizumab (pembro) plus capecitabine (cape) in metastatic triple negative breast cancer (mTNBC). *First Author: David B. Page, Earle A. Chiles Research Institute, Portland, OR*

Background: In mTNBC, anti-PD-1/L1 monotherapy was associated with objective response rates (ORR) of 23-26% in the first-line setting, but ORR of 5-6% in later lines. We hypothesize that concurrent pembro plus standard-of-care chemotherapy is safe, and may increase clinical benefit by allowing for earlier treatment with anti-PD-1, when tumor burden and iatrogenic immunosuppression are minimized. This is the first study to explore the combination cape with PD-1/L1 blockade in breast cancer. **Methods:** In a pilot/phase II study, we evaluate the tolerability and preliminary efficacy of concurrent pembro (200mg IV q21 day) plus investigator-selected 1st/2nd line paclitaxel (80mg/m^2 IV weekly) or oral cape (2,000mg BID, weekly 1 on/1 off). The primary endpoint of the pilot phase is tolerability, defined as the proportion of subjects receiving $>$ 6 weeks concurrent therapy without dose discontinuation. Toxicities are reported per CTCAE v4.0. The secondary endpoint is 12-week ORR by RECIST1.1, with potential phase II expansion according to a Simon 2-stage design (if $\geq$4/14 ORR). Exploratory objectives include intratumoral/peripheral immunologic assessments by T-cell receptor sequencing, multispectral immunofluorescence, and real-time multiparametric flow cytometry. Here, we report the results of the pilot phase of the cape cohort (NCT02734290). **Results:** As of 1/1/2018, 100% (9/9) of safety-evaluable subjects tolerated concurrent cape+pembro for at least 6 weeks. Toxicities were generally consistent with monotherapy experience (diarrhea: grade I-II 56%; hand-foot: grade I-II 67%), and improved with dose-reduction. Partial responses have been observed in three subjects, two having metaplastic pathology. A fourth subject experienced durable stable disease, with ongoing response at 48 weeks. **Conclusions:** This study met the primary endpoint of safety for cape plus pembro in mTNBC and the combination will be explored for efficacy in the next stage of this study. These data may also inform the evaluation of concurrent anti-PD-1/L1 plus cape in the adjuvant setting. Clinical trial information: NCT02734290.

1034 Poster Session (Board #115), Sat, 8:00 AM-11:30 AM

Effect of breast tumor subtype and site of distant metastatic disease on prognostic outcome among patients with brain metastases and stage IV denovo breast cancer. *First Author: Shaheenah S. Dawood, Mediclinic City Hospital, Dubai, United Arab Emirates*

Background: The objective of this study was to examine the impact of breast tumor subtype and site of distant metastatic disease on prognostic outcome among patients with stage IV denovo breast cancer who have brain metastases at diagnosis. **Methods:** We searched the SEER registry to identify 1025 patients(pts) with stage IV denovo breast cancer and upfront brain metastases diagnosed between 2010 and 2014. Pts were divided into four groups depending on the breast tumor subtype: a) triple negative (TNBC), b) HER2-ve/HR+ve, c) HER2+/HR-ve, d) HER2+/HR+ve. The presence of distant metastatic disease (DM) other than the brain was defined as disease in the lung, liver or bone. Overall survival (OS) was computed using the Kaplan Meier product limit method. Multivariable cox models were then fit to look at the association of breast tumor subtype and OS adjusted for various pt and tumor characteristics. **Results:** Median age at diagnosis was 60 years and median OS was 9m. 225 (21.5%), 480 (46.8%), 138(13.4%) and 186 (18.15%) pts had TNBC, HER2-ve/HR+ve, HER2+/HR-ve and HER2+/HR+ve disease respectively. Median OS was 5m(TNBC), 13m(HER2-ve/HR+ve), 9m (HER2+/HR-ve), and 21m(HER2+/HR+ve) across the subtypes($p < 0.0001$) respectively. Median OS among those who did and did not have surgery of their primary tumor was 14m and 7m respectively ($p < 0.0001$). Median OS among those with lung , liver , bone only or no distant metastases was 8m, 6m, 15m and 10m respectively ($p < 0.0001$). In the multivariable cox model compared to pts who had TNBC pts who had HER2-ve/HR+ve (HR0.59, CI 0.48-0.73, $p < 0.001$), HER2+/HR-ve (HR0.79, CI 0.60-1.04, $p = 0.09$) and HER2+/HR+ve (HR0.35, CI 0.27-0.47, $p < 0.001$) had a lower risk of death. 250 (24%)pts did not have DM at presentation. Median OS in this cohort was 5m(TNBC), 10m (HER2-ve/HRve+), 14m(HER2+/HR-ve) and 34m (HER2+/HR+ve) across the subtypes respectively($p = 0.0003$). **Conclusions:** Among pts with stage IV denovo breast cancer and brain metastases at diagnosis factors such as bone only or no distant metastatic disease and HER2+v/HR+ve subtype was associated with the best prognostic.

1035 Poster Session (Board #116), Sat, 8:00 AM-11:30 AM

Phase ib study of trastuzumab emtansine (TDM1) in combination with lapatinib and nab-paclitaxel in metastatic HER2-neu overexpressed breast cancer patients: Stela results. *First Author: Tejal Amar Patel, Methodist Cancer Center, Houston, TX*

Background: Based on our preclinical data, we conducted a phase I study oftrastuzumab-emtansine (T-DM1) in combination with Lapatinib and Nab-paclitaxel in patients with HER2 over-expressed stage IV breast cancer. **Methods:** Phase Ib study was conducted using 3+3 dose de-escalation design, with TDM1 with Lapatinib and nab-paclitaxel administered for a total of 4 cycles. Primary purpose was to evaluate the maximum tolerated dose (MTD) of T-DM1 with Lapatinib and Nab-paclitaxel. Safety, tumor response and pharmacokinetics (PK) were also assessed. Dose limiting toxicities (DLTs) were defined as $\geq$ grade 3 non hematological toxicity attributed to the study drugs. Key inclusion criteria were stage IV HER2 positive breast cancer, LVEF $\geq$ 45%, and peripheral neuropathy $<$ grade 2. **Results:** The MTD was T-DM1 3.0 mg/kg every 3 weeks along with Lapatinib 750mg oral daily and Nab-paclitaxel 80mg/m^2 weekly. Twenty four patients, median age 50 (47.9-55.9) years were enrolled. The dose limiting toxicities were diarrhea and elevated liver function tests. At MTD, 42.9% (6/14) experienced grade 3 or higher toxicity. Fourteen patients with median of 1 (range 0-5) prior metastatic treatments were evaluable for response. 12 patients (85.7%) had an objective response including 6 CR and 2 PR. T-DM1 pharmacokinetics was unaffected by Lapatinib. **Conclusions:** T-DM1 with Lapatinib and Nab-paclitaxel therapy was relatively well tolerated with significant anti-tumor activity observed. Clinical trial information: NCT02073916.

1036 Poster Session (Board #117), Sat, 8:00 AM-11:30 AM

A phase Ib trial of copanlisib and tratuzumab in pretreated recurrent or metastatic HER2-positive breast cancer "PantHER". *First Author: Niamh M. Keegan, Beaumont Hospital, RCSI, Dublin, Ireland*

Background: PI3K pathway activation is implicated in resistance to trastuzumab (T) therapy in breast cancer (BC). Copanlisib (C) is a pan-class I PI3K inhibitor with particular activity against PI3Kα, the isoform encoded by the PIK3CA gene. PIK3CA mutation may predict response to PI3K inhibition. **Methods:** The maximum tolerated dose (MTD) and safety of C + T were evaluated in an open label, single arm, adaptive multicenter phase Ib dose escalation clinical trial in patients (pts) with HER-2 positive BC. Eligible pts had disease progression following at least one line of (T) or TDM-1 based therapy in the metastatic setting. Pts were treated with T (4mg/kg loading dose then 2mg/kg weekly) given with C intravenously on Day 1, 8 + 15 of 28 day cycle at one of two dose levels (DL) according to a modified 3+3 (6+6) design. Cycle 1 safety data were used to determine dose limiting toxicities (DLTs). Disease assessments were made every 8 weeks. PIK3CA mutation status was determined in formalin-fixed paraffin-embedded (FFPE) primary tumor blocks by standard sequencing and in serial samples of plasma circulating tumor DNA (ctDNA) during treatment by droplet digital PCR. **Results:** Twelve pts were treated with C + T, 6 on DL1 (45mg) and 6 on DL2 (60mg). Median age was 53yrs. Pts had 15 to 85 months of prior therapy in the metastatic setting with a median of 4 prior lines. There were no DLTs. The MTD and recommended dose for phase II is 60mg. Eleven SAEs were reported. Of these, 36% (n = 4) were infections requiring hospitalization and all resolved with no changes in dose. Grade(G) 3 lung infection and G3 abdominal pain SAEs were reported possibly related to C. All others were considered unlikely or not related to C. G3 liver enzyme rise was reported in 1 pt with a single episode of G4 rise in GGT. G3 hypertension was reported in 33% (n = 4) pts. Best response was stable disease in 9/12 pts and 6 pts continued treatment $\geq$16 weeks. PIK3CA mutation was positive in 6/12 (50%) of tumors. Concordance between PIK3CA mutation in tissue and plasma pre-treatment was 80% with evidence of dynamic change in quantity of mutation during treatment. **Conclusions:** C+T is a safe, well tolerated combination. Efficacy of C+T will be assessed in a phase 2 study at the MTD of 60mg. Clinical trial information: NCT02705859.

1037 Poster Session (Board #118), Sat, 8:00 AM-11:30 AM

Real-world (RW) characteristics, treatment (tx) patterns, and overall survival (OS) in US patients (pts) with metastatic breast cancer (mBC) and CNS metastases (CNS mets). *First Author: Ashwini Shewade, Genentech, Inc., South San Francisco, CA*

Background: About 10–16% of mBC pts are reported to have a CNS mets diagnosis (dx; Lin *JCO* 2004). Data on the management of these pts are limited because they are often excluded from clinical trials due to significant morbidity and mortality. We aim to describe RW characteristics, tx patterns, and OS of mBC pts with CNS mets using an oncology electronic health record database (EHR Db). **Methods:** Flatiron Health's Db is longitudinal, demographically and geographically diverse, and derived from EHR data. Female pts with $\geq$2 clinic visits within the Flatiron network following mBC dx made between Jan '11–Jul '17 were included and followed until Oct '17. CNS mets dx was ascertained based on dx codes and/or unstructured part of EHR. mBC subtype was defined using HER2 and hormone receptor (HR) status. Demographic, clinical, systemic tx, and mortality data were used to characterize mBC pts with CNS mets. **Results:** As of 10/31/'17, the analysis cohort included 10145 mBC pts; 1837 had CNS mets dx during the study period. The table describes incidence of CNS mets by subtype, characteristics at mBC dx for pts with CNS mets, and median OS after CNS mets. Depending on whether CNS mets dx was made at or after mBC dx, among pts with CNS mets and a tx recorded after CNS mets, pts with HER2+ dx commonly (70%/65%, respectively) received tx regimens containing HER2-targeting monoclonal antibodies (MAb), HER2–/HR+ dx commonly (51%/74%) received regimens containing hormonal/other targeted tx or chemotherapy, and triple-negative (TNBC) dx commonly (90%/82%) received chemotherapy. **Conclusions:** CNS mets continues to be an unmet medical need. HER2+/HR– and TNBC have the highest prevalence and/or incidence of CNS mets, whereas HER2–/HR+ has the lowest. HER2+ mBC pts with CNS mets commonly receive subsequent tx including HER2-targeting MAbs and show a trend towards better survival from CNS mets dx than HER2–/HR+ and TNBC.

	All mBC (n = 10145)	HER2+/HR+ (15%)	HER2+/HR– (6%)	HER2–/HR+ (66%)	TNBC (13%)
% CNS mets	18	24	32	13	31
Prevalence at mBC dx, %	8	10	15	5	15
Incidence rate/100 person yrs	7	8	12	5	19
For CNS mets pts					
Median age, yrs	58	56	55	60	57
% *de novo* mBC	29	32	40	25	28
Median OS after CNS mets dx, mo	11	20	19	10	7

1038 Poster Session (Board #119), Sat, 8:00 AM-11:30 AM

SAFE-HEaRt: A pilot study assessing the cardiac safety of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function. *First Author: Filipa Lynce, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC*

Background: HER2 targeted therapies have substantially improved the prognosis of patients with BC however they can be associated with cardiac toxicity. SAFE-HEaRt is the first investigator-initiated trial that prospectively tests whether HER2 therapies may be safely administered in patients with reduced LV function in the setting of ongoing cardiac treatment and monitoring. **Methods:** Eligibility criteria: stage I-IV HER2 positive BC candidates for non-lapatinib therapy; LV ejection fraction (LVEF) $\geq$40% and $<$ 50% and no symptoms of heart failure (HF). All patients had cardiology visits and echocardiograms at baseline, during treatment and 6 months after treatment, and received beta blockers (BB) and ACE inhibitors (ACEi) unless contraindicated. Primary endpoint was completion of planned oncologic HER2 therapy without development of a cardiac event (CE), defined as HF symptoms or asymptomatic decline in LVEF $\geq$10% points from baseline and/or to LVEF $\leq$35%. **Results:** Of 31 enrolled patients, 30 were evaluable. Mean age was 54 years, 18 had early stage and 13 metastatic disease. Seventeen patients had prior exposure to anthracyclines and 13 had hypertension. On study 15 patients were treated with trastuzumab, 14 trastuzumab/pertuzumab and 2 ado-trastuzumab emtansine. Mean LVEF was 45% at baseline and 46% at the end of treatment. Twenty-two patients completed HER2 therapy as defined per protocol without development of a CE and 5 are still on study. Three patients met CE criteria: 2 developed symptomatic HF (at 24 and 36 wks) and 1 had protocol defined LVEF decline to 35% at 12 wks, all were taken off study. Two of these 3 patients are alive and in follow up and 1 died of disease progression. Demographics, previous anthracyclines and baseline LVEF did not predict development of CEs. Elevation of highly sensitive troponin preceded 2 of 3 CEs which was significant (p = 0.003). **Conclusions:** Patients with BC and mildly reduced LVEF can safely receive HER2 therapies in the setting of regular cardiac monitoring and treatment with BB and ACEi. Our results provide new safety data in this unique population and have potential to contribute to clinical practice changes. Clinical trial information: NCT01904903.

1039 Poster Session (Board #120), Sat, 8:00 AM-11:30 AM

Impact of HER2 mutation status on personalized molecular targeted therapy in advanced breast cancers. *First Author: Zongbi Yi, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC), Beijing, China*

Background: Previous studies have indicated that the mechanism of HER2 activation include not only HER2 protein overexpression and gene amplification but also HER2 somatic mutations. The impact of HER2 mutations may be different in HER2-positive (amplified) and HER2-negative (non-amplified) breast cancers. **Methods:** We used next generation sequencing to detect HER2 mutations in circulating tumor DNA and analyzed the relationship between these mutations and the efficacy of anti-HER2 therapies. **Results:** Twenty three HER2 somatic point mutations were identified in 16 of the 120 patients (13.3%) studied. HER2 amplified patients with HER2 point mutations have shorter progression-free survival (PFS) compared to non-HER2 mutations, the median PFS was 5.0 months versus 8.4 months. There were three cases identified where HER2 mutation status impacted the selection of personalized anti-HER2 therapies. Case 1 was a HER2 positive patient with an ERBB2 mutation (c.1900T>C/p.C634R) who was resistant to trastuzumab and lapatinib but sensitive to afatinib. Case 2 was a HER2-negative patient with an ERBB2 mutation (p.L755_T759del) was response to afatinib and trastuzumab. Case 3 was a HER2-negative breast cancer patient with two detected mutations in *ERBB2* (p.S310F and p.D769Y mutations) who benefited from lapatinib combined with endocrine therapies. **Conclusions:** Our data suggest that HER2 mutation-positive patients might be resistant to trastuzumab but sensitive to irreversible kinase inhibitors of HER2, whereas HER2-negative patients with HER2 somatic mutations may still be sensitive to anti-HER2 therapies.

1040 Poster Session (Board #121), Sat, 8:00 AM-11:30 AM

Phase Ib study of gedatolisib in combination with palbociclib and endocrine therapy (ET) in women with estrogen receptor (ER) positive (+) metastatic breast cancer (MBC) (B2151009). *First Author: Andres Forero-Torres, University of Alabama at Birmingham, Birmingham, AL*

Background: The majority of women with ER+ MBC develop resistance to ET. ET plus a CDK4/6 inhibitor (CDKi 4/6) demonstrate improved progression-free survival (PFS) in first/later line MBC. Preclinical evidence in PI3K mutant cell-line xenografts (PIK3CA) supported developing a triplet combination of gedatolisib (G), a dual inhibitor of PI3K/mammalian target of rapamycin (mTOR), with CDKi 4/6 palbociclib (P)+letrozole (L) or fulvestrant (F) for patients (pts) with $ER^+/HER2^-$ MBC. **Methods:** This ongoing dose escalation/expansion study in pts with $ER^+/HER2^-$ MBC, in first/later line MBC, evaluates dose-limiting toxicities/recommended phase 2 dose (DLTs/RP2D) for triplet regimens of G+P+L or G+P+F. A 3-arm expansion investigates objective response rate (ORR) compared to historical controls of Arm A) G+P+L in first-line, B) G+P+F in pts with no prior CDKi 4/6 in second-line and C) G+P+F in pts with prior CDKi 4/6. Pts receive G (180 mg IV/week) combined with P+L or P+F at standard of care doses. Secondary endpoints include safety, ORR, PFS, and pharmacokinetics (PK); exploratory endpoints include genomic analysis of PI3K/mTOR pathway. **Results:** 35 pts received G at RP2D of 180 mg with P+L (n = 15) or P+F (n = 20). Median numbers of prior therapies: G+P+L: 2 (range: 1-2); G+P+F: 1 (range 1-3). Most common (≥50%), drug-related adverse events (%): G+P+L: nausea (80), stomatitis (73), fatigue (60), neutropenia (60), dysgeusia (53); G+P+F: stomatitis (70), fatigue (70), neutropenia (60), nausea (60), dysgeusia (55). Cycle 1 DLTs: G+P+L: grade (gr) 3 neutropenia (n = 2), gr 3 stomatitis (n = 1), gr 3 febrile neutropenia (n = 1); G+P+F: gr 3 stomatitis (n = 2), gr 3 mucositis (n = 1), gr 3 abdominal pain (n = 1). Preliminary stable disease/partial response: G+P+L: 53%/33%; G+P+F: 55%/20%. No PK interactions were observed. PIK3CA and ER mutation status from circulating free deoxyribonucleic acid and duration of response will be reported. Genomic analysis of tumor tissue is underway. **Conclusions:** G can be combined with P+L or P+F with manageable toxicity and promising preliminary antitumor activity. Dose escalation is completed and expansion is ongoing. Clinical trial information: NCT02684032.

1041 Poster Session (Board #122), Sat, 8:00 AM-11:30 AM

Maintenance of health-related quality of life in elderly patients treated with ribociclib + letrozole in MONALEESA-2. *First Author: Howard A. Burris, Sarah Cannon Research Institute, Nashville, TN*

Background: First-line ribociclib + letrozole significantly prolongs progression-free survival vs letrozole alone in patients aged ≥65 y with hormone receptor–positive (HR+), HER2− advanced breast cancer (ABC). Despite the efficacy benefits observed with combination therapy, elderly patients may be receiving single-agent therapy because of toxicity and health-related quality of life (HRQoL) concerns. Here we present key HRQoL outcomes in patients aged ≥65 y in MONALEESA-2. **Methods:** Postmenopausal patients with HR+, HER2− ABC (N = 668) were randomized 1:1 to receive either first-line ribociclib 600 mg or placebo once daily (QD) for 3 wk on, 1 wk off, + letrozole 2.5 mg QD. Patient-reported outcomes were the EORTC QLQ-C30 questionnaire for overall HRQoL/symptom scores and the breast cancer–specific QLQ-BR23 questionnaire for breast symptom score; changes from baseline were determined by a linear mixed-effect model, including responses through treatment cycle 28 day 1 and at end of treatment. Time to 10% deterioration in HRQoL was compared between treatment arms via a stratified log-rank test. **Results:** Among 295 patients aged ≥65 y in this analysis (ribociclib group, n = 150; placebo group, n = 145), HRQoL was maintained with ribociclib + letrozole treatment and at the end of treatment with no significant difference between treatment groups (mean difference, −1.88; 95% CI, −4.58–0.82). Median time to 10% deterioration of HRQoL was similar between the ribociclib group (27.7 mo) and placebo group (28.0 mo; HR, 1.03; 95% CI, 0.69–1.55). In an analysis of the EORTC QLQ-C30 symptom scales, a clinically relevant improvement (> 5 points) was observed for mean pain score in the ribociclib group through the first year of treatment, while mild improvement was observed with the placebo group. Results of the QLQ-BR23 questionnaire showed similar breast symptom scores between treatment groups through end of treatment. **Conclusions:** Consistent with the full study population of MONALEESA-2, HRQoL was maintained in patients aged ≥65 y treated with ribociclib + letrozole. Preliminary analysis indicated a clinically meaningful improvement in pain score for patients aged ≥65 y treated with ribociclib + letrozole. Clinical trial information: NCT01958021.

1042 Poster Session (Board #123), Sat, 8:00 AM-11:30 AM

Activity of tesetaxel, an oral taxane, given as a single-agent in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study. *First Author: Andrew David Seidman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Chemotherapy treatments that offer improved quality of life are needed. Tesetaxel (T) is a novel, oral taxane that has potential advantages over currently available taxanes, including: oral administration with a low pill burden and Q3W dosing; no history of hypersensitivity reactions (HSRs); and improved activity against chemotherapy-resistant tumors (Shionoya 2003; Chan 2006). 555 pts have been treated with T in clinical studies. In MBC, T was shown to have robust single-agent activity in 2 multicenter, Phase 2 studies. In TOB203, 46 pts with HER2- MBC received single-agent T Q3W, including 38 pts with HR+ MBC, the population being enrolled in CONTESSA, an ongoing Phase 3 study. **Methods:** Pts eligible for TOB203 had HER2- MBC, ECOG PS 0-1, measurable disease and adequate organ function. Adjuvant chemotherapy (including taxanes) was allowed. T was administered orally as first-line chemotherapy at 27 mg/m^2 on Day 1 of a 21-day cycle, with escalation to 35 mg/m^2 in subsequent cycles depending on tolerability, without anti-allergy premedication. ORR was the primary endpoint. Final results are provided for all 38 HR+ pts who received T Q3W. **Results:** Median age: 58 (36-80 yrs); 74% received prior endocrine therapy; 68% received prior chemotherapy in the adjuvant setting (53% taxane-containing regimen; 50% anthracycline-containing regimen); median organ systems involved: 2 (1-4); 82% had visceral disease. The confirmed ORR per RECIST 1.1 in all 38 pts was 45% (95% CI: 29% - 62%); median duration of response was 8.7 mo (95% CI: 4.3 – 13.6 mo); median PFS was 5.7 mo (95% CI: 4.1 – 9.8 mo). In the 24 HR+ pts receiving 27 mg/m^2 without escalation, Grade ≥ 3 neutropenia, the most common Grade ≥ 3 AE, occurred in 29% of pts (febrile neutropenia 4%), there were no cases of Grade ≥ 3 peripheral neuropathy, and the incidence of Grade 1/2 alopecia was 29%/21%. There were no HSRs or study drug-related deaths. **Conclusions:** T, as a single agent, was well tolerated with significant activity in pts with HER2-, HR+ MBC. T is currently being investigated in CONTESSA, a multinational, multicenter, randomized, Phase 3 study in pts with HER2-, HR+ MBC (NCT03326674). Clinical trial information: NCT01221870.

1043 Poster Session (Board #124), Sat, 8:00 AM-11:30 AM

Neutropenia and response to single agent palbociclib. *First Author: Nicholas Patrick McAndrew, Basser Research Center for BRCA, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: CDK 4/6 inhibitors have been practice-changing in the treatment of metastatic breast cancer. Their activity against retinoblastoma protein positive (Rb+) breast cancer cells is mediated through cell-cycle arrest at the G1/S checkpoint. The most frequent dose-limiting toxicity is neutropenia (NTP), which, in preclinical studies, also occurs via reversible cell-cycle inhibition. The goal of this study is to determine whether NTP is associated with disease response to single agent palbociclib (PAL) as a predictive biomarker of efficacy. **Methods:** Blood count and response data were analyzed from two phase II clinical trials at different institutions using single agent PAL in 1) advanced Rb+ solid tumors (the "Penn trial", n = 137) and 2) advanced liposarcoma (the "MSK trial", n = 59). The majority of subjects in the Penn trial had breast cancer (45%). The primary endpoint was progression free survival (PFS). For each patient, NTP was examined as cycle 1 nadir absolute neutrophil count (C1ANC) and occurrence of any NTP ≥ Grade 1 (per CTCAE version 3) at any point on trial. **Results:** Results are shown in the table below. Subjects with C1ANCs in the lower quartile had significant improvement in PFS (compared to those in the upper quartile), as did those with any grade NTP (compared to those without NTP). Results were similar in breast cancer subjects, as well as in multivariate cox regression models. Increasing depth of NTP was also associated with increasing PFS days, and subjects requiring dose modification for NTP also had improved PFS. **Conclusions:** NTP on single agent PAL is significantly and independently associated with improved PFS. This should prompt both physicians and patients to avoid stopping the drug prematurely because of neutropenic concerns. Future studies should address dosing based on target ANC. Clinical trial information: NCT01037790; NCT01209598.

Parameter	Subgroup	Median PFS (Days)	HR (95% CI)
C1ANC	> 1.9 K/μL	47	-
	< 0.9 K/μL	144	0.56 (0.37-0.84)
Max Grade NTP	None	42	-
	1	56	0.65 (0.38-1.09)
	2	109	0.33 (0.21-0.50)
	3	145	0.29 (0.20-0.44)
	4	291	0.15 (0.06-0.39)
	Any Grade	120	0.32 (0.23-0.47)
NTP, Breast Only	None	28	-
	Any	121	0.34 (0.12-0.95)
Dose Modification	No	60	-
	Yes	128	0.08 (0.03-0.18)
C1ANC ≤ 0.9 K/μL (Multivariate Cox)	-	-	0.54 (0.36-0.81)
Any Grade NTP (Multivariate Cox)	-	-	0.33 (0.23-0.48)

1044 Poster Session (Board #125), Sat, 8:00 AM-11:30 AM

Exhausted CD8+ cells (Tex) to predict response to PD-1 therapy in estrogen receptor (+) hormone therapy resistant breast cancer predictive of response to immune checkpoint inhibitors after epigenetic priming. *First Author: Pamela N. Munster, University of California, San Francisco, San Francisco, CA*

Background: Immune checkpoint inhibitors have revolutionized cancer therapy, yet have limited efficacy in estrogen receptor $(ER)^+$ breast cancer. Implicated factors include scarcity of tumor infiltrating lymphocytes (TILs), low PD-L1 expression, female gender and liver involvement. *In vitro* and *in vivo* studies suggest that epigenetic modulation with HDAC inhibitors modulate regulatory T cells (Treg) and change TIL composition which is further associated with the presence of a specific immune signature. **Methods:** Patients (pts) with $(ER)^+$ metastatic breast cancer, who progressed on multiple prior therapies, were treated with tamoxifen in combination with vorinostat and pembrolizumab either immediately or after 3 weeks of epigenetic priming in a phase II trial. Comprehensive flow-cytometric immunophenotyping, PD-L1 staining and histone acetylation were evaluated on tumor and blood cells. **Results:** 34 patients (median age 56 years (32-81), heavily pretreated with a median of 5 (2-13) prior regimens received at least one dose of vorinostat and evaluable for response. Grade $^3/_4$ toxicities in 2 pts each (6%) included immune hepatitis, fatigue and thrombocytopenia. Grade 2 toxicities were pneumonitis and colitis in 3%, fatigue in 27% and thrombocytopenia in 12% pts. Six patients did not receive pembrolizumab due to rapid progression or toxicity. Clinical benefits rate defined as CR, PR and stable disease $>$ 6m was seen in 5/28 (18%) pts. Tumor lymphocyte infiltration and PD-L1 expression were low. High expression of PD-1/CTLA-4 dual staining in CD8 cells of $>$ 20% in tumor or blood was seen in 5 pts overall, 4/5 (80%) patients with benefit and in one other patient, who was withdrawn due to immune hepatitis in week 3. Both tumor and peripheral blood CD8 PD-1/CTLA-4 dual expression strongly correlated with time to progression and reduction in $Foxp3^+/CTLA\text{-}4^{high}$ Treg population in tumors by vorinostat. **Conclusions:** Our data highlight the potential for patient selection based on exhausted CD8+ cells in blood or tumor to predict response to immune checkpoint inhibitors in a small subset of $(ER)^+$ breast cancer patients. Clinical trial information: NCT02395627.

1045 Poster Session (Board #126), Sat, 8:00 AM-11:30 AM

EORTC QLQ-C30 (QLQ-C30) symptoms in patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (g*BRCA*m) receiving olaparib vs chemotherapy treatment of physician's choice (TPC) in OlympiAD. *First Author: Mark E. Robson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In the Phase III OlympiAD study, pts with HER2-negative mBC and a g*BRCAm* who received olaparib vs TPC showed statistically significant and clinically meaningful benefit in progression-free survival (NCT02000622; Robson *et al. NEJM* 2017). Global health status/quality of life also favored olaparib. This analysis reports the impact of treatment on symptoms using the QLQ-C30 questionnaire. **Methods:** Pts were randomized (open label) to olaparib tablet monotherapy or single-agent TPC (capecitabine, vinorelbine or eribulin). QLQ-C30, completed by patients at baseline and every 6 weeks until disease progression, evaluated three multi-item symptom scales and five single items (common cancer symptoms). Symptoms were scored on a 0 to 100 scale (higher scores indicated worse symptoms). Statistical analysis included clinically meaningful improvement (reduction in score of $\geq$10 points) and adjusted mean change from baseline scores. **Results:** Overall questionnaire compliance rates were 93.2% for olaparib and 77.3% for TPC. Improvement (symptom response) was more frequent with olaparib vs TPC for all symptoms (Table). Adjusted mean changes in pain scores (estimated difference [ED] −7.4; 95% CI −12.68, −2.03) and dyspnea scores (ED −5.8; 95% CI −10.84, −0.66) favored olaparib over TPC. An increase was seen in nausea/vomiting scores (ED 3.7; 95% CI 0.63, 6.82), despite a numerically higher proportion of pts in the olaparib arm having improvement in nausea/vomiting. **Conclusions:** Overall, more pts demonstrated a clinically meaningful improvement in symptom scores with olaparib than with TPC. Clinical trial information: NCT02000622.

Pts (%) with clinically meaningful improvement in QLQ-C30 symptoms.

	Olaparib N = 205	TPC N = 97	Odds ratio* (95% CI)
Fatigue†	32.7	18.6	2.16 (1.21, 4.00)
Pain†	34.6	16.5	2.70 (1.50, 5.10)
Nausea/vomiting†	16.6	13.4	1.30 (0.66, 2.68)
Dyspnea‡	18.0	7.2	2.85 (1.29, 7.24)
Insomnia‡	23.9	12.4	2.24 (1.16, 4.63)
Appetite loss‡	19.5	8.2	2.73 (1.28, 6.53)
Constipation‡	16.6	5.2	3.69 (1.51, 11.05)
Diarrhea‡	11.2	7.2	1.63 (0.70, 4.24)

*Odds ratio $>$ 1 favors olaparib; †multi-item; ‡single item

1046 Poster Session (Board #127), Sat, 8:00 AM-11:30 AM

A randomized phase II trial evaluating *CYP2D6* genotype-guided tamoxifen dosing in hormone receptor-positive metastatic breast cancer: TARGET-1. *First Author: Toshimi Takano, Toranomon Hospital, Tokyo, Japan*

Background: Tamoxifen (TAM) is a prodrug that requires metabolic activation by CYP2D6. Genetic polymorphism of *CYP2D6* has been speculated to cause suboptimal efficacy of TAM. **Methods:** In a phase II multicenter open-label randomized controlled study, we enrolled candidates for first-line TAM therapy who had hormone receptor–positive (HR+) metastatic breast cancer. *CYP2D6* genotyping was performed using DNA extracted from whole blood at baseline. Patients with heterozygous (wt/V) or homozygous (V/V) variant alleles of decreased or no function were randomly assigned to TAM at regular dose (20 mg/day, RD arm) or increased dose (40 mg/day, ID arm), and patients with homozygous wild-type alleles (wt/wt) received TAM at 20 mg/day. The primary endpoint was 6-month (6M) progression-free survival (PFS) rate. Secondary endpoints included PFS and plasma levels of TAM and its metabolites. **Results:** From December 2012 to July 2016, 186 Japanese patients were enrolled. Of 184 evaluable patients, 136 carried wt/V or V/V (ID arm, 70; RD arm, 66), and 48 carried wt/wt. Patient characteristics (genotype; proportion of HR+ cells; status by recurrent or stage IV disease, bone metastasis, menopause, concurrent LHRH agonist therapy) did not differ significantly between the ID arm and RD arm. PFS rates at 6M were not significantly different between arms (67.6% ID arm vs. 66.7% RD arm; P = .45). Median PFS was longer in the ID arm than in the RD arm (14.2 M vs. 11.7 M; HR, 0.75; P = .15) with a median follow-up of 22.9 M. The trough levels of key active metabolite endoxifen (END) were significantly higher in the ID arm than in the RD arm (median 89.2 nM vs. 51.1 nM; P $<$ .0001). Compared with the levels of END in patients with wt/wt receiving TAM 20 mg/day (72.0 nM), those in patients in the ID arm were not significantly different (P = .0680), and those in patients in the RD arm were significantly lower (P = .0026). Adverse events did not differ significantly between arms. **Conclusions:** In patients with *CYP2D6* variant alleles, increasing TAM dosing resulted in higher plasma END levels. There was no PFS rate difference at 6M, but there was a trend for longer PFS for TAM at 40 mg/day than at 20 mg/day. Long-term follow-up is needed. Clinical trial information: UMIN000009155.

1047 Poster Session (Board #128), Sat, 8:00 AM-11:30 AM

Ribociclib (RIB) + tamoxifen (TAM) or a non-steroidal aromatase inhibitor (NSAI) in premenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) who received prior chemotherapy (CT): MONALEESA-7 subgroup analysis. *First Author: Sara A. Hurvitz, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Although endocrine therapy (ET) and ovarian function suppression is an established first-line treatment for premenopausal patients (pts) with HR+, HER2– ABC, in some cases first-line CT is administered before ET. In the Phase 3 MONALEESA-7 trial (NCT02278120), RIB + TAM/NSAI and goserelin significantly prolonged progression-free survival (PFS) vs placebo (PBO) + TAM/NSAI and goserelin in premenopausal pts with HR+, HER2– ABC. Here, we report results in pts with and without prior CT for ABC. **Methods:** 672 pts with $\leq$1 line of prior CT and no prior ET for ABC were randomized 1:1 to RIB (600 mg/day, 3-weeks-on/1-week-off) or PBO + TAM (20 mg/day) or an NSAI (letrozole [2.5 mg/day] or anastrozole [1 mg/day]) and goserelin (3.6 mg every 28 days). The primary endpoint was PFS. Secondary endpoints included overall response rate (ORR) and safety. Prespecified subgroup analyses were performed in pts with and without prior CT for ABC. **Results:** 47 (14%) pts in each arm had received prior CT for ABC. The most common reason for treatment discontinuation in the RIB vs PBO arm was disease progression (prior CT: 47% vs 55%; no prior CT: 35% vs 51%). Median PFS was increased in the RIB vs PBO arm both in pts with prior CT (16.6 vs 9.0 months; hazard ratio: 0.547; 95% confidence internal [CI]: 0.314–0.954) and without prior CT (24.7 vs 14.5 months; hazard ratio: 0.566; 95% CI: 0.443–0.724). In pts with measurable disease (n = 559), the ORR was 32% vs 27% for those with prior CT (RIB vs PBO arm; P= 0.262) and 54% vs 38% for those with no prior CT (P= 2.90×10^{-4}). Common all-grade adverse events ($\geq$35% of pts in either arm; RIB vs PBO arm) were neutropenia (prior CT: 77% vs 4%; no prior CT: 76% vs 8%), leukopenia (prior CT: 36% vs 4%; no prior CT: 31% vs 6%), and hot flash (prior CT: 23% vs 36%; no prior CT: 36% vs 33%). **Conclusions:** Although pt numbers were small, those with prior CT had a numerically shorter PFS and lower ORR vs pts with no prior CT. However, consistent treatment benefit with RIB + TAM/NSAI vs PBO + TAM/NSAI was observed in premenopausal pts with HR+, HER2– ABC, regardless of prior CT for ABC. Clinical trial information: NCT02278120.

1048 Poster Session (Board #129), Sat, 8:00 AM-11:30 AM

Impact of abemaciclib on the time to subsequent chemotherapy and the time to second disease progression across the MONARCH 2 and 3 studies. *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Abemaciclib is a selective oral inhibitor of CDK4 & 6 dosed on a twice-daily continuous schedule. Abemaciclib was an effective treatment with a generally tolerable safety profile in combination with fulvestrant (F) (MONARCH 2) and as initial therapy (MONARCH 3) when combined with a nonsteroidal aromatase inhibitor (NSAI) in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. To evaluate the impact of abemaciclib in subsequent treatment, we analyzed time to subsequent chemotherapy (TCT) and time to second disease progression (PFS2). **Methods:** Enrollment criteria and study designs of MONARCH 2 and 3 were previously reported (Sledge et al., 2017; Goetz et al., 2017). Exploratory analyses were performed to assess TCT and PFS2 using the Kaplan-Meier (KM) method. Hazard ratios (HR) were estimated using a Cox model. TCT was defined as time from randomization (R) to time to first chemotherapy (CT). Since exact progression date on post-therapies was not available, PFS2 was calculated from R to the discontinuation date of next-line (first line of post-discontinuation treatment), or starting date of the second line of post-discontinuation treatment, whichever was earlier. **Results:** Among randomized patients, 51% and 49% of patients in the MONARCH 2 and 3 trials, respectively, received a post-discontinuation systemic therapy (CT [35%, 26%], endocrine [28%, 38%], targeted agent [18%, 15%], or other [6%, 7%]). Initiation of CT was deferred by adding abemaciclib to F (median: abemaciclib arm, not reached; placebo [P] arm, 26.33 months [m]; HR 0.65, 95% CI 0.50-0.85; $p < .01$) or NSAI (median: abemaciclib arm, not reached; P arm, 32.52 m; HR 0.54, 95% CI 0.38-0.76; $p < .001$). KM analyses of PFS2 showed an improvement in the abemaciclib + F vs P + F arms (HR 0.78, 95% CI 0.61-1.00; $p < .05$) and in the abemaciclib + NSAI vs P + NSAI arms (HR 0.74, 95% CI 0.55-0.99; $p < .05$). **Conclusions:** Adding abemaciclib to F or NSAI delayed the start of subsequent chemotherapy, which is a patient-relevant outcome. Overall, the treatment benefit of abemaciclib + F or + NSAI was extended to the next line of the therapy after the initial disease progression. Clinical trial information: NCT02107703, NCT02246621.

1049 Poster Session (Board #130), Sat, 8:00 AM-11:30 AM

Health-related quality of life (HRQoL) in MONARCH 2: Abemaciclib plus fulvestrant in women with HR+, HER2- advanced breast cancer (ABC) who progressed on endocrine therapy. *First Author: Peter A. Kaufman, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Compared to placebo (P) + fulvestrant (F), the MONARCH 2 HR+, HER2- ABC trial showed abemaciclib + F significantly improved PFS and ORR with a generally tolerable safety profile. Here, patient-reported HRQoL, functioning, and symptoms are reported. **Methods:** Study details were previously reported (Sledge et al. 2017). Data from the modified Brief Pain Inventory short form (mBPI-sf), EORTC QLQ-C30 and EORTC BR23 were collected at baseline, cycle 2 (C2), every 2 cycles from C3 - C13, and then every 3 cycles until short term follow up. Time to worsening (TTW) of pain ($\geq$2 point increase of "worst pain" or $\geq$ 1 level increase of WHO analgesic class) were analyzed by Cox model. Change from baseline for EORTC QLQ-C30 and BR23 subscales and mBPI-sf were analyzed by mixed model. Differences of change from baseline (for each and across all visits) between arms were analyzed. **Results:** PRO completion rates were $>$ 85% for baseline and on-treatment visits; duration of treatment was longer for abemaciclib + F patients (median 15 vs 9 cycles). The TTW for pain was similar between abemaciclib + F and P + F arms (HR = 0.900; p = .4005). No clinical and statistical significance was observed in the EORTC QLQ-C30 and BR23 function and symptom scales or the mBPI-sf; exceptions were higher diarrhea, appetite loss (AL) and nausea/vomiting (N/V) in the abemaciclib + F arm, which were consistent with reported adverse events (AE). The by-cycle analysis showed these higher mean symptom scores were transient for AL and NV, which increased in the first few cycles then gradually returned to near-baseline after cycle 7. Mean diarrhea scores returned to near-baseline levels post-therapy. **Conclusions:** In addition to significantly improved PFS and ORR, abemaciclib + F did not show statistically significant and clinically meaningful differences in patient-reported global health, functioning, or most symptoms compared to P + F. Increased GI-related symptoms were transient and consistent with the manageable, reversible AE profile; the highest symptom burden was reported during early visits. Clinical trial information: NCT02107703.

1050 Poster Session (Board #131), Sat, 8:00 AM-11:30 AM

Combination of paclitaxel and a LAG-3 fusion protein (eftilagimod alpha), as a first-line chemoimmunotherapy in patients with metastatic breast carcinoma (MBC): Final results from the run-in phase of a placebo-controlled randomized phase II. *First Author: Francois P. Duhoux, Department of Medical Oncology, King Albert II Cancer Institute, Cliniques universitaires Saint-Luc and Institut de Recherche Expérimentale et Clinique (Pôle MIRO), Université Catholique de Louvain, Brussels, Belgium*

Background: Eftilagimod alpha (efti, previously IMP321) is a recombinant LAG-3Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. The activation of the dendritic cell network with efti the day after chemotherapy may lead to stronger anti-tumor CD8 T cell responses. We report final results of the safety run-in of a phase IIb trial (NCT02614833) in patients (pts) with hormone receptor positive MBC receiving weekly paclitaxel as first line chemotherapy. **Methods:** In the safety run-in phase 15 pts with MBC received paclitaxel (80 mg/m^2; D1, D8, D15; IV) in a 4-week cycle in conjunction with either 6 mg (n = 6; cohort 1) or 30 mg (n = 9; cohort 2) efti injections (D2 and D16; SC) for 6 cycles. Pts without progressive disease could continue for a maximum of 12 additional efti injections every 4 weeks. Blood samples for pharmacokinetics and immuno-monitoring were taken in cycle 1, 4 and 6. The primary endpoint was determination of the recommended phase 2 dose of this combination. **Results:** Between Jan and Oct 2016 15 pts (median age 53 years) were enrolled. A majority (67 %) of pts were pre-treated with hormonal therapy. Nine (67 %) pts had a serious adverse event, out of which 1 was related to paclitaxel (dizziness grade 3) and 1 to efti (cytokine release syndrome grade 1). No grade 4 and 4 grade 3 adverse events (AEs) in 4 pts were related to efti. Grade 1 and 2 injection site reactions were the most common efti related AEs and occurred in 14 pts (93 %). Increased number of circulating monocytes, dendritic cells and CD8 T cells as well as increased cellular activation were observed. This sustained ($\geq$ 6 months) activation of the cellular response was associated with increased Th1 markers (IFN-g, CXCL10) levels in the plasma. Seven pts (47 %) had a partial response according to RECIST 1.1 (mean duration of 9 months). The disease control rate was 87 %. **Conclusions:** Thirty mg efti SC is the recommended phase 2 dose and is currently investigated in the ongoing phase II part of the study. Efti leads to a steady and sustainable APC and T cell activation. Clinical trial information: NCT02614833.

1051 Poster Session (Board #132), Sat, 8:00 AM-11:30 AM

RIBECCA: A phase IIIb, multi-center, open label study for women with estrogen receptor positive locally advanced or metastatic breast cancer treated with ribociclib (LEE011) in combination with letrozole—Results of the first interim analysis. *First Author: Peter A. Fasching, University Hospital Erlangen, Erlangen, Germany*

Background: RIBECCA is a national, multi-center, open-label, single-arm phase IIIb trial assessing the efficacy and safety of ribociclib in combination with letrozole in a patient population similar to the populations of MONALEESA-2, -3 and -7. Here we present the results of the first pre-planned interim analysis. **Methods:** Main inclusion criteria allow enrollment of men or women with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy, and histological or cytological confirmation of ER+, HER2- breast cancer, irrespective of their menopausal status. The primary objective is to assess the clinical benefit rate (CBR) after 6 months, secondary objectives include progression free survival (PFS), overall survival (OS), safety and changes in quality of life. **Results:** The cut-off date for this first interim analysis was 12 months after the enrollment of the first patient (24-Oct-2017). Here we describe the baseline characteristics and safety data of patients (pts) with at least 12 weeks follow up (n = 338). Baseline characteristics: of 338 pts, 336 were female and 2 male. Median age: 64 yrs; 46 pts pre-or perimenopausal, 290 postmenopausal; ECOC 0-1: 97.3%; median time since first recurrence: 2 months; 74.3% pts had bone metastases, 31.4% liver, 26.9% lung and 28.4% other metastases. 79.6% of pts had received at least one prior endocrine therapy or chemotherapy: 39.5% in the (neo-) adjuvant setting, 39.9% in the palliative setting. Median relative dose intensity was 0.944 for ribociclib and 1 for letrozole. The most common treatment emergent AEs (all grades) were neutropenia (42.3%), nausea (36.7%), fatigue (33.4%), alopecia (29%), diarrhea (20.7%), leukopenia (19.5%), constipation (17.8%), ALT increased (17.1%), AST increased (15.7%) headache (15.9%) and neutrophil count decreased (12.7%). **Conclusions:** The results of the first interim analysis in this additional patient population are in line with data published from the pivotal phase III studies MONALEESA-2 and MONALEESA-7. No new safety signals were detected. Clinical trial information: NCT03096847.

1052 Poster Session (Board #133), Sat, 8:00 AM-11:30 AM

Olaparib versus chemotherapy treatment of physician's choice in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer (OlympiAD): Efficacy in patients with visceral metastases. *First Author: Nadine M. Tung, Beth Israel Deaconess Medical Center and Dana-Farber Harvard Cancer Center, Boston, MA*

Background: The OlympiAD study showed a significant progression-free survival (PFS) benefit for olaparib over chemotherapy treatment of physician's choice (TPC) in patients with HER2-negative metastatic breast cancer (mBC) and a germline *BRCA* mutation (g*BRCA*m; HR 0.58, 95% CI 0.43–0.80). Objective response rate (ORR) was 59.9% in the olaparib arm and 28.8% in the TPC arm. Prognosis may vary by location of metastases, so we investigated the overall efficacy of olaparib vs TPC in mBC patients with specific sites of visceral metastasis. **Methods:** OlympiAD was a randomized Phase III study in patients with HER2-negative mBC and a g*BRCA*m who had ≤2 chemotherapy lines for mBC (NCT02000622). Patients were randomized 2:1 to olaparib tablet monotherapy (300 mg bd) or single-agent TPC (capecitabine, eribulin or vinorelbine). Cox proportional hazard models were used for these *post-hoc* analyses. **Results:** The study was not powered to detect differences in treatment effect between subgroups, and results should be interpreted with caution due to modest patient numbers and baseline imbalances. Key baseline characteristics and PFS by site of metastases are shown in the table. Within these subgroups, overall ORR in evaluable patients was: lung/pleura, 61.2% vs 22.2%; liver, 59.5% vs 25.8%; and brain/CNS metastases, 64.7% vs 20.0%, for olaparib vs TPC, respectively. **Conclusions:** Among patients with HER2-negative mBC and a g*BRCA*m who had metastases in the lung/pleura, liver or brain/CNS, the benefit for olaparib vs TPC appeared consistent with that seen overall, for both PFS and ORR. Clinical trial information: NCT02000622.

	Lung/pleura		Liver		Brain/CNS	
	Olaparib	TPC	Olaparib	TPC	Olaparib	TPC
N	117	54	79	37	18	8
Median age, years	44	44	46	44	44	39
Triple negative BC, %	60 (51.3)	33 (61.1)	26 (32.9)	16 (43.2)	10 (55.6)	6 (75.0)
Prior chemo for mBC	81 (69.2)	35 (64.8)	62 (78.5)	28 (75.7)	16 (88.9)	6 (75.0)
Prior platinum	35 (29.9)	13 (24.1)	24 (30.4)	9 (24.3)	5 (27.8)	4 (50.0)
Median PFS, months	5.7	3.0	5.6	2.9	8.3	2.8
HR_{PFS} (95% CI)	**0.59 (0.41, 0.88)**		**0.73 (0.48, 1.15)**		**0.51 (0.19, 1.58)**	

HR, hazard ratio

1053 Poster Session (Board #134), Sat, 8:00 AM-11:30 AM

The association of early toxicity and outcomes for patients treated with abemaciclib. *First Author: Hope S. Rugo, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Abemaciclib is a CDK4 & 6 inhibitor dosed on a continuous schedule and has demonstrated efficacy with an acceptable safety profile in patients (pts) with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer as monotherapy and in combination with endocrine therapy in the MONARCH 1, 2, and 3 trials. Early onset, low grade diarrhea was the most common toxicity and was typically manageable and reversible with antidiarrheal medication and/or dose reduction. Neutropenia was the most frequent grade 3/4 toxicity in the abemaciclib arms, typically occurring in the first 2 cycles. Here we provide an assessment of the association between these early toxicities, dose adjustment, and progression-free survival (PFS). **Methods:** Enrollment criteria, study designs, and endpoints were previously reported (Dickler et al. 2017; Sledge et al. 2017; Goetz et al. 2017). To examine the impact of dose reductions on efficacy, a time-dependent covariate analysis of dose level versus PFS was performed. A landmark analysis was performed for pts with/without toxicity occurring early in treatment (diarrhea: 7 days; neutropenia: 56 days) by comparing PFS for each of these arms to the placebo arm using a Cox model. **Results:** Discontinuation of abemaciclib due to diarrhea or neutropenia were each < 3% in the abemaciclib arms. Management of toxicity included dose adjustment as necessary. An exploratory time-dependent covariate analysis showed no difference in PFS for pts who dose-reduced compared to those who did not. Compared to placebo, pts in the abemaciclib arms received benefit whether or not diarrhea or neutropenia was observed early in treatment. **Conclusions:** The dose adjustment strategy used in the MONARCH trials appeared to be an effective way to manage toxicity without compromising efficacy. Clinical trial information: NCT02102490, NCT02107703, NCT02246621.

	HR	95% CI
MONARCH 1		
150 vs 200 mg	1.45	.90, 2.33
100 vs 200 mg	1.24	.59, 2.62
MONARCH 2 / 3		
100 vs 150 mg	1.03 / .76	(.68, 1.57) / (.47, 1.25)
50 vs 150 mg	.92 / .99	(.50, 1.71) / (.51, 1.90)
MONARCH 2* / 3*		
With diarrhea	.50 / .49	(.39, .64) / (.35, .67)
Without diarrhea	.61 / .58	(.48, .77) / (.43, .78)
With neutropenia	.58 / .54	(.45, .74) / (.39, .75)
Without neutropenia	.56 / .52	(.43, .73) / (.38, .70)

*HR is compared to placebo arm

1054 Poster Session (Board #135), Sat, 8:00 AM-11:30 AM

The tumor-immune microenvironment (TME) in HR+/HER2- metastatic breast cancer (mBC): Relationship to non-metastatic (met) tumors and prior treatment (tx) received. *First Author: Adrienne Gropper Waks, Dana-Farber Cancer Institute, Boston, MA*

Background: HR+/HER2- primary breast tumors demonstrate less anti-tumor immune activity than HER2+ or triple-negative BC. However, minimal data exist about the TME of HR+/HER2- met tumors, particularly in the tx-refractory setting. Prior analyses also have not looked at macrophages (macs), which may be important in HR+ BC. **Methods:** We obtained met tumor biopsies (bx) from HR+/HER2- mBC patients (pts) on a prospective tissue collection protocol. Tumor-infiltrating lymphocytes (TILs) were scored histologically, and cytokeratin, CD68, CD163, and PD-L1 on tumor cells (tPD-L1) were assessed by multiplex immunofluorescence (IF). Correlation between biomarkers and prior lines of tx was assessed by Spearman coefficient. A previously presented cohort of HR+/HER2- non-met tumors is included for comparison. Biomarker differences between non-mBC and mBC samples were assessed by Wilcoxon rank sum (TILs) and chi2 (tPD-L1) tests. **Results:** 33 HR+/HER2- mBC bx were analyzed from 30 pts (31 assessed for TILs, 21 by IF). Bx sites were 17 (52%) liver, 8 (24%) breast, and 8 (24%) other. Bx were obtained after a mean of 3.9 (range 0-10) lines of tx. Median TILs were 1% (range 0-20%). Ratio of M2 (CD68+CD163+) to M1 (CD68+CD163-) macs was ≥1 in 19/21 samples, suggesting dominance of M2 (immunosuppressive) macs. tPD-L1 was < 1% in 20/21 (95%) pts. There was no significant correlation between level of any cell type (TILs, M1 or M2 macs) and lines of hormonal tx, chemotx, or both received before bx. There was a trend toward lower TILs and lower tPD-L1 in mBC bx compared to a separate cohort (N = 55) of HR+/HER2- non-mBC (Table). Analysis of additional samples, IF stains, and RNA/exome sequence is in process and will be presented. **Conclusions:** HR+/HER2- mBC tumors show a trend toward lower TILs and tPD-L1 than unmatched non-met bx, which may help explain low response rates to checkpoint inhibitors. Immune biomarker levels did not change significantly based on a tumor's degree of pre-tx.

	Value	Non-mBC (N (%))	mBC (N (%))	Test of difference
TILs	Median	5%	1%	p= 0.068
	0-5%	19 (38%)	17 (55%)	
	≥5-10%	22 (44%)	8 (26%)	
	≥10%	9 (18%)	6 (19%)	
tPD-L1	< 1%	40 (78%)	20 (95%)	p= 0.082
	≥1-5%	6 (12%)	1 (5%)	
	≥5%	5 (10%)	0	

1055 Poster Session (Board #136), Sat, 8:00 AM-11:30 AM

Plasma and tumor genomic correlates of response to BYL719 in *PI3KCA* mutated metastatic ER-positive breast cancer (ER+/HER2- BC). *First Author: Sarah-Jane Dawson, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Mutations of genes involved in the PI3K signalling pathway occur frequently in BC. We performed a phase II study of BYL719, a selective PI3Kα inhibitor, in BC to evaluate its efficacy and identify biomarkers that correlate with tumor response. **Methods:** Eligible patients had advanced ER+/HER2- BC and documented genetic alteration of the PI3K pathway detected in either tumor or plasma. Patients received BYL719 350mg orally daily. The primary end point was RECIST objective response rate (ORR). Secondary endpoints were clinical benefit rate (CBR) including stable disease for ≥24 weeks, progression-free survival (PFS) and efficacy according to baseline and week 8 change in ctDNA levels. ctDNA analysis was performed through droplet digital PCR. **Results:** Of the total 17 patients treated, 16 (94%) had a *PIK3CA* mutation (mt) and 1 had a *PTEN* deletion. Of the *PI3KCA* mutant patients, 8 (47%) had a kinase domain mt, 7 (41%) had a helical domain mt and 1 (6%) patient had 2 *PIK3CA* mts. 16/17 (94%) patients had their alteration detected in plasma at baseline; concordance between plasma and tumor was 94% (15/16). Median age was 60 years (45-77). Patients had received a median of 3 prior treatment lines (1-7) in the metastatic setting; 16 (94%) had received prior endocrine therapy and 14 (82%) prior chemotherapy. 15 (88%) had visceral disease. The ORR (centrally reviewed) was 41% (7/17) and CBR was 59% (10/17). Median PFS (mPFS) was 5.49 months (mo) (95% CI, 3.63 – 13.78). The most common grade ≥ 3 adverse event was hyperglycaemia (5/17; 29%). Co-existent *MAP3K1* or *ESR1* mt (N = 7, 41%) had a longer clinical benefit (mPFS 11.02 mo (95%CI, 5.44-NR) with 3 (18%) ≥1 yr) compared with co-existent *TP53* mt, *CCND1* or *FGFR1* amplification (N = 10, 59%) (mPFS 3.66 mo (95%CI, 3.63-NR)). Patients who achieved clinical benefit had a significantly greater decrease in ctDNA levels at week 8 from baseline (median 97.34% vs 9.14% decrease, p = 0.04). **Conclusions:** BYL719 in previously treated advanced ER+/HER2- BC with *PIK3CA* mt detectable in plasma at baseline demonstrated robust clinical benefit. This biomarker should be considered in the Phase III setting. Clinical trial information: NCT02506556.

1056 Poster Session (Board #137), Sat, 8:00 AM-11:30 AM

Ribociclib (RIBO) + letrozole (LET) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) with no prior endocrine therapy (ET) for ABC: Preliminary results from the phase 3b CompLEEment-1 trial. *First Author: Michelino DeLaurentiis, National Cancer Institute "Fondazione G. Pascale", Napoli, Italy*

Background: CDK4/6 inhibitor RIBO has been approved for use in combination with LET for the treatment of HR+, HER2– ABC in postmenopausal women with no prior therapy for advanced disease, based on the significantly prolonged PFS versus placebo + LET observed in the pivotal phase 3 MONALEESA-2 trial (Hortobagyi et al. *NEJM* 2016). Here, we report baseline characteristics and early safety results for the first 1,000 pts enrolled in CompLEEment-1, an open-label, phase 3b trial evaluating RIBO+LET as first-line therapy in an expanded pt population. **Methods:** Pts (N≈3,000) with HR+, HER2– ABC, ≤1 line of prior chemotherapy, and no prior ET for ABC received RIBO (600 mg/day, 3 wk on/1 wk off) + LET (2.5 mg/day); men and premenopausal women received concomitant goserelin (3.6 mg subcutaneous implant every 28 days). The primary outcome was safety and tolerability. A pre-planned interim analysis was conducted ~12 months after first pt first visit. **Results:** Demographics and baseline characteristics for the first 1,007 pts enrolled in the study were captured in the database snapshot (January 17, 2018) and are summarized in Table 1. Details on safety results from the interim database lock (February 2018) will be presented. **Conclusions:** Initial population characteristics from CompLEEment-1 demonstrate a diverse group of pts, more reflective of those seen in a real-world setting. NCT02941926 Clinical trial information: NCT02941926.

Demographics	
Median age, y	60
Pre/postmenopausal/male, %	15/83/2
ECOG PS 0/1/2, %	63/34/3
Disease history	
Histologic grade 1/2/3/4, %	9/39/19/1*
Stage at initial diagnosis I/II/III/IV, %	15/30/19/33*
Median time from initial diagnosis, mo	57
***Current extent of disease*, %**	
Bone	72
Bone only	29
CNS	1
Visceral	55
Lung	22
Liver	39
Skin	3
Lymph nodes	27
***Number of metastatic sites*, %**	
0-2	68
3-5	32
Prior (neo)adjuvant medication, %	57
Chemotherapy for advanced disease, %	19
***Setting at last therapy*, %**	
(Neo)adjuvant	50
Advanced disease	18

*Remaining cases unknown/unavailable

1057 Poster Session (Board #138), Sat, 8:00 AM-11:30 AM

Mutation signature of patients with ER+ metastatic breast cancer who received endocrine therapy. *First Author: Fei Ma, National Cancer Center/ Cancer hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Approximately eighty percent of breast cancer patients are estrogen receptor alpha (ER-α) positive. Although women initially respond well to endocrine therapies, resistance often emerges. In this study we try to analyze the mutations in ER+ metastatic breast cancer patients (MBC) who have received endocrine therapies. **Methods:** Using next-generation sequencing (NGS)–based gene panel test (NGS), we analyzed the mutation profiling in 194 patients (pts) with MBC who were treated by endocrine therapies. **Results:** Somatic genomic alterations in ctDNA including copy number variants and point mutations were identified in 179 of 194 patients (92.3%). *ESR1* activating point mutations or amplifications were identified in 28.9% (56/194) patients, which has been described to be associated with resistance to tamoxifen and AI therapies in patients with ER+ MBC. The most described hotspot activating mutations Y537C/S/N and D538G were detected in 26 and 21 patients, and other described mutations E380Q (13 pts), S463P (2 pts), L536R/H (2 pts), *ESR1* amplifications (2 pts) were also detected. Additionally, nine novel point mutations were identified in *ESR1* (including A58T, T311M, P406A, F435L, R436H, H488N, Q580L, V560E, Y526C). Polyclonal *ESR1* mutations were identified in 13 patients. Another mechanism of resistance to endocrine therapy *FGFR1* amplification was identified in 10 patients and one co-occurring with *ESR1* mutation. For other genes associated with target therapies, *PIK3CA* mutations or *PTEN* deficiency were more common detected in patients with *ESR1* mutation than *ESR1 WT* (50.0% *vs* 35.5%, p= 0.01). *CDKN2A* deficiency/*CCND1* amplification were detected in 4 (7.1%) and 15 (10.9%) patients with or without *ESR1* mutation. In addition, *HER2* amplifications were less common detected in patients with *ESR1* mutation than *ESR1 WT* (3.6% *vs* 14.5%, p= 0.03). **Conclusions:** In ER+ MBC patients with endocrine therapies, *ESR1* and *FGFR1* activating variants were common resistance to endocrine therapies and other targetable variants were also detected. Thus, These patients may benefit from combined treatment, such as endocrine therapies combined with mTOR inhibitors, CDK4/6 inhibitors when other pathways activating together.

1058 Poster Session (Board #139), Sat, 8:00 AM-11:30 AM

Phase IB trial of ACY-1215 (Ricolinostat) combined with nab-paclitaxel in metastatic breast cancer. *First Author: Kevin Kalinsky, Columbia University Medical Center, New York, NY*

Background: HDAC6, a cytoplasmic histone deacetylase, plays an important role in cell-cell interactions, motility, chaperone function, and protein degradation. ACY-1215 is an orally active, selective HDAC6 inhibitor. Preclinical studies have demonstrated ACY-1215 to have synergistic activity with taxanes. We have developed an algorithm (HDAC6 score) based on mRNA expression profiling to evaluate the HDAC6 activity of individual tumor samples. **Methods:** In this open-label phase Ib, patients (pts) received ACY-1215 daily for 21 days of each 28-day cycle with nab-paclitaxel 100 mg/m2 on days 1, 8, and 15 until progression of disease or unacceptable toxicity. The primary objective was to establish the maximum tolerated dose of ACY-1215 with nab-paclitaxel. Dose escalations were performed according to the time to event continual reassessment method (TITE-CRM), starting at 120 mg to a maximum dose of 240 mg daily (qd). The TITE-CRM used an empirical dose-toxicity model, with a sample size of 15 evaluable patients. HDAC score was performed retrospectively on primary and/or metastatic tissue. **Results:** 17 pts were accrued between 3/16-2/18: 15 were evaluable. Of evaluable pts, 3 had triple negative BC and 12 hormone receptor (HR)+/HER2-. The mean number of prior lines was 4 (range: 0-9). The first pt started at 120 mg qd, the second at 180 mg qd, and the rest at 240 mg qd. No dose limiting toxicities were seen. The only grade 3 event thought to be medication-related was syncope in 1 pt. No grade IV events were seen. In evaluable pts, the following were best responses: 1 partial response (PR), 9 stable disease (SD), and 3 progressive disease (PD: 2 TNBC, 1 HR+/HER2-). Two pts recently started and were too early to report. In the first 6 evaluable pts, the HDAC6 score (network size = 243) could significantly dichotomize those with PD vs. SD/PR (p = 0.05). **Conclusions:** ACY-1215 240 mg qd is safe and tolerable with weekly nab-paclitaxel. Clinical activity has been observed, with the majority of pts demonstrating SD and 1 with a PR. Notably, the HDAC6 score appears to preliminarily predict activity. We plan on presenting updated data, including HDAC6 score on additional pts, with data maturity. Clinical trial information: NCT02632071.

1059 Poster Session (Board #140), Sat, 8:00 AM-11:30 AM

Updated efficacy, safety, & PD-L1 status of patients with HR+, HER2- metastatic breast cancer administered abemaciclib plus pembrolizumab. *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Abemaciclib is a selective inhibitor of CDK4 & 6 approved to treat HR+, HER2- metastatic breast cancer (MBC) patients (pts) as monotherapy and in combination with fulvestrant. In preclinical models, abemaciclib administered with anti-programmed death-ligand 1 (PD-L1) antibody therapy synergistically induced anti-tumor response and immunologic memory. A Phase I study (JPBJ, NCT02079636) of abemaciclib plus pembrolizumab (Merck & Co.), a programmed death receptor 1 (PD-1) antibody, demonstrated stable disease in 65% of pts with stage IV NSCLC along with a generally manageable safety profile. **Methods:** JPCE is a multicenter, nonrandomized, open-label, Phase 1b study of abemaciclib plus pembrolizumab in pts with HR+, HER2- MBC or stage IV NSCLC. Key eligibility criteria for the MBC cohort were: HR+, HER2- MBC with 1 - 2 prior chemotherapy regimens, measurable disease, adequate organ function, ECOG PS ≤1, and no prior treatment with CDK4 & 6 or PD-1 & PD-L1 inhibitors. The primary objective was to assess safety of the combination per CTCAE v4.0. Secondary objectives were: objective response rate (ORR), progression-free survival, duration of response, disease control rate, overall survival, pharmacokinetics and pt-reported disease-related symptoms. Pts received the maximum tolerated dose established in JPBJ; orally administered abemaciclib 150 mg twice daily plus IV administered pembrolizumab 200 mg, day 1 of each 21-day cycle. **Results:** Twenty-eight pts were enrolled in the MBC cohort. Abemaciclib plus pembrolizumab demonstrated a generally manageable safety profile in pts with HR+, HER2- MBC. Single agent toxicity profiles reported previously were not exacerbated, and no new safety signals were detected. Initial ORR was 14.3%. Patient PD-L1 status by IHC staining (positive ≥1%; negative < 1%), efficacy, and safety data from the 24-week analysis will be presented. **Conclusions:** Abemaciclib plus pembrolizumab demonstrated a generally manageable safety profile upon initial review (Rugo et al. SABCS 2017). Assessment of the effectiveness of this novel combination, with reference to PD-L1 status, for the treatment of pts with HR+, HER2- MBC is ongoing. Clinical trial information: NCT02779751.

1060 Poster Session (Board #141), Sat, 8:00 AM-11:30 AM

Hematologic adverse events following palbociclib (PAL) dose reduction in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Pooled analysis from randomized phase 2 and 3 studies. *First Author: Sunil Verma, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: A previous pooled analysis showed that 36.9% of pts receiving PAL required dose reduction, most occurring during the first 6 mo of treatment and with decreasing frequency during subsequent 28-d treatment cycles (C). Previous data have also shown that PAL dose reductions do not affect efficacy (Im S-A, et al. ESMO Asia 2017). **Methods:** This analysis evaluated the frequency of hematologic adverse events (AEs) 30 d before and after dose reduction (during each treatment C1–C6) among pts who required PAL dose reduction. Data were pooled from 3 randomized studies: PALOMA-1, a phase 2, open-label study of postmenopausal pts untreated for ABC receiving PAL+letrozole (L) or L alone; PALOMA-2, a phase 3, double-blind study of postmenopausal pts untreated for ABC receiving PAL+L or placebo (PBO)+L; PALOMA-3, a phase 3, double-blind study of pre- or postmenopausal pts who progressed on prior endocrine therapy receiving PAL+fulvestrant (F) or PBO+F. **Results:** A total of 311 pts with HR+/HER2– ABC required a PAL dose reduction (93.6% due to AEs) from 125 to 100 mg. Mean age was 59.9 y, and 46.9% of pts had visceral disease. Median time to dose reduction was 70 d. Incidences of grades 3/4 hematologic AEs were lower after dose reduction (Table), with decreased severity after dose reduction. **Conclusions:** A decrease in frequency and severity of hematologic AEs, including febrile neutropenia, following PAL dose reduction was observed, supporting the use of dose reduction in AE management. Funding: Pfizer (NCT00721409, NCT01740427, NCT01942135). Clinical trial information: NCT00721409, NCT01740427, NCT01942135.

		After Dose Reduction					
Incidence of AEs (Grades 3/4), %	Before Dose Reduction (N = 311)	C1 (N = 310)	C2 (N = 284)	C3 (N = 267)	C4 (N = 253)	C5 (N = 241)	C6 (N = 228)
Neutropenia	66.2/17.4	35.5/2.9	41.2/3.2	34.8/3.4	36.0/2.4	30.3/2.9	36.8/0.9
Leukopenia	27.7/0.6	8.1/0	7.7/0	8.2/0	6.7/0	5.0/0	6.6/0
Thrombocytopenia	1.6/0.3	1.0/0	1.1/0	0.7/0	0.8/0	0/0	0.4/0
Febrile neutropenia	1.9/0.3	0/0	0/0	0/0	0/0	0.4/0	0/0
Anemia	2.6/0	1.6/0	1.1/0	0.7/0	0.8/0	0.8/0	0.4/0

Funding: Pfizer (NCT00721409, NCT01740427, NCT01942135)

1061 Poster Session (Board #142), Sat, 8:00 AM-11:30 AM

G1T38, an oral CDK4/6 inhibitor, dosed continuously in combination with fulvestrant for HR+ breast cancer: Preliminary phase 1b results. *First Author: Iurie Bulat, ARENSIA Exploratory Medicine Research Unit, Institute of Oncology, Chisinau, Moldova, The Republic of*

Background: CDK4/6 inhibition has demonstrated significant improvements in PFS when combined with fulvestrant (F) in patients with breast cancer (BC). G1T38 (38) is a potent, selective oral CDK4/6 inhibitor with best-in-class potential. Continuous daily dosing in preclinical models inhibits tumor growth and leads to a dose-dependent ANC decline and subsequent plateau. A completed Phase 1 trial supports this Phase 1b/2a trial (NCT02983071) in BC patients. **Methods:** Patients with metastatic or locally advanced HR+ HER2(-) BC who had progressed following endocrine therapy are eligible. Patients receive 38 QD or BID continuously with 500 mg F. Primary objectives are to evaluate DLTs, safety, and tolerability and to determine the RP2D and schedule of 38 administered with F. **Results:** To date, 24 patients (median age 55.5) have enrolled and received 38 doses ranging from 200-500 mg QD and 100-150 mg BID for up to 367 days. Dose escalation is ongoing. 38 is well tolerated: no 38-related SAEs have been reported and no patient has withdrawn due to an AE. 1 DLT of Grade 4 neutropenia occurred at 200 mg QD. The most common 38-related TEAEs are cytopenias and GI AEs. There have been no reports of VTE, QT prolongation, or DILI. Incidence/severity of diarrhea is less than abemaciclib, and similar to palbociclib and ribociclib. The degree of neutropenia is consistent with effective CDK4/6 inhibition with 79% all-grade neutropenia. Following an initial decline, ANCs plateau beginning at Week 5, which is consistent with preclinical findings. The % ANC change at Week 5 ranges from -48% (200 mg QD) to -74% (500 mg QD). Confirmed PR rate is 20% in evaluable patients, with a median time to response of 12 weeks. The CBR (CR + PR + SD $\geq$ 24 weeks) is 57%. **Conclusions:** G1T38 is a potential best-in-class CDK4/6 inhibitor. Continuous daily dosing with G1T38 + F is well tolerated with non-dose-limiting ANC decrease that plateaus at week 5, thus eliminating the need for a drug holiday. Early efficacy results are encouraging, and data support continued dose escalation and dose expansion. Combinations of G1T38 in other indications are anticipated; a Phase 1/2a trial of G1T38 + Tagrisso in EGFRm NSCLC will initiate in March 2018. Clinical trial information: NCT02983071.

1062 Poster Session (Board #143), Sat, 8:00 AM-11:30 AM

Everolimus exposure and early metabolic response as predictors for treatment outcomes in breast cancer patients treated with everolimus and exemestane. *First Author: Annelieke Willemsen, Radboud university medical center, Nijmegen, Netherlands*

Background: Treating breast cancer patients (BC pts) with everolimus and exemestane can be challenging due to toxicity and suboptimal treatment responses. We investigated whether everolimus exposure, elderly age, and early metabolic response are predictive of toxicity and effectiveness in these pts. **Methods:** We collected blood samples from BC pts, 14 and 35 days after starting everolimus and exemestane, to measure everolimus trough level (C_{min}). Toxicity, defined as dose interventions (reduction or discontinuation) $<$ 3 months, and progression free survival (PFS) according to RECIST 1.1 were recorded. 18F-FDG-PET was performed at baseline, and 14 and 35 days after start of therapy. SUV normalized by lean body mass was calculated for the maximum voxel and highest peak (SUL_{max} and SUL_{peak}), for up to 5 target lesions. **Results:** In 44 evaluable pts, the geometric mean (GM) C_{min} was higher in pts with dose interventions $<$ 3 months compared to pts without: 17.4 vs 12.3 μg/L (p = .02). The optimal cut-off value to predict toxicity was C_{min} $>$ 19.2 μg/L (AUC 0.71, sensitivity 0.55, specificity 0.92). Elderly pts ($>$ 70 years) compared to pts $<$ 70 years had a shorter median time to dose intervention: 42 vs 141 days (p = .001), but no significant difference in everolimus GM C_{min}: 17.6 vs 13.5 μg/L (p = .12). GM C_{min} of pts with and without progressive disease (PD) $<$ 3 months was not significantly different: 12.0 μg/L vs 15.2 μg/L, respectively (p = .12). FDG-PET scans of 30 pts were analyzed. The percentage decrease in SUL_{peak} of the lesion with highest avidity at day 14 ($SUL_{peak\ high}$ d14) was the best predictor of PD $<$ 3 months. Pts with $>$ 11% vs $<$ 11% decrease in $SUL_{peak\ high}$ at d14 had a median PFS of 411 days vs 90 days respectively (p = .001), and 11 vs 70% of these pts had PD $<$ 3 months. **Conclusions:** Our results show that everolimus toxicity is related to everolimus C_{min} and by monitoring everolimus C_{min}, toxicity might be prevented. We recommend diligent monitoring of elderly pts, as they have toxicity more frequently. No relation was observed between everolimus exposure and effectiveness. FDG-PET is able to early identify pts at high risk of early progression. Further validation of these results is required. Clinical trial information: NCT01948960.

1063 Poster Session (Board #144), Sat, 8:00 AM-11:30 AM

^{18}F-Fluoroestradiol (FES) and ^{18}F-Fluorodeoxyglucose (FDG) PET imaging in lobular breast cancer. *First Author: Poorni Manohar, University of Washington/ Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The histology and pattern of spread in lobular breast cancer has presented challenges in estimating extent of disease by traditional imaging methods. ^{18}F-FES is an estrogen analogue PET imaging tracer which measures tumor ER expression at multiple tumor sites simultaneously. We compared quantitative FES-PET and clinical FDG-PET SUV uptake between patients with metastatic lobular and ductal carcinoma. **Methods:** We retrospectively compared FES and FDG SUV uptake between ER+ lobular and ductal metastatic breast cancer patients (199 ductal, 44 lobular) enrolled in various studies at our institution. Up to nine lesions in each patient were evaluated by FES SUVmax and/or FDG SUVmax for a total of 619 lesions in FES images (n = 509 ductal, n = 110 lobular) and 466 lesions in FDG images (n = 378 ductal, n = 88 lobular). Using linear mixed-effects models, we assessed differences between lobular and ductal histologies in both FES SUVmax and FDG SUVmax. Overall survival (OS), from time of FES-PET scan to death, was evaluated between histologies using Kaplan-Meier curves and the Log-Rank test. **Results:** Among metastatic breast cancer patients with positive FES scans, approximately 10% of patients with ductal histology and 9% with lobular histology had absent FES uptake in at least one lesion. Mean (range) SUVmax in FES and FDG respectively for ductal was 3.48 (0.32, 20.5) and 5.2 (1.1, 26.7) and for lobular was 3.34 (0.61, 9.62) and 4.42 (1.09, 20.0). Difference in FES and FDG SUVmax between histologies was marginal and non-significant. On the natural log scale, lobular carcinomas demonstrated a higher SUVmax (Difference = 0.05, 95%CI = [-0.16, 0.26], p = 0.63) and a lower FDG SUVmax (Difference = -0.53, 95%CI = [-1.61, 0.56], p = 0.34. Following FES-PET imaging, patients with ductal carcinomas had a lower, non-significant median survival time (2.97 vs. 3.03 years, p = 0.81). **Conclusions:** In the metastatic setting, FES and FDG uptake in multiple lesions in ER+ lobular breast cancer patients did not statistically differ from ductal breast cancer. Metastatic lobular breast cancers have similar FES and FDG avidity to metastatic ductal tumors, suggesting these patients may benefit from similar diagnostic and treatment algorithms.

1064 Poster Session (Board #145), Sat, 8:00 AM-11:30 AM

Outcome of everolimus based therapy in hormone receptor positive metastatic breast cancer patients after progression on palbociclib combination. *First Author: Ajay Dhakal, Roswell Park Cancer Institute, Buffalo, NY*

Background: BOLERO 2 trial showed improved progression free survival (PFS) with everolimus (EV) + exemestane combination over exemestane alone in hormone receptor positive, HER2 non-amplified metastatic breast cancer patients (HR+ HER2- MBC) who progressed on an aromatase inhibitor (AI). Recent studies have established CDK 4/6 inhibitors (CDKI) as front line therapy in HR+ HER2- MBC. There are no clinical outcome data of HR+ HER2- MBC on EV after they progress on CDKI. Objective of our study is to analyze clinical outcomes of HR+ HER2- MBC on EV after progression on palbociclib (PA) & compare them with BOLERO 2 results. **Methods:** This is a retrospective, two-institute review of HR+ HER2- MBC from Jan 2015-July 2017 treated with EV after progression on PA. Women who received EV or PA $<$ 4 weeks were excluded. PFS was defined as the time from the initiation of EV to the date of progression as determined by treating physician based on radiological, biochemical and/or clinical criteria. Response rates were determined based on available radiological data. **Results:** 26 women with median age 61 (33-70) were identified. 76% had prior sensitivity to endocrine therapy, 69% had adjuvant chemo/hormonal therapy, 54% had visceral disease, 23% had 3 or more metastatic sites, 100% had ECOG performance status 0 or 1, 92% had prior AI, 65% had received chemotherapy, 35% had received chemotherapy for metastatic disease, 81% had 3 or more lines of prior therapy. Kaplan Meier estimate showed median PFS (95% CI) of 4.4 months (3.3-6.1) and median overall survival (OS) of 18.7 months (9.0- not reached). Median PFS and OS of EV cohort of BOLERO 2 (EV BOL) were 6.9 months (6.4-8.1) and 31.0 months (28.0-34.6). Fisher's exact test comparing current study cohort vs. EV BOL showed significant difference in objective response (complete + partial responses) of 6/26 (23%) vs. 46/485 (9.5%), p = 0.04. **Conclusions:** EV showed shorter PFS and OS but significantly higher objective response in HR+ HER2- MBC who have progressed on PA compared to EV BOL. This small study, for the first time, suggests that EV has evidence of clinical benefit after progression on PA in HR+ HER2- MBC. Larger studies are needed to confirm the results.

1065 Poster Session (Board #146), Sat, 8:00 AM-11:30 AM

Phase II study of Ra-223 combined with hormonal therapy and denosumab for treatment of hormone receptor-positive breast cancer with bone-dominant metastasis. *First Author: Naoto T. Ueno, Morgan Welch Inflammatory Breast Cancer Research Program and Clinic, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Radium-223 dichloride (Ra-223) is a targeted alpha therapy that induces a localized cytotoxic effect on bone metastases. We evaluated the efficacy of combined Ra-223, hormonal therapy, and denosumab in patients with hormone receptor (HR)-positive, bone-dominant metastatic breast cancer. **Methods:** In this single-center phase II study (NCT02366130), patients received Ra-223 (55 kBq/kg intravenously) on day 1 and then every 4 weeks for 6 cycles. Patients also received a hormonal agent (i.e., tamoxifen, aromatase inhibitor, or fulvestrant) at standard dosage and denosumab (120 mg) every 4 weeks. One non-bone metastatic site was allowed. There was no limit on the number of prior hormonal therapies, and one prior chemotherapy was allowed for metastasis. Response was evaluated by PERCIST on FDG PET-CT at baseline, 6 and 9 months (mo). Primary objective was disease control rate at 9 mo. Secondary objectives were tumor response rate at 6 mo and safety. **Results:** After patient accrual (n = 36), the first 30 patients who had 6 mo follow-up or progression prior to 6 mo were analyzed. The median number of prior therapies for metastasis was 1 (range, 0-4). Five patients (16%) received chemotherapy and 7 (23%) a CDK4/6 inhibitor. The median follow-up time was 12.2 mo (95% confidence interval [CI], 9.6–31.7). The disease control rates were 60% at 6 mo and 48% at 9 mo (5 patients had complete response). The median progression-free survival (PFS) was 7.4 mo (95% CI, 4.8–not reached [NR]). The bone-PFS was 15.9 mo (95% CI, 7.4–NR). The median PFS was significantly superior in patients with bone only metastasis than bone with other metastatic site at baseline (NR vs 4.4 mo; $p < 0.0001$). There were no grade 3 or 4 adverse events (AEs). The hematologic AEs were neutropenia (23%), anemia (20%), and thrombocytopenia (13%). **Conclusions:** Our results suggest that addition of Ra-223 to a hormonal agent and denosumab is a potentially effective approach in patients with HR-positive breast cancer with bone metastasis, with no major toxic effects. The impact of metastatic site outside of the bone at baseline must be factored into future clinical trial designs. We will report the updated result. Clinical trial information: NCT02366130.

1066 Poster Session (Board #147), Sat, 8:00 AM-11:30 AM

Sperm associated antigen 5 (SPAG5) as a predictor and monitor for response and distant relapse risk (DRR) to endocrine (ET) and chemo-therapies (CT) in oestrogen receptor positive (ER+) breast cancer (BC). *First Author: Tarek Mohamed Ahmed Abdel-Fatah, Nottingham University City Hospital NHS Trust, Nottingham, United Kingdom*

Background: SPAG5 is an ultimate proliferation marker and important driver that is commonly amplified in "luminal B" BC. **Methods:** SPAG5 copy number aberrations (CNAs), mRNA and protein expression and their association with BC specific survival (BCSS) were determined in 4998 cases of ER+ BC. The association between the pathological complete response (pCR) to neoadjuvant anthracycline based CT (NACT) and SPAG5 expression was evaluated in 1073 (mRNA) and 332 (protein) patients with ER+ BC . The association between the dynamic response to the neoadjuvant ET (NAET) and SPAG5 mRNA expression was evaluated in 101 cases of ER+ BC. The association between distant relapse risk (DRR) and SPAG5 expression were tested in ER+/HER2- patients who received (if eligible) NACT or adjuvant CT in addition to 5-year tamoxifen (mRNA: n = 2819; protein: n = 2501). **Results:** SPAG5 amplification (CNA) and overexpression (SPAG5+, mRNA, protein) were all associated with shorter BCSS (HR: 1.55, 1.31, and 1.90, ps $<$ 0.001); respectively). After receiving NACT, multivariable logistic regression analyses confirmed that SPAG5+ mRNA and protein expression were independently associated with higher pCR (OR: 1.90; p = 0.041 and 23.03; p $<$ 0·0001; respectively). Downregulation of SPAG5 has been observed after 2-weeks on NECT and this predicted the dynamic clinical response ($p < 0.01$). In patients received Tamoxifen alone with either lymph node positive (LN+) or LN negative disease, SPAG5+ BC (mRNA, protein) exhibited a two-fold increase in DRR compared to patients with SPAG5- disease (ps $<$ 0·0001). In contrast, in patients received CT+Tamoxifen with LN+ or LN-disease, SPAG5+ (mRNA, protein) exhibited a similar DRR to that with SPAG5- disease. ER+ patients with SPAG5+ mRNA tumours receiving CT+Tamoxifen has improved 5-year-DRFS by 28% for those with LN- disease (89% vs., 67%; p $<$ 0·001) and 22% for those with LN+ disease (76% vs., 54%; p $<$ 0·001), as compared to receiving Tamoxifen alone. **Conclusions:** SPAG5 could be used as a prognostic and predictive tool for selecting systemic therapies and monitoring response to the selected therapy in patients with ER+ BC.

1067 Poster Session (Board #148), Sat, 8:00 AM-11:30 AM

Healthcare medical costs among post-menopausal women with hormone receptor positive and human epidermal growth factor receptor 2 negative (HR+/HER2-) metastatic breast cancer (mBC) managed with systemic therapy following CDK 4/6 inhibitor (CDKi) in the real-world setting. *First Author: Nicole Princic, Truven Health Analytics, an IBM Company, Cambridge, MA*

Background: To examine US healthcare costs among HR+/HER2- women with mBC having systemic therapy with chemotherapy, endocrine therapy, or everolimus following CDKi. **Methods:** This population-based analysis used MarketScan Commercial and Medicare administrative claims data to select post-menopausal women diagnosed with HR+/HER2- mBC between 1/1/2012-10/31/2017 (index = first evidence of metastatic disease). Eligible patients had ≥1 line of systemic therapy on a chemotherapy, endocrine only, or everolimus-based regimen following a CDK4/6i-based line. All-cause and BC-related medical (excluding pharmacy) costs were measured per-patient per-month (PPPM) during each line of therapy. Generalized linear models were used to compare costs for post-CDKi systemic therapy lines after adjusting for key patient characteristics, including health status and line of therapy. **Results:** In total, 193 chemotherapy,186 endocrine only, and 70 everolimus-based lines following CDKi-based therapy were included. Patients with everolimus-based therapy had significantly ($p < 0.001$) lower all-cause (Δ = \$6,462 PPPM) and BC-related (Δ = \$5,706 PPPM) medical costs compared with chemotherapy and similar medical costs (all-cause and BC-related) compared with endocrine therapy after accounting for BC-related office administered treatment (Table). Results were consistent after adjusting for patient characteristics. **Conclusions:** Patients with HR+/HER2- mBC on everolimus-based therapies relative to chemotherapy following treatment with a CDKi incurred lower medical costs, after accounting for observable confounders.

	Chemotherapy	Endocrine	Everolimus	Everolimus vs. Chemotherapy	Everolimus vs. Endocrine
Total medical	\$11,505	\$6,767	\$5,043	$<$ 0.001	0.083
Total medical without BC-related office administered treatment	\$9,075	\$5,254	\$4,970	0.005	0.767
Total BC- related medical	\$8,506	\$4,899	\$2,800	$<$ 0.001	0.004
Total BC-related medical without office administered treatment	\$6,076	\$3,387	\$2,727	$<$ 0.001	0.311

1068 Poster Session (Board #149), Sat, 8:00 AM-11:30 AM

A phase I study of palbociclib (PALBO) plus everolimus (EVE) and exemestane (EXE) in hormone-receptor positive (HR+)/HER2- metastatic breast cancer (MBC) after progression on a CDK4/6 inhibitor (CDK4/6i): safety, tolerability and pharmacokinetic (PK) analysis. *First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA*

Background: Although adding a CDK4/6i to endocrine therapy (ET) has proved to prolong progression-free survival in patients (pts) with HR+/HER2- MBC, it is unclear if continuing a CDK4/6i, together with subsequent lines of ET, is beneficial. Preclinical data showed that the combination of PI3K inhibitors and CDK4/6i are synergistic, and could restore sensitivity to both CDK4/6i and ET. We present phase Ib data of PALBO + EVE + EXE in pts with HR+/HER2- MBC. **Methods:** In this phase Ib/II study (NCT02871791), pts received escalating doses of PALBO (once daily, days 1–21 of 28-day cycle) + EVE (5 mg/d) + EXE (25 mg/d). Eligible pts had HR+/HER2- MBC, with measurable disease, and prior progression on any CDK4/6i and a non-steroidal aromatase inhibitor. Pts may have received any number of prior lines of ET, and 0-1 prior line of chemotherapy. Exclusion criteria included prior intolerance to 125mg of PALBO and prior use of mTORi or EXE. The primary objective of the phase Ib was to evaluate the safety, tolerability, and to define the maximal tolerated dose (MTD)/recommended Phase II dose (RP2D) of the triplet. Secondary objectives included PK analyses and characterization of genomic alterations by circulating tumor DNA (ctDNA). **Results:** 9 pts were treated on the phase 1 portion of the trial. In the first dose level of PALBO (100mg), 1 out of 3 pts experienced a DLT (G3 neutropenia and G2 mucositis). None of the 3 pts subsequently enrolled had a DLT. PALBO dose was escalated 125mg, and all the 3pts had a DLT (all had G3 neutropenia). PALBO 100mg/d (21 of 28 days) was declared the MTD. Most common G3/4 treatment-related adverse events were neutropenia (77%), and thrombocytopenia (22%). Five pts developed G2 oral mucositis; prophylactic oral dexamethasone rinse was not mandatory. The RP2D was PALBO 100mg/d (21 of 28 days), EVE 5mg/d, and EXE 25mg/d. PK analysis and genomic alterations seen in ctDNA will be presented. **Conclusions:** The triplet combination of PALBO 100mg/d (21 of 28 days) + EVE 5mg/d + EXE 25mg/d is safe in pts with HR+/HER2- MBC. The phase II portion of this trial is ongoing. Clinical trial information: 02871791.

1069 Poster Session (Board #150), Sat, 8:00 AM-11:30 AM

EMBRACA: Efficacy outcomes in clinically relevant subgroups comparing talazoparib (TALA), an oral poly ADP ribose polymerase (PARP) inhibitor, to physician's choice of therapy (PCT) in patients with advanced breast cancer and a germline *BRCA* mutation. *First Author: Hope S. Rugo, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: TALA is a dual-mechanism PARP inhibitor that traps PARP on DNA, preventing DNA damage repair and causing cell death in *BRCA1/2*-mutated cells. **Methods:** EMBRACA (NCT01945775) is an open-label, randomized, 2-arm, phase 3 trial comparing the efficacy and safety of TALA (1 mg/day) with standard single-agent PCT (capecitabine, eribulin, gemcitabine, or vinorelbine) in pts with advanced breast cancer (aBC) and a germline *BRCA1/2* mutation (g*BRCA*^{mut}). PFS by blinded independent central review (BICR) and ORR by investigator were investigated in clinically important subgroups. **Results:** Of 431 pts randomized, 287 were assigned to receive TALA and 144 to PCT. PFS and ORR are shown (Table). **Conclusions:** In pts with advanced g*BRCA*^{mut} breast cancer, TALA demonstrated a statistically significant improvement in both ORR and PFS in clinically relevant subgroups compared with PCT, including pts with CNS metastases, poor performance status, younger age, and visceral disease. Clinical trial information: NCT01945775.

	PFS by BICR n; hazard ratio (95% CI)	ORR by investigator n; odds ratio (95% CI)
Age < 50	249; 0.511 (0.348, 0.750)	191; 5.77 (2.54 - 13.67)
ECOG > 0	192; 0.436 (0.284, 0.668)	147; 3.32 (1.47 - 7.37)
BRCA1	183; 0.595 (0.393, 0.900)	142; 7.01 (2.99 - 19.54)
BRCA2	225; 0.474 (0.320, 0.702)	174; 4.15 (1.90 - 8.52)
TNBC	190; 0.596 (0.406, 0.874)	150; 11.89 (4.54 - 41.37)
HR(+)	241; 0.474 (0.318, 0.708)	183; 2.89 (1.43 - 5.83)
CNS metastases	63; 0.322 (0.154, 0.675)	57; 8.95 (1.86 - 52.26)
Visceral disease	303; 0.505 (0.366, 0.698)	278; 5.27 (2.87 - 9.74)
Prior platinum	76; 0.762 (0.400, 1.451)	63; 3.16 (0.88 - 15.67)
DFI < 12 months	150; 0.562 (0.352, 0.897)	122; 4.86 (1.85 - 19.71)
Prior cytotoxic therapy for advanced breast cancer		
Zero regimens	165; 0.567 (0.339, 0.948)	124; 6.86 (2.65 - 16.81)
1 regimen	161; 0.511 (0.328, 0.797)	119; 5.06 (1.95 - 14.18)
2+ regimens	105; 0.564 (0.336, 0.948)	90; 2.66 (0.88 - 7.80)

1070 Poster Session (Board #151), Sat, 8:00 AM-11:30 AM

Analysis of germline *BRCA1/2 m*utated (g*BRCA*^{mut}) hormone receptor-positive (HR+) and triple negative breast cancer (TNBC) treated with talazoparib (TALA). *First Author: Wolfgang Eiermann, Interdisziplinäres Onkologisches Zentrum München, München, Germany*

Background: TALA is a dual-mechanism PARP inhibitor that traps PARP on DNA in *BRCA1/2*-mutated cells, preventing DNA damage repair and causing cell death. **Methods:** EMBRACA (NCT01945775) is a randomized phase 3 trial comparing TALA (1 mg/day) with physician's choice of therapy (PCT) (capecitabine, eribulin, gemcitabine, vinorelbine) in patients (pts) with g*BRCA*^{mut} advanced breast cancer (aBC). Pts had HR+ BC or TNBC (HER2+ BC pts were excluded). An analysis was conducted to determine if TALA had different efficacy and safety based on receptor expression. **Results:** Of 431 pts randomized, 241 had HR+ BC and 190 had TNBC. TNBC pts had a lower median age compared to HR+ pts (43 vs 50 years); only HR+ pts included males (n = 7). More TNBC pts had received prior platinum therapy (26% vs 11% HR+); both groups had received a median of 1 prior cytotoxic regimen for aBC. Duration of TALA therapy was longer for pts with HR+ compared to TNBC (7.3 vs 5.4 months); 19% of both TNBC and HR+ pts received 12+ months of TALA. The hazard ratio for PFS was similar between the 2 groups, but the median estimates for TALA were different: 0.596 (0.406, 0.874) for TNBC pts, with mPFS of 5.8 months; 0.474 (0.318, 0.708) for HR+ pts, with mPFS of 9.4 months. ORR for TALA was similar for the 2 groups: 61.8% for TNBC vs 63.2% for HR+. Duration of response median for TALA was longer for HR+ (6.8 months) compared to TNBC (4.3 months); both groups included a subset with a prolonged response to TALA (28% HR+ and 17% TNBC had a continued response at 12 months; no PCT patient had a continued response at 12 months). The majority of both HR+ and TNBC TALA pts achieved a CBR24 (74.5% vs 61.5%). The primary toxicity for both groups was hematologic: for HR+ and TNBC, grade 3+ anemia (38.5% vs 40.0%), neutropenia (16.7% vs 26.2%), and thrombocytopenia (12.8% vs 16.9%). Drug-related grade 3+ nonhematologic toxicities were rare in both groups. Serious AEs were similar (30.8% HR+ vs 33.1% TNBC). Few pts experienced an AE that resulted in permanent discontinuation (5.8% HR+ vs 6.2% TNBC). **Conclusions:** Talazoparib demonstrated improved PFS and ORR in pts both with g*BRCA*^{mut} HR+ BC and TNBC. The safety profile in these 2 groups was similar. Clinical trial information: NCT01945775.

1071 Poster Session (Board #152), Sat, 8:00 AM-11:30 AM

Clinical evaluation of germline polymorphisms (SNPs) associated with disease response to capecitabine in metastatic breast cancer (MBC) (TBCRC 015). *First Author: Noura Choudhury, The University of Chicago, Chicago, IL*

Background: Capecitabine is an effective therapy for advanced breast cancer; however, response prediction is imprecise. In this study, we aimed to identify potential SNPs associated with response in MBC pts treated with capecitabine. **Methods:** Women with MBC about to receive single-agent capecitabine were enrolled and then dosed at 2000 mg/m^2/day for 14 d on/7 d off, until unacceptable toxicity or disease progression. Pts were assessed by RECIST criteria. Primary analysis was a genome-wide association study (GWAS) analysis conducted with best response during treatment (PD vs. PR/CR) and stratified for the presence of liver metastases (mets) and estrogen receptor (ER) status. Genotyping was performed on the Illumina Human OmniExpress chip. Analysis was restricted to Caucasian pts to remove confounding by population stratification. **Results:** 258 pts from 14 institutions were enrolled. Pt characteristics included median age 57 yrs (range 25-85), 47.4% with liver mets and 74% were ER+. 30 pts were excluded due to incomplete response data. Final analysis was conducted on 136 Caucasian pts. Response was as follows: 4 (1.9%) CR, 27 (13.1%) PR, 104 (50.4%) SD, 71 (34.4%) PD. While no SNPs reached genome-wide significance ($< 6.9 \times 10^{-8}$), top GWAS signals included a novel SNP upstream of *BP1FB2* (p = 0.0007, OR 27.6), an intronic variant SNP in *ADAMTS3* (p = 0.0007, OR = 51.6), and an intronic variant in *Wnt7a* (p = 0.0009, OR 28.4) as associated with response to capecitabine treatment. *Wnt7a* has been shown to promote tumor aggressiveness through fibroblast activation, and *ADAMTS3* is downregulated in breast cancer compared to normal mammary tissue. *BP1FB2* has not been previously implicated in breast cancer. **Conclusions:** We identified several promising markers of disease response in women with MBC treated with capecitabine. Although these SNPs did not achieve genome-wide significance and may be due to false discovery, further investigation is merited to discern whether *Wnt7A* and *ADAMTS3* are merely markers of aggressive MBC or have a more specific role in influencing capecitabine response. Clinical trial information: NCT00977119.

1072 Poster Session (Board #153), Sat, 8:00 AM-11:30 AM

Anti-tumor activity of PM1183 (lurbinectedin) in combination with capecitabine in metastatic breast cancer patients: Results from a phase I trial. *First Author: Ahmad Awada, Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

Background: PM1183 (lurbinectedin, Zepsyre) is a new anticancer drug that blocks transcription, induces DNA double-strand breaks, and modulates the tumor microenvironment. Single-agent PM1183 has antitumor activity in various solid tumors, including metastatic breast cancer (MBC), and pre-clinical synergism/additivity with fluoropyrimidines. A phase I trial determined the recommended dose (RD) for the oral fluoropyrimidine capecitabine (XEL) as 1650mg/m^2 BID Day (D) 1 to D14 plus PM1183 2.2 mg/m^2 D1, every 3 weeks. Here we present results of the MBC patients (pts) treated in this trial. **Methods:** MBC pts with adequate organ function and < 3 prior chemotherapy lines for advanced disease were treated with PM1183+XEL until disease progression, or unacceptable toxicity. Stable asymptomatic brain metastases were allowed. **Results:** A total of 28 female MBC pts were treated between April 2013 and September 2016; 15 at RD. At cut-off, 5 pts (3 at RD) were still on treatment. Baseline characteristics and efficacy data are shown in Table 1. At RD, hematological toxicities consisted of neutropenia [40% grade (G) 3; 7% G4] and anemia (13% G3). No febrile neutropenia was observed. Non-hematological toxicities were generally mild to moderate, including nausea, fatigue, palmar-plantar erythrodysesthesia syndrome, diarrhea, and decreased appetite. All AEs were reversible and manageable with dose reductions, omissions and/or delays. Main dose-limiting toxicities (DLTs) at maximum tolerated dose were hematological. **Conclusions:** The PM1183+XEL combination showed encouraging clinical activity in MB. Further development is warranted in this indication. Clinical trial information: NCT02210364.

Baseline characteristics and efficacy of PM1183+XEL.

	All dose levels (*n*= 28)	RD (*n*= 15)
Median Age (range; years)	51 (29-71)	46 (29-71)
ECOG 0/1 (%)	64/36	73/27
Visceral disease (%)	96	100
HR+/triple negative (%)	71/29	60/40
Efficacy of PM1183+XEL		
ORR (95% CI; %)	57 (39-79)	47 (21-73)
ORR of HR+ (95% CI; %)	60* (36-81)	56** (21-86)
Clinical benefit rate (%)	68	67
Duration of response (95% CI; mo)	6.8 (3.9-10.2)	6.8 (1.3–not reached)
Progression free survival (95% CI; mo)	7.3 (3.9-10.2)	5.5 (1.1-10.2)

*12/20 pts; **5/9 pts.

1073 Poster Session (Board #154), Sat, 8:00 AM-11:30 AM

Concordance of genomic alterations (GA) in synchronous tumor biopsies (tBx) and circulating tumor (ct) DNA from metastatic breast cancer (MBC) patients (pts). *First Author: Mafalda Oliveira, Medical Oncology Department, Breast Cancer Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Next generation sequencing (NGS) of tBx is the basis for precision medicine. Most tBx used for NGS are archival primary tumors, often acquired several years before starting matched treatment. Analysis of ctDNA may better capture the GA landscape of MBC. We aimed to compare the concordance of GA detection by NGS in synchronously acquired tBx and ctDNA in MBC pts. **Methods:** MiSeq Amplicon-based NGS (panel of 59 cancer-related genes) was performed in both tBx and ctDNA at disease progression. The concordance of GA in tBx vs ctDNA was determined at patient level and at mutation (mut) level in clinically actionable genes (*PIK3CA, AKT1, ERBB2, ESR1, PTEN).* False negative result in ctDNA (FN-ctDNA) defined as mut detected in tBx but not in ctDNA. **Results:** 28 pts identified (luminal [lum] 21, HER2+ 5, triple negative 2), median prior lines of therapy 4.5 (0-15). Most pts had visceral metastasis (71%); most biopsies were from non-visceral sites (67%), mainly breast/nodes/skin (59%). In 16 pts (57%), tBx and ctDNA had complete concordant results (4 were wild-type). Concordance was 100% in non-lum and 43% in lum pts (P=0.01). Clinically actionable GA were found in 20/28 (71%) pts. FN-ctDNA rate was 25%; these pts had a trend towards having non-visceral metastasis (OR 3.1, P=0.32). Focusing in clinically actionable genes, concordance was 52% at mut level, being lower for *ESR1* mut (Table). Interestingly, ctDNA analysis identified 6 *ESR1* mut that were not detected in tissue, including 3 pts with a double *ESR1* mut. **Conclusions:** NGS in ctDNA is feasible and the results may be informative for pts management. Our results suggest that ctDNA may be useful for assessing GA in non-lum MBC and the emergence of *ESR1* mut in lum MBC. Double *ESR1* mut in ctDNA suggests a mechanism of convergent evolution in acquired resistance to endocrine treatment. Causes of discordant tBx/ctDNA (e.g. tumor burden / heterogeneity, technical issues related to ctDNA isolation / processing), warrant further study in larger datasets.

	N mut detected			Concordant mut
	tBx	ctDNA	Overall	N (%)
ERBB2	1	1	1	1 (100)
PIK3CA	9	7	9	7 (78)
ESR1	10	13	16	7 (44)
AKT1	2	0	2	0
PTEN	0	1	1	0
Overall	**22**	**22**	**29**	**15 (52)**

1074 Poster Session (Board #155), Sat, 8:00 AM-11:30 AM

Efficacy of olaparib monotherapy in patients (pts) with HER2-negative metastatic breast cancer (MBC) with germline *BRCA* mutation (g*BRCAm*) or lesional *BRCA* mutation (l*BRCAm*). *First Author: Eleanor Meisner, University of Illinois at Rockford, Rockford, IL*

Background: A recent Phase III study in MBC with g*BRCA*m, olaparib monotherapy provided a statistical significant and clinically meaningful PFS benefit compared to standard physician of choice treatment. (Robson M, NEJM 2017) Recently, olaparib was FDA approved for MBC with g*BRCAm*. **Methods:** IRB-approved analysis of pts underwent to genomic or genetic analysis. Retrospective review charts for pts with MBC who had received ≥2 chemotherapy lines for MBC were tested with genomic or genetic studies. The objective of this analysis was to determine the PFS2/PFS1 ratio. [von Hoff DD, 2014]. l*BRCAm* were detected in 12 out 19 pts [8 Foundation One, 3 Foundation Act and 1 Guardant 360] where somatic versus germline nature was not determined and g*BRCAm* 7 out 19 pts. **Results:** From 03/2014 to 08/2017, 319 pts with advanced cancer were treated with targeted therapy based on molecular abnormality. Overall 19 out 319 (6%) consisted on olaparib for MBC with g*BRCAm* or l*BRCAm*. Median age 45.1 years (range, 31-67), 18 out 19 pts were female, 14/19 were Caucasians, median number of previous lines of treatment for MBC was 4 (range, 2-8). Olaparib was dosed at 300 mg po bid until disease progression. A total of 12 out 19 pts (63%) the PFS ratio was ≥ 1.3, with a Wilson score 95% CI of (0.7, 3.). Nine out 12 pts (75%) with l*BRCAm* had increased PFS ratio. The 6-month PFS was 69.4% [95% CI: (40%, 86.4%)], and the 6-month OS was 88.8% [95% CI: (62.1%, 97.1%)] There was no Grade 3-4 toxicity. **Conclusions:** Olaparib monotherapy provided a statistically significant increment of PFS in almost 2/3 (63%) of heavily pretreated MBC pts harboring g*BRCAm* and l*BRCAm*. Interestingly, 75% of patients with l*BRCAm* resulted in improvement the PFS with minimal toxicity. Further research is necessary to extend the olaparib approval for l*BRCAm* in MBC pts.

1075 Poster Session (Board #156), Sat, 8:00 AM-11:30 AM

Differences of TILs, hormone receptor, and HER2 status between primary and metastatic tumors. *First Author: Makiko Ono, Department of Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Tumor-infiltrating lymphocytes (TILs) are reported to be associated with response to chemotherapy in early breast cancer. However, it is uncertain whether immunological microenvironment alters when tumors recur. The purpose of this study is to compare TILs and HR and HER2 status between paired primary and recurrent tumors. **Methods:** The patients were eligible if they had primary surgery at our institute and their breast cancer recurred, and specimens of recurrent disease were available. High TILs were defined as ≥10%. **Results:** Among 173 recurrent tumors, specimens were metastatic lesion to liver, lung, bone, skin or soft tissue, lymph nodes, and others in 19%, 27%, 16%, 15%, 14%, and 8%, respectively. In primary tumors, 89% were HR positive and 11% were HER2 positive. ER, PgR and HER2 status changed from positive in primary tumors to negative in recurrent tumors in 8%, 40%, and 6%, and changed from negative to positive in 15%, 15%, and 7%, respectively. Accordingly, breast cancer subtype change between primary and recurrent tumors was seen in 13%. High TILs in primary tumors were seen in 22% of patients and significantly associated with breast cancer subtype; HR+HER2-, HR+HER2+, HR-HER+, and HR-HER- in 16%, 36%, 67%, and 62%, respectively ($p < 0.001$). On the other hand, high TILs in recurrent tumors were not correlated with breast cancer subtype, but the site of metastasis; high TILs in 6%, 39%, 12%, 8% and 19% of liver, lung, bone, skin or soft tissue, and lymph node metastases, respectively ($p = 0.002$). In 71% of recurrent tumors, TILs did not change or decreased compared with primary tumors, whereas in 29% TILs increased in recurrent tumors. Among recurrent tumors with increased TILs, most frequent metastatic lesions were lung (40%), and bone metastases were less likely to have tumors with increased TILs (7%). High TILs in recurrent tumors were a positive prognostic marker after recurrence, whereas those in primary tumors were not. **Conclusions:** TILs as well as hormone and HER2 status altered between primary and metastatic tumors. Immunological tumor microenvironment may depend on the site of recurrence and evaluation of recurrent tumors is required in the immunotherapy era.

1076 Poster Session (Board #157), Sat, 8:00 AM-11:30 AM

Poly(ADP-Ribose) Polymerase Inhibitors (PARPi) for patients (pts) with locally advanced or metastatic breast cancer (BC): A meta-analysis. *First Author: Martin Tio, Royal North Shore Hospital, St Leonards, Australia*

Background: We performed a quantitative meta-analysis of randomized clinical trials of PARPi in pts with BC. **Methods:** 2 registries (ClinicalTrials.gov, WHO ICTRP) and 4 electronic databases (CBCG SR, CENTRAL, Medline, EMBASE) were searched from 2008 to 1/2018 for randomized clinical trials (RCTs) of PARPi therapy vs. control in BC. RCTs that reported overall survival (OS) or progression-free survival (PFS) were included. Pooled hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using a fixed effects model. **Results:** We identified 418 citations, of which 2 RCTs with a pooled sample size of n = 733 were included. There was a low/moderate risk of bias in both RCTs (Table). Both RCTs compared a PARPi to physician's choice of chemotherapy in pts with germline BRCA mutated HER2-negative BC in first or later line setting, with PFS as the primary outcome. The pooled analysis of PFS showed a statistically significant improvement with PARPi therapy, with an HR 0.56 (95% CI 0.45-0.68). The pooled analysis of OS did not show a statistically significant improvement, with an HR of 0.82 (95% CI 0.64-1.05). There was an acceptable safety profile with PARP therapy in both RCTs, with a grade $\geq$ 3 adverse event rate of 25.5% and 36.6% in the 2 RCTs respectively. **Conclusions:** The use of PARPi in pts with germline BRCA mutated HER2-negative BC offers a PFS benefit compared to physician's choice of chemotherapy in the first or later line setting, with an acceptable adverse events rate. Lack of OS benefit may be explained by availability of further lines of therapy, relative immaturity of the trials and not being powered to assess OS. This systematic review is part of a planned Cochrane Breast Cancer Group protocol.

	Sequence generation	Allocation concealment	Blinding pts & staff	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Intention to treat
Robson et al, 2017	Centralized random number generator	Allocation concealed	Not blinded	Blinded.	Primary outcome reported 98% of pts	No selective reporting	Yes
Risk	L	L	H	L	L	L	L
Litton et al, 2017	Not described	Not described	Not blinded	Blinded	Primary outcome reported 96% of pts	No selective reporting	Yes
Risk	H	H	H	L	L	L	L

H: High; L: Low

1077 Poster Session (Board #158), Sat, 8:00 AM-11:30 AM

Multi-omic profiling of metastatic lesions to guide treatment selection: The Side Out 2 trial experience. *First Author: Mariaelena Pierobon, George Mason University, Manassas, VA*

Background: The aim of this prospective pilot study, the Side Out 2 trial (NCT01919749), was to explore if treatment selection based on Multi-omic Profiling (MoP) provides clinical benefits superior to empiric treatment selection in progressive metastatic breast cancers (MBC). **Methods:** Fresh core biopsies were collected from the metastatic lesions of 32 MBC patients. Samples underwent genomic and proteomic profiling, including: exome sequencing, RNA-Seq, IHC, and quantitative phosphoprotein-based protein pathway activation mapping by Reverse Phase Protein Microarray (RPPA). Whole tissue lysates were used for the exome sequencing, RNA-Seq and IHC; the RPPA data were obtained from microdissected tumor epithelia. A sample size of 25 evaluable patients was determined a priori according to the exact single-stage design for phase II studies, using a type I error rate of 5% (one-sided) and a power of 90%. Clinical benefit was defined as Growth Modulation Index (GMI) $\geq$ 1.3 assuming that MoP selected therapy would warrant further investigation if $\geq$ 35% of the patients demonstrate a PFS ratio of $\geq$ 1.3. GMI was calculated as a ratio between PFS on MoP selected therapy versus PFS on prior therapy (PMID:25209003). **Results:** Between 2014 and 2016, four US sites enrolled 32 previously treated MBC patients. Of the 32 patients enrolled, 29 received treatment based on their MoP and 25 met the follow-up criteria established by the trial protocol. Of the 25 patients, 14 (56%) met or exceeded a GMI of 1.3. The most frequently selected treatments were irinotecan based on TOPO1 expression (n = 12; single agent n = 6) and capecitabine based on TS expression (n = 9; single agent n = 3). Of the 7 patients that received endocrine therapy, 3 were treated with exemestane+ everolimus. Based on HER2 amplification/pathway activation, HER2 targeted agents were given to 4 patients. **Conclusions:** This study confirmed the unique role of MoP to select effective treatments for MBC. This approach provided clinical benefit for 56% previously treated MBC patients, which met the primary objective of the study. Thus, this approach merits further investigation. This study also suggests that irinotecan may be an under-developed drug for MBC patients. Clinical trial information: NCT01919749.

1078 Poster Session (Board #159), Sat, 8:00 AM-11:30 AM

Efficacy of mirtazapine in preventing delayed nausea and vomiting induced by highly emetogenic chemotherapy: An open-label, randomized, multicenter phase III trial. *First Author: Jun Cao, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: We examined the efficacy of mirtazapine for the prevention of delayed nausea and vomiting in patients who received highly emetogenic chemotherapy (HEC). **Methods:** Patients with breast cancer who experienced delayed emesis after receiving AC or cisplatin containing regimens, and would subsequently accept at least 3 cycles of the same chemotherapy were randomly assigned to a mirtazapine group (15 mg daily on days 2 to 4) or control group, both with aprepitant, a 5-HT3 receptor antagonist and dexamethasone (7.5 mg on day 2 to 4). Primary end point was complete response (CR) to vomiting (no emesis and no rescue treatments) in the delayed phase (25 to 120 h). Secondary end points included CR during acute (0 to 24 h) and overall (0 to 120 h) periods, complete control (CC) (no emesis, no rescue medication use, and no more than grade 1 nausea) during the 3 periods above. **Results:** The study was closed early in January, 2018 due to the slow enrollment. Of 95 patients, 46 in the mirtazapine group and 49 in the control group. Compared with control group in the 1st cycle, delayed and overall CR rates were significantly higher with mirtazapine: 78.3% versus 49.0% (P = 0.003) and 58.7% versus 34.7% (P = 0.019), respectively. Similar result was observed in the 3rd cycle, which showed that delayed CR rates was significantly higher with mirtazapine: 88.2% versus 55.0%, respectively (P = 0.010). Delayed and overall CC rates were significantly higher with mirtazapine both in the 1st and 2nd cycles: 76.1% versus 49.0% (P = 0.006) and 56.5% versus 32.7% (P = 0.019), respectively in the 1st cycle and 70.0% versus 45.7% (P = 0.049) and 50.0% versus 25.7% (P = 0.043), respectively in the 2nd cycle. In the 3rd cycle, delayed CC rates was significantly higher with mirtazapine: 88.2% versus 50.0% (P = 0.010). Adverse effects were mild to moderate. The mirtazapine group had increased somnolence and weight gain. **Conclusions:** Mirtazapine with aprepitant, a 5-HT3 receptor antagonist and dexamethasone significantly improved HEC-induced delayed nausea and vomiting prevention in patients with breast cancer who experienced delayed emesis in the same chemotherapy previously. Clinical trial information: NCT02336750.

1079 Poster Session (Board #160), Sat, 8:00 AM-11:30 AM

Breast cancer stem cell autoantibodies to identify women with advanced breast cancer. *First Author: Sasha E. Stanton, University of Washington, Seattle, WA*

Background: Cancer stem cells have properties of self-renewal, inducing drug resistance, and metastases. Breast cancer stem cells (BCSC) are associated with epithelial to mesenchymal transformation (EMT), increased invasiveness, and metastases. We identified a panel of BCSC proteins involved in EMT that predicted aggressive disease and could be targets for breast cancer vaccines. A therapeutic vaccine of five of the BCSC antigens is currently in a phase 1 clinical trial (NCT02157051) in breast cancer patients. We now demonstrate that autoantibodies of eight BCSC proteins (CDC25b, YB1, CD105, SOX2, CDH3, HIF1alpha, Survivin, and MDM2) identify women with increasing disease in breast cancer and may be a marker of progression of disease. **Methods:** Autoantibodies were evaluated by ELISA from sera of 253 individuals, 100 individuals with no breast atypia, 124 individuals with stage I and II invasive breast cancer (IBC), and 29 individuals with stage III and IV IBC. A positive autoantibody response was greater than 2 standard deviations above the mean of individuals with no IBC (control). **Results:** The percentage of individuals with a positive autoantibody response increased between control and stage I/II IBC and/or stage III/IV in 6 of the 8 autoantibodies. For example with CDC25b, there was 2% positive autoantibody response in control individuals, 13.7% in individuals with stage I/II IBC (p = 0.0014), and 17.2% of individuals with stage III/IV breast cancer (p = 0.0064). There were no differences in mean autoantibodies between breast cancer subtypes except increased autoantibodies to HIF1 alpha in ER+ HER2- disease as compared to HER2+ disease (p = 0.01). The panel of 8 autoantibodies predicted patients with stage I/II IBC from control individuals with AUC of 0.66 (95% CI 0.589 to 0.732, $p < 0.0001$). The panel could predict patients with III/IV IBC from control individuals with AUC of 0.84 (95% CI 0.0.753 to 0.931, $p < 0.0001$). **Conclusions:** These data demonstrate an increasing humoral immune response against 8 BCSC proteins at higher stages of breast cancer and suggests that these autoantibodies indicate more aggressive disease. Future studies will prospectively evaluate the antibody panel as a biomarker for breast cancer progression.

1080 Poster Session (Board #161), Sat, 8:00 AM-11:30 AM

Detection, dynamic monitoring, and resistance mechanism exploration of genomic alterations in circulating cell free tumor DNA (ctDNA) in Chinese metastatic breast cancer (mBC). *First Author: Huiping Li, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Circulating DNA fragments (ctDNA) are using to longitudinal non-invasive molecular monitoring and resistance mechanism interrogation of the disease by detecting genomic alteration change and clonal evolution including somatic mutation and copy number alteration. **Methods:** We performed a retrospective analysis of blood samples from mBC patients (pts) collected at pre-treatment, on-treatment, and disease progression. A highly sensitive, plasma-derived ctDNA-based NGS assay was conducted to detect somatic mutations and copy number variations using pre-specified algorithms. Descriptive statistics and hypothesis tests were performed in R. **Results:** Total 350 blood samples were collected from 160 mBC pts who undertook therapy at Beijing cancer hospital after approved by Research Ethics Committee. Among these pts, the percent of HR+, HER2+ and triple-negative pts is 45%, 27% and 28% respectively. FFPE tissue slides at initial diagnosis were also available for a subset of pts. The most frequent mutations detected are TP53 (40%), PIK3CA (30%), and CDKN2A (12.5%). 24% showed mutations in DNA damage repair such as BRCA1, BRCA2 and ATM. HER2 copy number amplifications was detected amplification events in all IHC-based HER2 positive cases, resulted in 100% specificity and overall 91% accuracy in predicting HER2 amplification status for pre-treatment baseline samples, only a few on-treatment/disease progression samples detected HER2 amplifications. The result is further confirmed and validated by ddPCR assay. The study also identified additional genomic alterations that change dynamically along with the course of treatment or associate with drug response and/or resistance. **Conclusions:** This study showed ctDNA-based genomic analysis was highly sensitive, and consistent with sequencing data generated from matched tissues. it provides comprehensive mutation information of individual pts, enables molecular monitoring of disease and targeted therapy, suggesting that HER2 copy number variations could serve as a value tool for monitoring of treatment effect and disease progression.

1081 Poster Session (Board #162), Sat, 8:00 AM-11:30 AM

Racial disparity in breast cancer immune microenvironment. *First Author: Ahmed Elkhanany, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Racial disparity in breast cancer (BC) goes beyond access to care. Biology of HER2- and Triple Negative (TNBC) tumors has been shown to differ between African Americans (AF) and Caucasians (CF), contributing to survival difference. Additionally, tumor infiltrating lymphocytes (TILs) incurred favorable response to neoadjuvant therapy in ER- and TNBC. We hypothesized that TIL composition of immune microenvironment (IME) differs between AF and CF, potentially explaining such biologic disparity. **Methods:** Using The Cancer Genome Atlas (TCGA), we applied recently described gene expression deconvolutional algorithm CIBERSORT, estimating 22 IME cell proportions. Clinical and PAM50 data were accessed from XENA. Cytolytic activity appended from Rooney et al. **Results:** 183 AF Pts had worse disease-free survival (5-year DFS 21% vs. 26%, HR 1.67[1.02-2.73]) and cumulative incidence of disease (sHR 1.75 [1.09-2.81]) compared with 752 CF Pts, adjusted for age and stage. DFS gap was most prominent in Basal subtype (HR 3[1.03-9.1]). Certain TILs impacted DFS and OS. Higher CD8 T cell fractions improved DFS and OS (HR 0.75[0.59-0.9] and 0.8[0.65-0.95]). Higher activated NK and γδT cell fractions predicted better DFS (HR 0.64 and 0.06). M2 macrophages incurred poor DFS (HR 11.6[1.07-126]). On adjusting for race, activated NK, γδT and M2 macrophage retained respective outcome, but not CD8 T cells. Regulatory T cells (Tregs) did not impact DFS or OS. Comparing AF to CF IME, CD8 T cells were higher in ER+ Pts only. Tregs were higher in whole cohort, Basal and TNBC subtypes. T follicular helper cells were higher in TNBC/Basal, and activated dendritic cells were higher in ER +/Luminal subtypes. Higher memory B, Plasma cells and Macrophages were seen in all subtypes except Basal ($p < 0.01$). Cytolytic activity was similar between AF and CF. It correlated with γδT cells (r^2 0.41, 0.49 in AF) and memory CD4 cells (r^2 0.4, 0.3 in AF), but not DFS or OS. **Conclusions:** IME in BC significantly differs by race, with AF having more Tregs in Basal/TNBC, and more CD8 T cells only in Luminal subtypes. This IME in Basal subtype (and TNBC phenotype) can explain independent worse outcome for this cohort. Incomplete deconvolution of heterogenous Tregs might explain lack of outcome correlation.

1082 Poster Session (Board #163), Sat, 8:00 AM-11:30 AM

Overall survival following locoregional surgery of the primary tumor in de novo stage IV breast cancer patients. *First Author: Herui Yao, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Current guidelines lack definitive evidences about the relative benefits of locoregional surgery for the primary tumor in de novo stage IV breast cancer. The aim of this study was to comprehensively investigate the role of locoregional surgery for primary tumor in de novo stage IV breast cancer. **Methods:** We conducted a Chinese multicenter real-world study of patient-level data to investigate the effect of locoregional surgery versus no surgery of the primary tumor in de novo stage IV breast cancer. We used propensity score matching to compare similar patients who underwent locoregional surgery and no surgery. Overall survival (OS) was estimated using the Kaplan-Meier method and the log-rank test. A meta-analysis also was performed of prospective and retrospective studies, respectively. **Results:** Among 353 patients, 189 (53.6%) received locoregional surgery and 164 (46.4%) underwent no surgery. We matched 202 patients treated with locoregional surgery with similar patients who received no surgery. The median follow-up time was 22.1 (95%CI, 18.8 to 25.9) months, 5-year overall survival was 62.4% in the locoregional surgery group versus 60.3% in the no surgery group, and there was no significant difference in OS (Hazard ratio [HR] 0.88, 95%CI 0.49 to 1.57, $P = 0.66$). In stratified analysis, the association between locoregional surgery and improved survival was particularly marked in patients with Ki67 $\geq$ 20% (HR 0.47, 95%CI 0.22 to 0.97). In addition, pooled results from 42 retrospective studies with 130,153 individuals indicated that locoregional surgery resulted into a significantly prolonged OS (HR 0.65, 95% CI 0.61 to 0.69) compared with no surgery. In contrast, we analyzed the meta-analysis from five prospective trials with 857 participants, finding that there was no significant difference in OS (HR 0.84, 95% CI 0.61 to 1.15) between two groups. **Conclusions:** Based on the evidences of our real-world study, prospective and retrospective meta-analysis, we concluded that locoregional surgery of the primary tumor have no significant survival benefit in de novo stage IV breast cancer. Patients with Ki67 $\geq$ 20% improved survival while receiving locoregional surgery.

1083 Poster Session (Board #164), Sat, 8:00 AM-11:30 AM

Predictors of survival after loco-regional therapy (LRT) in stage 4 breast cancer (BC). *First Author: Anuhya Kommalapati, University of South Carolina, Columbia, SC*

Background: Recent randomized trials evaluating the role of surgery in de novo stage 4 BC yielded mixed results indicating that patient/tumor characteristics might influence the survival. We analyzed the predictors of survival after LRT in stage 4 BC by using National Cancer Data Base (NCDB). **Methods:** Retrospective analysis of histologically confirmed infiltrative ductal (IDC), lobular (LC) and metaplastic stage 4 BC patients from 2004-2015 using NCDB. The study cohort was divided into 2 subsets based on the therapy received: no LRT and LRT (surgery ± radiation). The LRT subset was randomized into training and validation cohorts. In the training cohort, Cox proportional method was used to calculate HRs based on which a 17 point survival prediction scoring system was developed (Table). Both the cohorts were stratified into 3 groups based on the scores- group (G)1 (0-3), G2 (4-7) and G3 (8-17). Kaplan Meier (KM) method and log-rank test were used to compare survival among the 3 groups. We validated the prognostic score by comparing the OS between the respective groups in each cohort. **Results:** A total of 67,978 patients met the inclusion criteria (median age 61 y). The patients in LRT subset (21,120) had significantly better survival (median: 45 vs 24 m) ($p < .0001$). The 3 groups in training cohort showed significant difference in the OS ($p < 0.0001$) – G1 having better prognosis. The 3-year OS rates of the groups were 84% (G1), 66% (G2), and 38% (G3). On validation, comparable OS was seen between the respective groups in each cohort ($p = 0.77$). **Conclusions:** LRT was associated with improved OS in de novo stage 4 BC. Based on the patient/tumor characteristics, we developed a prediction model to characterize the prognostication in patients undergoing LRT for stage 4 BC.

Parameter	HR (CI does not include 1);$p < 0.05$	Score
Age	-	-
≤49	-	0
50-74	1.17	1
≥75	2.19	2
Race	-	-
White	-	0
Black	1.18	1
CDCC	-	-
0-1	-	0
2-3	1.72	1
Grade	-	-
1-2	-	0
3-4	1.45	1
Histology	-	-
IDC	-	0
LC	1.21	1
Metaplastic	2.06	2
Receptor status	-	-
TP	-	0
HR+/HER-	1.60	1
HR-/HER+	1.46	1
TN	4.54	3
Metastasis	-	-
Bone	1.36	1
Brain	2.48	2
Liver	1.44	1
Lung	1.31	1
All	4.36	3
Combos	2.65	2
T4	1.25	1
No Radiation	1.40	1
Surgical margins positive	1.39	1
Lymphovascular invasion	1.23	1

1084 Poster Session (Board #165), Sat, 8:00 AM-11:30 AM

Analysis of circulating tumor cells (CTCs) in patients across multiple metastatic breast cancer (mBCa) cohorts identifies marked inter- and intra-patient heterogeneity in CTC size, shape, and overall morphology. *First Author: Gordon Vansant, Epic Sciences, Inc., San Diego, CA*

Background: The choice between hormonal therapies and chemotherapy is a frequent decision in the care of mBCa pts. We previously developed quantitative measures of phenotypic CTC heterogeneity in mCRPC, and found higher heterogeneity was associated with better survival on chemotherapy vs. targeted hormonal therapies, and the reverse was true in low heterogeneity patients (Scher et al. 2017 Cancer Research). We sought to apply our previous heterogeneity quantitation methodologies to a cohort of mBCa patient CTCs to ascertain feasibility in mBCa. **Methods:** 295 blood samples from mBCa patients were processed for CTC analysis utilizing the Epic Sciences platform. Following enumeration, multi-dimensional phenotypic characterization analysis was performed utilizing protein expression and digital pathology features. Features from each CTC (3994 CTCs from 165 pts, 84 HR+, 19 Her2+, 8 HR+/Her2+, 54 TNBC) were compared by unsupervised clustering, Shannon Index and intra-patient variance analyses to assess the intra-patient heterogeneity among mBCa CTC phenotypes. **Results:** CTCs were detected in 76.9% (227/295) of mBCa patients (med = 2.4 CTC/mL, Range 0 - 747). Distinct CTC phenotypes were identified and associated with mBCa subtypes. Subset of CTCs from TNBC pts had larger nuclear area and higher CK expression vs. other subtypes. In addition, we observed marked differences in heterogeneity in CTCs across patients, with some patients having relative uniform CTC profiles, and others with high phenotypic diversity. mBCa subtypes had similar intra-patient heterogeneity level. **Conclusions:** Distinct CTC phenotypes can be visualized reproducibly across patients and associated with specific mBCa subtypes. Our analysis revealed significant heterogeneity between individual CTCs both between and within patients. Identification of patients with high heterogeneity may help to find patients unlikely to respond to targeted therapies. Studies to link heterogeneity to therapeutic efficacy and pt outcome are ongoing.

1085 Poster Session (Board #166), Sat, 8:00 AM-11:30 AM

Polymorphisms of MTHFR and TYMS to predict capecitabine-induced hand-foot syndrome in patients with metastatic breast cancer. *First Author: Shaoyan Lin, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, P.R.CHINA, Beijing, China*

Background: Breast cancer is a global problem, and 1.7 million new cases are diagnosed per year. Capecitabine, an oral prodrug of fluorouracil, has been reported to be effective in patients with metastatic breast cancer (MBC) and approved by the Unites States Food and Drug Administration for treatment of MBC. Hand-foot syndrome (HFS) is one of the most relevant dose-limiting adverse effects of capecitabine. If HFS is not handled well, it can deteriorate rapidly and lead to the treatment interruptions which may influence on the treatment efficacy. **Methods:** In our study, we investigated the association between single nucleotide polymorphism (SNP) and capecitabine-based HFS in patients with MBC in Chinese Han population, in an attempt to identify some predictive genetic biomarkers. We selected 3 genes involved in capecitabine metabolism and screened genetic variants in the target genes. We genotyped a total of 22 SNPs in the thymidylate synthase gene (*TYMS*), the methylene tetrahydrofolate reductase gene (*MTHFR*) and the ribonucleotide reductase M1 gene (*RRM1*) in 342 patients treated with capecitabine-based chemotherapy. **Results:** Logistic regression analyses showed that genotype AG of rs3737964 [odds ratio (OR) = 0.54,95% confidence interval (CI) = 0.31-0.97, P = 0.038] and genotype AG of rs4846048 (OR = 0.54,95%CI = 0.30-0.98,P = 0.042) in *MTHFR* were protective factors for HFS. That was to say, patients with these two kinds of genotypes in the Chinese Han population might have 0.54-fold lower risk of suffering from HFS. Genotype GT of rs2606241 (OR = 1.27,95%CI = 0.73-2.23,P = 0.012) and genotype CT of rs2853741 (OR = 2.25,95%CI = 1.31-3.87,P = 0.012) in *TYMS* increased the incidence of HFS. Patients with genotype GT of rs2606241 and genotype CT of rs2853741 were found to have 1.27-fold and 2.25-fold higher risk of suffering from HFS. **Conclusions:** In summary, we have identified a panel of clinically useful pharmacogenetic markers predicting capecitabine-induced HFS in MBC patients.

1086 Poster Session (Board #167), Sat, 8:00 AM-11:30 AM

Role of circulating miRNAs in detecting metastasis and having prognostic significance in metastatic breast cancer. *First Author: Sofia Agelaki, Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Greece*

Background: Metastasis is the leading cause of breast cancer associated death. In the current study we evaluated the expression of (a) micro-RNA (miR)-23b and miR-190 which are involved in tumor dormancy (b) miR-21 which is involved in metastasis and (c) miR-200b and miR-200c which are involved in EMT and metastasis, in the plasma of patients with early and metastatic breast cancer (BC) in order to investigate whether they could distinguish the two disease states. Furthermore the prognostic significance of the above miRNAs was investigated in patients with metastatic disease. **Methods:** Plasma samples were obtained from patients with early (n = 84) or metastatic (n = 57) BC before adjuvant or 1st-line treatment, respectively. Plasma miR-21, miR-23b, miR-190, miR-200b and miR-200c expression levels were assessed by RT-qPCR and expression was classified as high or low according to the median values. **Results:** miR-21 ($p < 0.001$), mir-23b ($p = 0.012$), miR-200b ($p < 0.001$) and miR-200c ($p = 0.001$) were higher and miR-190 ($p = 0.013$) was lower in metastatic compared to early BC patients. ROC analysis showed that miR-21 (AUC = 0.772; $p < 0.001$), miR-23b (AUC = 0.625; $p = 0.012$), miR-190 (AUC = 0.629; $p = 0.013$), miR-200b (AUC = 0.744; $p < 0.001$) and miR-200c (AUC = 0.668; $p = 0.001$) could distinguish between patients with metastatic and early BC. However, logistic regression and combined ROC analysis revealed that a panel of four miRs (miR-21, miR-190, miR-200b and miR-200c) discriminated with higher accuracy (AUC = 0.857; $p < 0.001$) between the two disease states. In patients with metastatic disease, miR-21 high was correlated with premenopausal ($p = 0.013$) and HER2 status ($p = 0.017$). The combined expression of miR-23b high and miR-190 high was correlated with progressive disease at the end of treatment ($p = 0.034$). Patients with miR-23b high had shorter PFS and OS ($p = 0.024$ and $p = 0.031$, respectively). **Conclusions:** Circulating micro-RNAs discriminate between patients with metastatic and early breast cancer. In addition, their expression holds predictive information in patients undergoing first-line chemotherapy.

1087 Poster Session (Board #168), Sat, 8:00 AM-11:30 AM

Androgen receptor expression in circulating tumor cells of metastatic breast cancer patients. *First Author: Ingeborg Elisabeth de Kruijff, Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands*

Background: The androgen receptor (AR) is of clinical relevance in metastatic breast cancer (mBC): AR has been associated with resistance to endocrine therapy and could be a potential target for therapy, especially in the triple negative (TN) subtype. A minimal-invasive way to determine AR expression is by characterization of circulating tumor cells (CTCs). We therefore assessed *AR* mRNA expression in CTCs (CTC-*AR*) from mBC patients representing different breast cancer subtypes in relation to outcome on endocrine therapy and 25 genes related to the ER and AR pathways. Furthermore, we assessed *AR* in matched primary tumors and CTC samples taken at advanced disease. **Methods:** *AR* and AR- and ER-related gene expression levels were measured in CellSearch-enriched CTCs from 133 mBC patients with ≥5 CTCs and in 48 matched formalin-fixed paraffin embedded primary tissues using quantitative reverse-transcriptase PCR. *AR* was considered positive if the expression was 1 standard deviation higher than the expression measured in 12 healthy blood donors. mBC subtypes were established based on ER, PR and HER2-status of the primary tumor (9 unknowns). **Results:** 31% of the CTC samples were *AR*-positive (*AR*+). The HER2+ subtype had most frequently *AR*+ CTCs (4/8, 50%), which was significantly higher than observed in the TN subtype (2/16, 13%) ($p = 0.046$). The ER+/HER2- subtype had 35% (27/78) *AR*+ samples and the ER+/HER2+ 23% (5/22). There was no significant difference between PFS in ER-targeting treated patients and CTC-*AR*-status (17 *AR*+ / 41 *AR*-negative (AR-) cases, $p = 0.991$). 65% of the matched CTC samples and primary tissues were discordant with respect to *AR*, observing both switches from *AR*+ to *AR*- and vice versa. **Conclusions:** *AR* can be determined in RNA isolated from CTCs from different mBC subtypes, with in our set 31% *AR*-positive samples. Because there was a 65% discordancy between *AR* in CTC samples and the primary tumor, it seems that AR should be determined in CTCs, but more research should be conducted in a larger set. In our current analysis patients had similar outcome on ER-targeting therapy regardless of their CTC-*AR* status. Thus, determination of AR expression in CTCs might be a promising tool to select mBC patients for AR inhibiting agents.

1088 Poster Session (Board #169), Sat, 8:00 AM-11:30 AM

Benefits and risks from maintenance therapy after first-line chemotherapy in patients with metastatic breast cancer. *First Author: Yunfang Yu, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Current guidelines lack definitive evidence regarding the clinical outcomes associated with different maintenance strategies for metastatic breast cancer (MBC). We aimed to investigate the benefits and risks of different maintenance therapy after first-line treatment of MBC. **Methods:** We searched for randomized clinical trials (RCTs) investigating maintenance chemotherapy, endocrine therapy or immunotherapy after first-line chemotherapy in MBC. The primary endpoint was progression-free survival (PFS); overall survival (OS) and adverse events (AEs) were secondary endpoints. Direct and indirect evidence for data were combined using random-effects meta-analysis. The GRADE system was used to assess the quality of evidence. The PROSPERO registry number is CRD42017071858. **Results:** A total of 3,290 patients from 16 RCTs were included. Maintenance chemotherapy resulted into a significantly prolonged PFS (hazard ratio [HR] 0.63, 95% confidence interval 0.54 to 0.73, $P = 0.000$; high certainty) and OS (HR 0.87, 95% CI 0.78 to 0.97, $P = 0.016$; high certainty) compared with observation, although higher odds of G1-G2 AEs (moderate certainty). Among patients who developed an immune response, maintenance immunotherapy combined with chemotherapy extended PFS (HR 0.57, 95% CI 0.33 to 0.97, $P = 0.04$; low certainty) and OS (HR 0.71, 95% CI 0.52 to 0.97, $P = 0.029$; low certainty) than chemotherapy alone. Hormone-receptor-positive patients who received maintenance endocrine therapy might provide similar PFS (HR 1.0, 95% CI 0.70 to 1.50, $P = 0.998$; very low certainty) and OS (HR 1.15, 95% CI 0.59 to 2.22, $P = 0.679$; very low certainty) versus chemotherapy, but with lower odds of G1-G2 AEs (moderate certainty). **Conclusions:** Our study provided strong evidence for OS and PFS benefits of maintenance chemotherapy over observation after first-line chemotherapy in MBC patients. Limited prospective trial indicated that maintenance endocrine therapy was noninferior to chemotherapy with less treatment-related toxicity, which was worthy of a clinical recommendation. Support: ChiCTR-IIR-17014036, SYS-C-201801.

1089 Poster Session (Board #170), Sat, 8:00 AM-11:30 AM

Phase II study of cabazitaxel as second-line treatment in patients with HER-2 negative metastatic breast cancer previously treated with taxanes. *First Author: Angelos Koutras, Hellenic Cooperative Oncology Group (HeCOG), Athens, Greece*

Background: Cabazitaxel is a new taxoid efficient in stabilizing microtubules against depolymerization. Preclinical and limited clinical data indicate that cabazitaxel might be effective in breast cancer patients resistant to first-generation taxanes. **Methods:** The purpose of the current multicenter phase II trial was to evaluate the activity and safety of cabazitaxel as 2nd-line treatment, given on day 1 of a 21-day cycle, in patients with HER-2 negative metastatic breast cancer (mBC), previously treated with taxanes. Prophylaxis with G-CSF was recommended to all patients. The primary endpoint was the objective response rate (ORR), while secondary endpoints included overall survival (OS), progression-free survival (PFS), duration of response (DOR) and the safety profile. **Results:** Eighty-four patients were enrolled between 2012 and 2016. Among them, 3 patients (3.6%) were ineligible but received at least two cycles of treatment. In total, 499 cycles of cabazitaxel were administered (median 4; range 1-39). Median relative dose intensity was 0.99 (range 0.79-1.49). Seven patients were not evaluated for tumor response. In the 77 patients with evaluable treatment response, the ORR was 24.7% (1 complete and 18 partial responses). The disease-control rate was 58.4%, while the median DOR was 5.6 months (range 0.7-51.3). Within a median follow-up of 32.2 months, the median PFS was 3.7 months (95% CI 2.23-4.36), whereas the median OS was 15.2 months (95% CI 11.21-21.54). Regarding toxicity, grades 3-4 neutropenia and febrile neutropenia were reported in 22.6% and 6.0% of patients, respectively. Two fatal events were reported (1 febrile neutropenia; 1 sepsis) related to study treatment. Most frequent non-hematological events were fatigue, diarrhea, nausea (grade 1-3). There were no unexpected serious AE, and no new safety signal was revealed. **Conclusions:** This phase II trial suggests that cabazitaxel is active (disease control rate of almost 60%) with a manageable toxicity profile as 2nd-line treatment in taxane-pretreated patients with HER-2 negative mBC. Clinical trial information: NCT01693549.

1090 Poster Session (Board #171), Sat, 8:00 AM-11:30 AM

Dynamic changes of interleukin 2 (IL-2) and circulating tumor cells (CTCs) in patients with advanced breast cancer (BCa) after systemic therapies. *First Author: Qiang Zhang, Northwestern University, Department of Medicine, Division of Hematology/Oncology, Chicago, IL*

Background: CTCs play a critical role in BCa metastasis and worse prognosis even after systemic treatments such as chemotherapy and biological therapy. The mechanisms that contribute to CTCs migration and tumor aggressiveness remain unknown. Herein, we report a novel finding of the correlation between plasma IL-2 and the changes of CTC for BCa patients after therapies. **Methods:** Duplicate whole blood samples (7.5ml/each) were collected in EDTA tubes from 43 patients with stage III/IV BCa patients before (baseline, BL) or 3 months after (first evaluation, FE) systemic therapies respectively from patients treated at NMH. CTC enrichment and enumeration were performed in FDA approved CELLTRACKS ANALYZERII System and were linked with clinical database. The CTCs were classified as CK^+, $EpCAM^+$, $DAPI^+$ and $CD25^-$. ELISA for IL-2 was performed by using patients' plasma. Kruskal-Wallis test was used for statistics. **Results:** CTCs were detected in 23 patients at BL and 21 patients at FE of blood draws respectively. CTCs count increased in 12 patients (Group 1: from 102.9 to 213.3), decreased in 14 patients (Group 2: from 23 to 13.6) and remained unchanged as 0 in 17 patients (Group 3) respectively when BL was compared to the FE. The corresponding changes of IL-2 were -17.4pg/ml, 8.04pg/ml and -4.59pg/ml in Group 1, 2 and 3 respectively. The BL level of IL-2 in Group 1 is significantly higher than the other two groups ($p = 0.027$), and decreased of CTCs is associated with increased IL-2 ($P < 0.01$), while decreased IL-2 in FE level is associated with increased of CTCs after therapy in whole population ($p < 0.001$). More important, IL-2 dropped significantly in patients with CTC stably ≥ 5 or who experienced a rise in CTC ≥ 5 at the FE compared to the BL time point ($p < 0.001$). **Conclusions:** The study demonstrated for the first time a reverse correlation between IL-2 level and CTCs count. The data suggest that the more aggressive BCa (CTC≥ 5) induce the immune response (high levels of IL2 at baseline), but subsequently the IL2 level will decrease in patients that fail to benefit from treatment. We propose that surveillance of immune cytokine will help to understand advanced BCa prognosis and predict treatment benefit.

1091 Poster Session (Board #172), Sat, 8:00 AM-11:30 AM

Prognosis in young women under 40 with brain metastasis from breast cancer. *First Author: Ariana Mustillo, CHUM, Montreal, QC, Canada*

Background: Breast cancer brain metastases in young women is doubly devastating as both quality of life and life expectancy are significantly reduced. With new radiation technology and drugs that have emerged survival of these young women is expected to increase **Methods:** Using OACIS and SARDO patient databases, we identified 121 patients diagnosed with breast cancer and brain metastasis at CHUM between 2006 and 2016. We divided our group into Group A: patients whose first metastasis was in the brain and Group B: patients who developed a brain metastasis during the evolution of the metastatic breast cancer. Then, we compared young patients < 40 to those ≥ 40 for each category. **Results:** For the 121 patients with brain metastasis, the < 40 had a significantly longer mOS 18 mo compared to 4 mo for ≥ 40 ($P < 0.001$). With respect to timing of brain metastasis, group A had also a significantly longer survival (7 months) than group B (4 months) ($P = 0.032$). For group A, 2years OS was 57% for patients < 40 vs 12% for patients ≥ 40 (mOS NR vs 7 months; $P = 0.259$). For group B, patients < 40 had a significantly longer mOS 18mo than patients ≥ 40y 3 mo ($P = 0.0089$). There was no statistically difference in groups regarding time to first metastasis. BRCA 1/2 mutations were known for only 23 of 121 patients (19%). The BRCA 1/2 positive patients (8/23 = 35%) were well distributed between both age groups and none were treated with PARP inhibitors. **Conclusions:** Young women with brain metastasis from breast cancer have a better prognosis than women≥ 40. Patients who had their first metastasis to the brain also had a longer survival than patients whose metastasis to the brain developed later in the disease course.

1092 Poster Session (Board #173), Sat, 8:00 AM-11:30 AM

What are the drivers of healthcare cost among patients with metastatic breast cancer (mBC)? Total cost of care analysis to inform value-based reimbursement. *First Author: Chakkarin Burudpakdee, IQVIA, Fairfax, VA*

Background: Given the move toward value-based payment in oncology, total cost of care data are needed to evaluate value. The objective of this study was to quantify cost of care and identify key drivers of healthcare cost in patients (pts) with mBC. **Methods:** Adults with systemic treatment for mBC from 1/1/2014 – 12/1/2016 were identified from IQVIA's claims database. Pts were indexed on the first mBC treatment, had ≥2 diagnoses for both breast and metastatic cancer, ≥12 months of continuous medical and drug coverage before and ≥30 days after index. Healthcare resource use and costs were measured during follow up, standardized as per patient per month (PPPM), and compared between overall and high cost (defined as top 10%) pts. **Results:** 7,032 pts with mBC were included; mean (±SD) age was 55.5 ± 9.6; mean follow up was 14.0 ± 9.1 months. Total cost of care is shown in Table 1. The mean total PPPM cost of high cost pts (n = 703) was 3.7-fold higher than that of the overall population. The largest difference in cost between overall and high cost pts was for outpatient drugs ($7,348 PPPM); 76% was related to breast cancer medications. Other cost drivers in high cost pts included hospitalization ($6,152 PPPM higher), radiology procedures ($2,238 PPPM higher), and pharmacy services ($1,755 PPPM higher). The proportion of total costs due to outpatient surgery, office visits, lab services, and ED visits was lower in high cost pts compared to the overall population (10.5% vs. 7.1%). **Conclusions:** Our findings suggest that medications, hospitalizations, and radiology services are the main drivers of high costs in mBC pts. Further research is needed to identify if there are services and costs that are unintended and avoidable. Findings from this study can help inform evidence-based decisions when developing alternative payment models for cancer care.

Total cost of care.

	Mean cost PPPM	
	All (N = 7,032)	High cost (N = 703)
Total	$7,828	$28,776
Pharmacy	$1,341	$3,096
Medical	$6,487	$25,680
Inpatient	$1,337	$7,489
Outpatient	$5,150	$18,191
Drug	$2,189	$9,538
Radiology	$1,133	$3,371
Other outpatient service	$1,001	$3252
Surgery	$320	$742
Office visit	$269	$564
Laboratory	$183	$544
ED visit	$55	$180

1093 Poster Session (Board #174), Sat, 8:00 AM-11:30 AM

Updated survival data and biomarker assessment of the CBCSG006 trial: A randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer. *First Author: Jian Zhang, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: It was previously reported in CBCSG006 trial that patients with metastatic TNBC were more likely to have higher response rate and longer PFS to cisplatin plus gemcitabine (GP) than to paclitaxel plus gemcitabine (GT) treatment. Here, we reported the updated survival data and the explorations of biomarkers for higher sensitivity to platinum doublet. **Methods:** 132 Blood and 114 archival tissue samples were collected prospectively. gBRCA1/2 genotyping and germ-line HRD panel status were detected by NGS. Core basal markers and PD-L1 expression were detected immunohistochemistry. Tumor-infiltrating lymphocytes (TILs) evaluation was performed on HE–stained sections. A model of composite measure of progression risk was developed to analyze the absolute survival benefits between two arms in CBCSG006 trial by a nonparametric sliding-window subpopulation treatment effect patter plot (STEPP) methodology. **Results:** Median PFS was 7.73 months (95% CI 6.46-9.00) for GP arm and 6.07 months (5.32-6.83) for GT arm (p = 0.005). No significant differences in OS were observed. Patients with gBRCA1/2 mutations had numerically higher ORR and prolonged PFS in GP than GT arm. Patients with germ-line HRD panel mutations had significantly higher ORR and longer PFS in GP than GT arm. Core basal subtype, lymphocyte-predominant breast cancer subtype and positive PD-L1 expression were not correlated with ORR or PFS. In STEPP analysis, patients with lower composite measure of progression risks had more absolute PFS benefits than those with high composite measure of progression risks, with absolute difference in 6-month PFS rates ranging from approximately 40% to none. **Conclusions:** gBRCA1/2 and germ-line HRD mutations are possible markers for platinum-based regimens. A composite risk model was developed to guide patient selection for GP treatment in TNBC. Clinical trial information: NCT01287624.

1094 Poster Session (Board #175), Sat, 8:00 AM-11:30 AM

Phase II (INSPIRE) trial of pembrolizumab (pembro) with serial immune and genomic profiling in patients (pts) with metastatic triple negative breast cancer (mTNBC). *First Author: Zachary William Neil Veitch, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Pembro is a PD-1 immune checkpoint inhibitor with a low response rate in pretreated mTNBC. In this biomarker driven, investigator-initiated trial we evaluate changes in immune and genomic landscapes of mTNBC pts treated with pembro monotherapy. **Methods:** Pts with mTNBC, ECOG 0-1, progressing after or ineligible for standard therapy were treated with Pembro 200mg IV q3w. Imaging (RECIST v1.1) was performed every 9 weeks. Pre- and on-treatment (week 6-9) tumor biopsies (bx) were assessed by IHC (C223 antibody) for PD-L1 expression; single cell suspensions were pooled for exome/RNA-sequencing and immunophenotyping (IP) by flow cytometry. Serial blood samples were collected for IP, cytokines, and ctDNA. **Results:** Of 20 mTNBC pts enrolled, median age was 40 years, 35% had ≥3 lines of therapy, 35% had LDH ≥1.5xULN, 60% had visceral metastases (liver 25%, lung 44%) and 30% had PD-L1+ (> 1%) tumors. Best response was 1 PR, 3 SD, and 16 PD. One pt discontinued Pembro after 3 cycles due to grade 3 pneumonitis and nephritis with 29% target lesion reduction (near PR). No other grade 3/4 AEs were observed. Grade ≤2 AEs were fatigue (30%), nausea (25%), and diarrhea (20%). After median follow-up of 6.5 months (range 1.8-19.8), mPFS was 2.1 months (95% CI 1.5-3.1) and mOS was 7.4 months (95% CI 6.2-10.7). Pre-/post-treatment bx were performed on 20 and 10 pts respectively, but at time of analysis only 8/20 had sufficient tumor cell content for IP, and 5/20 had genomic analysis. The two pts with PR/near-PR showed T-cell stimulation with increasing CD8 4-1BB levels on blood IP from baseline to cycle 2 (1.96 to 7.95 [% of CD3]; 10.1 to 13 [% of CD3]) relative to non-responders (4.06 to 3.13 [% of CD3]). A third patient with 26% reduction in target lesions but confirmed progression of non-target lesions had *POLE* (G1750E) mutation with germline *BRCA2* mutation. **Conclusions:** Consistent with previous reports, the response rate to Pembro monotherapy in pre-treated mTNBC was low. Increased expression of 4-1BB on peripheral blood CD8 cells was observed in patients with target lesion reduction. Further analyses are ongoing. Clinical trial information: NCT02644369.

1095 Poster Session (Board #176), Sat, 8:00 AM-11:30 AM

An open label, pilot study of veliparib (ABT-888) and lapatinib in patients with metastatic, triple negative (ER, PR, and HER-2 negative) breast cancer. *First Author: Erica Michelle Stringer-Reasor, University of Alabama at Birmingham, Birmingham, AL*

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer (BC), often resistant to standard of care therapies. We previously showed an induced synthetic lethal interaction with combined EGFR (epidermal growth factor receptor) and PARP (Poly (ADP-ribose)-polymerase) inhibition in TNBC cells. Therefore, we tested a pilot clinical trial using lapatinib and veliparib in patients with locally advanced unresectable or metastatic TNBC. Here we report safety results and clinical activity of the combination of veliparib and lapatinib. **Methods:** Key eligibility criteria include histologically confirmed TNBC (ER negative, PR negative, HER-2-Neu negative), measurable disease, failed anthracyclines and taxanes in the neoadjuvant, adjuvant, or metastatic setting, left ventricular ejection fracture ≥ 50, and ECOG PS of 0-2. Patients with known germline BRCA 1 or 2 mutations were excluded. Eligible patients received continuous doses of lapatinib 1250 mg PO daily and veliparib 200 mg PO twice daily. Dose limiting toxicity (DLT) evaluation period was 28 days (cycle 1). Adverse events (AEs) were assessed by CTCAE v4.03 and best objective response per RECIST v1.1. **Results:** Twenty patients were enrolled and 17 were evaluable for response. The median number of prior therapies for advanced BC was 1 (range 0-2). Fifty percent of the patients enrolled were Caucasian, 45% African-American, and 5% Hispanic. Of the evaluable patients, 4 had a partial response and 2 had stable disease. There were no dose-limiting toxicities. The majority of toxicities occurred during cycles 2 and 3. Toxicities were manageable. Most adverse events (AEs) were limited to grade 1 or 2 (no grade 5). Common treatment-related AEs were fatigue (6.4%), diarrhea (5.1%), constipation (5.5%), insomnia (4.5%), vomiting (2.9%), anemia (2.6%), headache (2.6%), dizziness (2.3%), dyspnea (2.3%), and rash (2.3%). **Conclusions:** Lapatinib plus veliparib in the treatment of advanced TNBC resistant to SoC has a manageable safety profile and promising antitumor activity. Further investigation of EGFR inhibition in combination with a PARP inhibitor is needed. Clinical trial information: NCT02158507.

1096 Poster Session (Board #177), Sat, 8:00 AM-11:30 AM

Mechanisms of immune evasion in triple-negative breast cancer patients. *First Author: Javier Ignacio Orozco, John Wayne Cancer Institute at Providence Saint John's Health Center, Santa Monica, CA*

Background: Immunotherapy has shown promising results in enhancing response rates for patients with triple-negative breast cancer (TNBC). The success of immunotherapy is affected by poor tumor antigen presentation. This immune evasion is facilitated by genetic and epigenetic alterations, including aberrant RNA splicing (AS). Here we examined the role of PTBP1, a key RNA splicing factor related to immune evasion in TNBC. **Methods:** Clinical and gene expression data from 3,614 breast cancer patients included in the METABRIC and TCGA projects were evaluated to identify the impact of PTBP1 on TNBC. Univariate and multivariate statistical modeling was performed to test the association of PTBP1 expression with relapse-free survival (RFS), disease-free survival (DFS), and overall survival (OS). CRISPR-Cas9 technology, followed by RNA sequencing (RNA-Seq) was utilized to identify differentially activated pathways in a TNBC cell model (MDA-MB-231). A portrait of infiltrating immune cells was compiled using the xCELL algorithm. Immunofluorescence (IF) and immunohistochemistry (IHC) were employed to validate our findings in TNBC cell lines, tissue microarrays, and FFPE specimens (n = 110). **Results:** We found that PTBP1 is significantly upregulated in patients with TNBCs ($P < 0.001$). TNBC patients with high PTBP1 presented significantly shorter RFS ($P = 0.018$; HR = 1.66, 95%CI 1.1-2.5; n = 255), DFS ($P = 0.017$; HR = 3.2, 95%CI 1.16-8.3; n = 151), and OS ($P = 0.037$; HR = 1.48, 95%CI 1.02-2.15; n = 162). To explore potential mechanisms linking PTBP1 expression and poor survival, CRISPR-guided knockout of *PTBP1*, followed by RNA-seq identified a significant enhancement on antigen presentation pathways, confirmed by IF staining. xCELL analysis showed that TNBC tumors with high PTBP1 present an immune infiltration profile compatible with immune evasion (low CD4+ naïve and memory T cells, low CD8+ T cells, low tumor-associated macrophages, and high suppressor T cells). These observations were further confirmed by IHC evaluation of TNBC clinical specimens. **Conclusions:** This study suggests an important and relatively unexplored role of AS in immune evasion, identifying new prognostic and potentially therapeutic targets for patients with aggressive TNBC.

1097 Poster Session (Board #178), Sat, 8:00 AM-11:30 AM

Preliminary report of a phase 1b/2a trial, an oral inhibitor of phosphorylated P68 (P-p68) which mediates β-catenin nuclear translocation in advanced triple-negative breast cancer (TNBC). *First Author: Jennifer Robinson Diamond, University of Colorado, Aurora, CO*

Background: RX-5902 is a novel oral anti-cancer compound targeting phosphorylated p68 (P-p68) (RNA helicase DDX5, a member of the DEAD box family of RNA helicases) affecting the Wnt canonical pathway. P-p68 may play a role in cell proliferation and cancer progression by blocking the nuclear translocation of β-catenin. RX-5902 inhibits tumor growth and enhances survival in numerous xenograft animal models, including breast, melanoma and ovarian. **Methods:** This is a Phase 1b/2a trial in patients with previously treated advanced triple-negative breast cancer. Eligible subjects received 250 mg of RX-5902 orally for 5 consecutive days followed by 2 days off and continued until unacceptable toxicity or disease progression. Primary objectives include efficacy and safety of the recommended phase 2 dose and schedule, as was previously determined in the phase 1 study. A pre-planned interim analysis will be performed when 10 response evaluable subjects have been enrolled and have completed 4 cycles of therapy or have discontinued therapy due to progressive disease. Tumor imaging is performed every 2 cycles. If at least 2 objective responses are seen in the first 10 evaluable patients, enrollment will continue to stage 2 of the Phase 2a portion of the study. **Results:** As of Feb 2018, 11 subjects with TNBC were enrolled and treated in Stage 1 of the Phase 2a component. These subjects had received a median of 3 prior therapies (range 2 to 6). Preliminary evidence after 2 cycles of therapy showed 5 subjects with stable disease as the best overall response; 3 subjects had progressive disease, 2 subjects stopped therapy early and 1 subject just started treatment. One subject had a tumor reduction of 18.2% and 1 subject remains on study with stable disease for 5 cycles. The most common related adverse events, were Grade (G)1/2 nausea (2.8%), G1 vomiting (1.8%), G1/G2 diarrhea (1.8%) and G1/G2/G3 fatigue (4.6%). **Conclusions:** Preliminary evidence suggests that oral administration of RX-5902 at 250 mg/day appears safe and well tolerated. Early anti-tumor activity was observed in 1 patient. Recruitment to Phase 2 is ongoing. Clinical trial information: NCT02003092.

1098 Poster Session (Board #179), Sat, 8:00 AM-11:30 AM

An open label, single arm, prospective phase II study to evaluate the efficacy and safety of bevacizumab with gemcitabine and carboplatin as first-line treatment for metastatic triple negative breast cancer patients. *First Author: Sudeep Gupta, Department of Medical Oncology, Breast Disease Management Group, Tata Memorial Centre (TMC), Mumbai, India*

Background: There is a higher burden (29.2%-46%) of TNBC patients in India. This single arm, phase II trial evaluated the efficacy and safety of bevacizumab in combination with gemcitabine and carboplatin as first line treatment in Indian patients with metastatic TNBC. **Methods:** TNBC patients with prior adjuvant anthracycline and taxane therapy and no prior treatment for metastatic disease received bevacizumab (15mg/kg) with gemcitabine and carboplatin, every three weeks until disease progression or unacceptable toxicity. **Results:** Forty patients were accrued at 10 Indian centers between February 2011 to April 2013. At median follow-up of 12 (0.5 –59.3) months there were 27 disease progressions and 23 deaths. Using EORTC QLQ-30 questionnaire, improvements were observed in physical function ($P = 0.0435$), emotional function ($P = 0.002$) and pain perception ($P = 0.0243$) domains from baseline to cycle 6. Median duration of study treatment was 4.6 (0.3 – 18.4) months. Overall, 24 (60%) patients reported 133 adverse events (99 non-serious, 34 serious) including proteinuria, rectal hemorrhage (grade 3) and fatigue (grade 4) in 1 patient each. A total of 34 serious adverse events were reported in 17 (42.5%) patients. No new safety signals were identified and bevacizumab was found to be well tolerated by Indian patients. **Conclusions:** Bevacizumab in combination with gemcitabine and carboplatin as first line treatment in metastatic TNBC, resulted in favorable survival outcomes with acceptable toxicity. The patients also experienced significant improvement in several domains of health related QoL during the first 6 cycles of this treatment. Efficacy results Clinical trial information: NCT01201265.

Primary Endpoint	N = 40
Median PFS	8.5 months (95% CI: 5.2 – 15.3)
Secondary Endpoints	N = 40
Median OS (protocol-defined end of study)	15.8 months (95% CI: 11.8 – 24.9)
Updated Median OS (additional 14.5 months follow-up)	23.1 months (95% CI: 9.6 – 36.0)
TTP	8.9 months (95% CI: 6.0 – 18.1)
Complete Response (CR)	2 (5%)
Partial Response (PR)	18 (45%)
Stable Disease (SD)	17 (42.5%)
Overall Response Rate (CR+PR)	20 (50%)
Clinical Benefit Rate (CR+PR+SD)	37 (92.5%)

1099 Poster Session (Board #180), Sat, 8:00 AM-11:30 AM

Characterization of the inflammatory infiltrate and association with expression of PD-1, PDL1 and PDL2 and survival in triple-negative mammary carcinoma. *First Author: Monique Celeste Tavares, Hospital A.C. Camargo, Sao Paulo, Brazil*

Background: However, recent evidences suggest that lymphocyte infiltration in tumors (LIT), which is presented in breast cancer prior to the treatment, may predict response to the therapy and a better prognosis. Not only the intensity of lymphocyte infiltration, but also the phenotype of that infiltrate, determine the clinical outcome.Objectives:To evaluate the intensity and composition of the LIT in an operated TNBC and its association with the expression of PD-1, PD-L1 and PD-L2. **Methods:** This is an observational, descriptive and a retrospective cohort study. The studied population consisted of patients diagnosed with invasive TNBC. **Results:** LIT was evaluated in 165 patients. The mean intensity of the inflammatory infiltrate was 20%. We observed that 47 (28%) had inflammatory infiltrate $\leq 5\%$, 86 (52%) between 5 and 50% and 32 (19%) $> 50\%$. The average OS in each group was, respectively, 85 months, 104 months and 148 months ($p = 0.002$). We established an ideal cutoff point of 5% of LIT for OS analysis, so that average overall survival was 85 months for patients with LIT$\leq 5\%$ and 136 months for those with infiltrate $> 5\%$ ($p = 0.001$) . We included 76 cases in the TMA for IHC analysis. We established an optimal cutoff point of 5% in this group, we observed that the majority 56 (78.87%) had an inflammatory infiltrate $> 5\%$. With a tendency to benefit in specific cancer survival, for patients with inflammatory infiltrate $> 5\%$, but with no statistical significance. We found an average of 4 and 12% expression of tumor-free PD-L1 and no stroma, respectively. The cutoff point for the labeling of PD-L1 in the stroma was 5%, with 17 (22.4%) presenting $> 5\%$ and 31 (40.8%) $\leq 5\%$; and in tumor was 1%, with 11 (14.5%) $> 1\%$ and 51 (67%) $\leq 1\%$. There was no association between PD-L1 expression and OS. We found a positive and statistically significant correlation of LIT with labeling PD-L1 in stroma ($p = 0.001$) and in tumor ($p = 0.028$). **Conclusions:** In TNBC, TII above 5% is associated with the increasing of OS. TII is associated with a number of cells labeled positively for PD-L1 both in stroma and in tumor. PD-L1 was not associated with OS. Increased number of FOXP3+ and of PTEN marking cells are associated with better OS.

TPS1100 Poster Session (Board #181a), Sat, 8:00 AM-11:30 AM

A phase II study of atezolizumab (Atezo) combined with pertuzumab (P) and high-dose trastuzumab (H) for the treatment of central nervous system (CNS) metastases in patients with Her2-positive (HER2+) metastatic breast cancer (MBC). *First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA*

Background: There is no clear standard of care to address the management of refractory CNS metastases in HER2+ MBC. The ongoing study (NCT03417544) is evaluating the efficacy of the combination of Atezo with P and high-dose H for the treatment of CNS metastases in patients (pts) with HER2-positive MBC. **Methods:** This is a phase II, single arm, multi-center trial assessing the efficacy of Atezo with Pertuzumab plus high-dose H for the treatment of CNS metastases in HER2+ MBC. Participants will receive Atezo [1200mg every 3 weeks (q3w)], P (840-mg loading dose, then 420mg q3w), and high-dose H (6 mg/kg weekly for 24 weeks, and then q3w). Eligibility Criteria include pts with HER2+ MBC, at least one measurable CNS metastasis ($\geq$10 mm), unequivocal evidence of new and/or progressive CNS metastases, and left ventricular ejection fraction (LVEF) $\geq$ 50%. Exclusion criteria include CNS complications for whom urgent neurosurgical intervention is needed; known leptomeningeal/brainstem metastases; and treatment with dexamethasone $>$ 2mg/day or bioequivalent within 7 days of initiating therapy. The primary endpoint is objective response rate (ORR) in the CNS per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. Secondary endpoints include the duration of CNS response, bi-compartmental progression-free survival according to RANO-BM, and the extracranial ORR according to RECIST 1.1. Tumor biopsies, peripheral blood, and cerebrospinal fluid will be obtained at baseline, on treatment and at progression. In the first stage, 19 pts will be enrolled. If there are at least 4 CNS responses, accrual will continue to the second stage where up to 14 additional pts will be enrolled. If at least 8 of these 33 pts have CNS response, the regimen will be considered worthy of further study. With this design, if the true response rate is 15%, the chance the regimen is declared worthy of further study is less than 10% (exact alpha = 0.096). If the true response rate is 35%, the chance that the regimen is declared worthy of further study is 90.4%. The trial opened in February 2018, with a target accrual of 33 pts. Clinical trial information: 03417544.

TPS1101 Poster Session (Board #181b), Sat, 8:00 AM-11:30 AM

SOLTI-1303 PATRICIA: A phase II study of palbociclib and trastuzumab (HR+ with or without letrozole) in trastuzumab-pretreated, postmenopausal patients with HER2-positive metastatic breast cancer. *First Author: Patricia Villagrasa, SOLTI Breast Cancer Research Group, Barcelona, Spain*

Background: Despite the high efficacy of anti HER2-agents, HER2-positive (HER2+) metastatic breast cancer (BC) remains incurable and in need of additional options. In this context, CDK4/6 inhibition combined with anti-HER2 therapy is currently being explored in phase II/III trials. Preclinical evidence from different HER2+ BC models have shown that CDK4/6 inhibition leads to deep cytostatic arrest and inhibition of its invasive properties, underlining the role of CDK4/6 in HER2 signaling. Moreover, Identification of the luminal subtype in HER2+/HR+ disease might be important since the median IC50 of palbociclib (P) in HER2+ BC cell lines falling into the luminal subtype is lower than in non-luminal HER2+ cell lines (47.5 vs. 300 nM). We have recently reported that PAM50 luminal subtype predicts progression-free survival (PFS) in HER2+/HR+ advanced BC treated with P and trastuzumab (T) compared to non-luminal disease (10.37 vs. 3.53 months, p-value = 0.023). PATRICIA is a Simon 2-Stage study to evaluate the efficacy of combining T plus P, +/- letrozole (L), assessed by PFS in heavily pretreated HER2+ patients. **Methods:** Postmenopausal HER2+ patients who had received 2-4 prior lines of anti-HER2-based regimens are included in 3 cohorts: A: HR-negative; B1: HR+, receiving both T and P; B2: HR+, receiving T, P and L. P is administered at 200 mg/day for 14 days of 21-day cycles. T and L are administered at usual doses. The primary objective is to assess clinical efficacy measured as PFS at 6 months (PFS6). Assuming an increase of at least 20% in PFS6 by the addition of P +/- L to T, PFS6 should be $\geq$30% for a cohort to be successful and proceed to stage 2. Thus, it will be necessary to include 15 patients in each cohort in stage 1. In stage 2, each cohort may continue recruitment for up to 46 patients. Translational research for predictive biomarkers will be implemented. To date, 55 patients, 15 in A and 20 in each B cohort, have been included in 14 sites across Spain. The 1st stage efficacy analysis was performed for B cohorts, leading 2nd stage accrual began in September 2017. Cohort A stage 1 effectiveness analysis is intended for June 2018. Clinical trial information: NCT02448420.

TPS1102 Poster Session (Board #182a), Sat, 8:00 AM-11:30 AM

A phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-positive, unresectable and/or metastatic breast cancer previously treated with T-DM1. *First Author: Jose Baselga, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There is no standard of care for HER2-positive breast cancer refractory to T-DM1. DS-8201a is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a showed a manageable safety profile and promising antitumor activity in HER2-positive breast cancer subjects previously receiving T-DM1 (confirmed objective response rate [ORR] of 61.4%; Oct 2017 data cutoff) (Modi et al, SABCS 2017). In August 2017, the FDA granted breakthrough therapy and fast track designations. **Methods:** The phase 2, open-label, multicenter, 2-part, DESTINY-Breast01 study will assess the efficacy and safety of DS-8201a in subjects with HER2-positive (confirmed by centralized testing) unresectable and/or metastatic breast cancer previously treated with T-DM1. Part 1 will enroll 120 subjects and includes pharmacokinetic (PK) and dose finding stages to identify the recommended phase 2 dose (RP2D). The PK stage will randomize 60 subjects (1:1:1) to 1 of 3 DS-8201a doses (7.4, 6.4, and 5.4 mg/kg; once every 3 weeks). In the dose finding stage, an additional 60 subjects will be randomized (1:1) to 1 of 2 doses selected in the PK stage. Part 2a will continue to enroll approximately 100 subjects at the RP2D. Part 2b will enroll an open-ended number of subjects who discontinued T-DM1 for reasons other than progressive disease. Overall, enrollment of $\geq$100 subjects with a history of prior pertuzumab treatment for metastatic breast cancer is planned at the RP2D. The primary endpoint, ORR, will be assessed in all subjects enrolled in parts 1 and 2a who received the RP2D and who had baseline measurable tumors assessed by an independent central imaging facility. Secondary endpoints include duration of response, disease control rate, progression-free survival, and overall survival. Enrollment began in August 2017. As of Feb. 12, 2018, 35 of approximately 230 subjects have been enrolled. Clinical trial information: NCT03248492.

TPS1103 Poster Session (Board #182b), Sat, 8:00 AM-11:30 AM

A multicenter, phase I/II trial of anastrozole, palbociclib, trastuzumab and pertuzumab in HR-positive, Her2-positive metastatic breast cancer. *First Author: Krystal Pauline Cascetta, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Overexpression or amplification of HER2 occurs in approximately 15 – 20% of patients and about half of these tumors are hormone receptor (HR) positive. Studies suggest that this 10% of all breast cancer cases may derive less benefit from endocrine therapy than those with HR+ disease without HER2 overexpression. The use of aromatase inhibitors in the metastatic setting is well established while significant improvement in overall survival has been established with the use of trastuzumab or pertuzumab in HER2-overexpressing tumors. To date, no studies have examined the combination of endocrine therapy, palbociclib, and dual HER2 therapy with pertuzumab and trastuzumab in this patient population. Trial Design: Multicenter, Phase I/II Trial of Anastrozole, Palbociclib, Trastuzumab and Pertuzumab in HR-positive, Her2-positive Metastatic Breast Cancer. Eligibility Criteria: Stage IV HR+, HER2+ breast cancer patients. Specific Aims: Phase I: To determine the maximum dose tolerated of palbociclib. Phase II: To determine the clinical benefit rate (CBR) of treatment with anastrozole, palbociclib, trastuzumab, and pertuzumab in HR+, HER2+ metastatic breast cancer patients. Exploratory: Examine potential biomarkers of response to palbociclib including expression of cyclin D1, cyclin E1 and E2, retinoblastoma, phosphorylated retinoblastoma, and p16 levels. RNA sequencing will be used to assess for other predictors of response in an unbiased manner to assess for correlation with inhibition of Ki-67 and phosphorylated retinoblastoma expression as well as evaluate for potential mechanisms of resistance. **Methods:** This study will evaluate the maximum tolerated dose (MTD) of the Anastrozole, Palbociclib, Trastuzumab and Pertuzumab. If $\geq$ 33 % of patients experience a dose limiting toxicity (DLT) at any dose level, the dose level below that level will be considered the MTD. Or, if the highest level has been reached and $<$ 33% of patients have experienced DLT, that will be considered the MTD. Once the MTD is reached, we will assess the clinical benefit rate using a Simon's II stage design among a maximum 30 patients. Accrual: Maximum of 36 subjects. Clinical trial information: NCT03304080.

TPS1104 **Poster Session (Board #183a), Sat, 8:00 AM-11:30 AM**

Palbociclib after CDK and endocrine therapy (PACE): A randomized phase II study of fulvestrant, palbociclib, and avelumab for endocrine pre-treated ER+/HER2- metastatic breast cancer. *First Author: Erica L. Mayer, Dana-Farber Cancer Institute, Waban, MA*

Background: CDK4/6 inhibition (CDK4/6i) has a well-established role in the management of hormone receptor positive/HER2 negative (HR+/HER2-) metastatic breast cancer (MBC). The addition of a CDK4/6i to endocrine therapy (ET) in HR+/HER2- MBC leads to prolongation of progression-free survival in the first-line and pre-treated settings. Mechanisms of resistance to CDK4/6i are not well described, and it is not known if continuation of CDK4/6i with subsequent lines of ET improves outcomes over ET alone. Further, preclinical data suggest combination therapy with ET, CDK4/6i, and anti-PDL1 may provide synergistic efficacy. The PACE trial was designed to determine optimal subsequent line of therapy in patients (pts) with HR+ / HER2- MBC that has progressed despite prior CDK4/6 inhibition and endocrine therapy. **Methods:** PACE is a multicenter phase II trial randomizing pts 1:2:1 to Arm A: fulvestrant alone (with option for palbociclib monotherapy crossover at time of progression); Arm B: fulvestrant and palbociclib; or Arm C: fulvestrant, palbociclib, and avelumab. The primary objective is to evaluate progression-free survival (PFS) with the combination of fulvestrant and palbociclib vs. fulvestrant alone; secondary objectives include overall response (OR) and PFS comparisons for other arms; assessment of outcomes in predefined molecular subgroups including ESR mutation, PI3K mutation, loss of Rb; safety and tolerability; and comparing OR by RECIST vs irRECIST. Extensive analysis of tissue, ctDNA, and CTC for markers of response and resistance to therapy is planned. Eligible pts have HR+/HER2- MBC, with prior response to and subsequent progression on CDK4/6i and ET, defined as at least 6 months of prior treatment, with confirmed subsequent progression, and no more than one prior P dose reduction for toxicity. Pts may have had 1-2 prior ET, and 0-1 prior lines of chemotherapy. A sample size of 220 patients is planned. NCT03147287.

TPS1105 **Poster Session (Board #183b), Sat, 8:00 AM-11:30 AM**

PADA-1: A randomized, open label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with hormone therapy driven by circulating DNA *ESR1* mutation monitoring in ER-positive, HER2-negative metastatic breast cancer patients. *First Author: Francois Clement Bidard, Institut Curie, Paris, France*

Background: Palbociclib (Pal) combined with an aromatase inhibitor (AI) is a standard of care as first line therapy in estrogen receptor-positive (ER+) HER2-negative (HER2-) metastatic breast cancer (MBC). The efficacy of Pal +AI may be however limited by the onset of *ESR1* mutations during therapy as a mechanism of resistance to AI, while pre-clinical and retrospective clinical data suggest that *ESR1*-mutated clones remain sensitive to fulvestrant (Ful). Rising *ESR1* mutation levels might be detected in ctDNA several months before actual tumor progression. This clinical utility trial tests whether switching from AI-Pal to Ful-Pal after the onset of rising *ESR1* mutations will turn into a clinical benefit for patients; the safety of these treatments will also be evaluated. **Methods:** Main inclusion criteria are patients with ER+ HER2-MBC with no prior systemic treatment for metastatic disease, no visceral crisis and theoretical AI-sensitivity. In the first step, all patients (N=800) are treated with Pal+AI; *ESR1* mutations in ctDNA are tracked by ddPCR (targeting E380, L536, Y537 and D538 ER hotspots) at baseline, after 1 cycle of treatment and then every other cycle. Upon the detection of rising *ESR1* mutation(s) in blood, patients without RECIST tumor progression proceed to the second step and are randomized (1:1) between the continuation of the same regimen or a switch to Pal+Ful. In a third step, patients that were randomized in standard regimen arm may crossover to Pal+Ful following tumor progression. The co-primary objectives of this ethically approved trial (NCT03079011), conducted in France by UCBG with GINECO, are (i) treatment safety (steps 1 to 3) and (ii) PFS in the two treatment arms (step 2). The 1st patient was included in March 2017; as of January 2018, 426 patients have been included. Clinical trial information: NCT03079011.

TPS1106 **Poster Session (Board #184a), Sat, 8:00 AM-11:30 AM**

Contessa: A multinational, multicenter, randomized, phase 3 registration study of tesetaxel in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC). *First Author: Joyce O'Shaughnessy, Texas Oncology - Baylor Charles A. Sammons Cancer Center and The US Oncology Network, Dallas, TX*

Background: Chemotherapy treatments that offer improved quality of life are needed. Tesetaxel (T) is a novel, oral taxane that has potential advantages over currently available taxanes, including: oral administration with a low pill burden and Q3W dosing; no history of hypersensitivity reactions; and improved activity against chemotherapy-resistant tumors (Shionoya 2003; Chan 2006). 555 pts have been treated with T in clinical studies (492 monotherapy; 63 in combination with capecitabine (C)). In MBC, T had robust single-agent activity in 2 multicenter, Phase 2 studies. In TOB203, 38 pts with HER2-, HR+ MBC received single-agent T Q3W for MBC; the confirmed ORR per RECIST 1.1 in all 38 pts was 45% (95% CI: 29% - 62%); the median PFS was 5.7 mo (95% CI: 4.1 – 9.8 mo). In a Phase 1 study, the combination of T plus a reduced dose of C was associated with a tolerable AE profile with minimal overlapping toxicity. C is a preferred agent for pts with MBC. Combining the approved dose of C with currently available taxanes results in robust efficacy but significant toxicity, while preclinical and clinical studies suggest that reducing the dose of C in combination with a taxane may result in reduced toxicity without a reduction in efficacy. CONTESSA investigates T plus a reduced dose of C as an all-oral regimen in HER2-, HR+ MBC. **Methods:** CONTESSA is a 600-pt, multinational, multicenter, randomized (1:1), Phase 3 registration study comparing T (27 mg/m^2 on Day 1 of a 21-day cycle) plus a reduced dose of C (1,650 mg/m^2/day on Days 1-14 of a 21-day cycle) to the approved dose of C alone (2,500 mg/m^2/day on Days 1-14 of a 21-day cycle) in pts with HER2-, HR+ MBC previously treated with a taxane in the (neo)adjuvant setting. Where indicated, pts must have received endocrine therapy with or without a CDK 4/6 inhibitor. The primary endpoint is PFS assessed by an Independent Radiologic Review Committee (IRC). CONTESSA is 90% powered to detect a 42% improvement in PFS (HR = 0.71). Secondary endpoints are OS, ORR assessed by IRC, disease control rate assessed by IRC and patient reported outcomes. Enrollment was initiated in Dec 2017. Clinical trial information: NCT03326674.

TPS1107 **Poster Session (Board #184b), Sat, 8:00 AM-11:30 AM**

BYLieve: A phase II study of alpelisib (ALP) with fulvestrant (FUL) or letrozole (LET) for treatment of *PIK3CA* mutant, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (aBC) progressing on/after cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy. *First Author: Hope S. Rugo, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Endocrine therapy (ET) is the standard of care for treatment of HR+, HER2– aBC. However, ET resistance occurs frequently due to dysregulation of the PI3K/AKT/mTOR pathway, specifically mutations in *PIK3CA,* the gene encoding the p110alpha subunit of PI3K. In a phase 1 study, ALP, a PI3Kα-specific inhibitor, in combination with FUL has shown antitumor activity in patients (pts) with *PIK3CA* mutant, HR+, HER2– aBC. The ongoing phase 3 SOLAR-1 trial (NCT02437318) is evaluating ALP + FUL combination in HR+, HER2– aBC. The present BYLieve study aims to assess the efficacy and safety of ALP + FUL/LET in *PIK3CA*-mutant, HR+, HER2– aBC progressing on/after prior CDK4/6i combination therapy. **Methods:** BYLieve is a phase 2, multicenter, open-label, 2-cohort, non-comparative study. Men and women (pre-menopausal and post-menopausal; $\geq$18 years) with *PIK3CA*-mutant, HR+, HER2– locally advanced or metastatic breast cancer that has progressed on/after prior CDK4/6i combination therapy are eligible. Other eligibility criteria include $\geq$1 measurable lesion (RECIST v1.1) or predominantly lytic bone lesion; ECOG PS $\leq$2; $\leq$1 line of prior chemotherapy in the advanced setting; and no prior PI3K inhibitor therapy. Pts are allocated to 2 cohorts; cohort A (pts who had received CDK4/6i + aromatase inhibitor): oral ALP (300 mg QD) + intramuscular FUL (500 mg) and cohort B (pts who had received CDK4/6i + FUL): oral ALP (300 mg QD) + oral LET (2.5 mg QD). The primary end point is the proportion of pts who are alive without disease progression at 6 months (RECIST v1.1; local assessment), and will be evaluated separately in each cohort. Evidence of treatment effect will be demonstrated if the lower bound of the 90% CI is greater than 30% with a planned sample size of 80 pts in each cohort. Secondary end points include progression-free survival (PFS), PFS on next-line treatment (PFS2), overall response rate, clinical benefit rate, duration of response, safety, and tolerability. Recruitment of the planned 160 pts is currently ongoing. Clinical trial information: NCT03056755.

TPS1108 Poster Session (Board #185a), Sat, 8:00 AM-11:30 AM

Study TTC-352-101: Phase 1 study of TTC-352 in patients with metastatic breast cancer (BC) progressing on endocrine therapy. *First Author: Ruth O'Regan, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: 75% of all breast cancers (BC) are hormone receptor-positive (HR+). Despite the efficacy of endocrine therapies, HR+ BC develop resistance, and cytotoxic chemotherapy is ultimately the only option to treat these patients. TTC-352 is a selective human estrogen receptor (ER) partial agonist (ShERPA) that was developed for treatment of HR+ BC. ShERPAs mimic the effects of estradiol (E2) in hormone-independent, endocrine-resistant BC cells, but since it has only partial agonist activity in HR+ BC cells, it could have an improved side effect profile. Specifically, TTC-352 does not support the growth of HR+, hormone-dependent BC xenografts that normally require E2 for growth nor result in uterine proliferation in mouse xenograft models as does E2. PKCa is a predictive biomarker for response to TTC-352 in endocrine-resistant BC xenografts. Thus, TTC-352 could be a promising treatment option for endocrine-resistant BC. **Methods:** This is an open-label, accelerated dose escalation study that will evaluate up to five dose levels of TTC-352 in patients with HR+ endocrine-resistant metastatic BC. The maximum tolerated dose (MTD) of TTC-352 will be determined using initial single-patient cohorts until grade 2 toxicity, then expansion to a modified-Fibonacci dose-escalation 3+3 design. Patients enrolled at each cohort must complete the first 28-day cycle before enrollment to the next dose cohort can start. The MTD dose level cohort will be expanded to a total of 9 patients, to further evaluate safety. The secondary objectives are: to determine patient best response (BR) to treatment, progression-free survival (PFS), overall survival (OS), treatment tolerability of TTC-352, and to establish the pharmacokinetic profile of TTC-352 in patients with metastatic ER+ BC. Correlative objectives include: tumor PKCa expression, steady-state values for Cmax, and AUC0-12 correlation with BR, PFS and OS. Patient population: patients with metastatic HR+ BC that has progressed on at least two lines of endocrine therapy, with one that included a CDK4/CDK6 inhibitor, and with adequate hepatic, renal, and bone marrow function at screening. This study is currently enrolling patients. Clinical trial information: NCT03201913.

TPS1109 Poster Session (Board #185b), Sat, 8:00 AM-11:30 AM

AIPAC (Active Immunotherapy PAClitaxel): A randomized, double blind, placebo controlled, multinational phase IIb trial evaluating the efficacy of eftilagimod alpha (a soluble LAG-3 fusion protein) in combination with paclitaxel in hormone receptor positive metastatic breast cancer. *First Author: Luc Dirix, Sint-Augustinus Hospital Oncology Center, Medical Oncology, Antwerpen, Belgium*

Background: Eftilagimod alpha (efti, previously IMP321) is a recombinant LAG-3Ig fusion protein that binds to MHC class II and mediates antigen-presenting cell (APC) activation followed by CD8 T-cell activation. The activation of the dendritic cell network with efti injected s.c. the day after chemotherapy at a time when these APC are loaded with tumor antigens may lead to stronger anti-tumor CD8 T cell responses. AIPAC (Active Immunotherapy PAClitaxel; NCT02614833) is a Phase IIb trial in hormone receptor-positive stage IV metastatic breast carcinoma patients receiving eftilagimod alpha (efti; also named IMP321) or placebo as adjunctive to weekly paclitaxel as a first-line chemotherapy. The safety run-in stage (stage 1) has been completed in 2016 and the randomized part (stage 2) is recruiting. **Methods:** This clinical trial is a placebo-controlled, double-blind, 1:1 randomized Phase IIb study aiming to enroll 226 patients at multiple centers across 7 different European countries. Patients with metastatic receptor positive breast adenocarcinoma receiving first line chemotherapy with weekly paclitaxel and with measurable disease according to RECIST 1.1 are enrolled. Patient eligible to Her2/neu targeted therapy are excluded from the trial. In the first treatment phase, paclitaxel (80 mg/m^2 IV at D1, D8, D15 plus efti (30 mg) or placebo at D2, D16 (i.e. injected SC the day after paclitaxel, every two weeks) will be administered for 6 cycles (1 cycle = 4 weeks). This is followed by a maintenance phase in which stable or responding patients will receive efti or placebo for up to additional 52 weeks (12 injections). The primary endpoint is progression-free survival. Secondary endpoints include overall survival, tumor response according to RECIST 1.1., time to and duration of response, duration of stable disease and quality of life. Clinical trial information: NCT02614833.

TPS1110 Poster Session (Board #186a), Sat, 8:00 AM-11:30 AM

Phase II study of a combination therapy of nivolumab, bevacizumab and paclitaxel in patients with HER2-negative metastatic breast cancer as a first-line treatment (WJOG9917B, NEWBEAT trial). *First Author: Yukinori Ozaki, Toranomon Hospital, Tokyo, Japan*

Background: In recent years, an immune checkpoint inhibitor, anti-PD-1 antibody, has been developed for various cancer types including breast cancer. The synergic effect of combination of nivolumab, paclitaxel and bevacizumab has been anticipated based on various preclinical data. Therefore, we initiated this investigator-initiated trial to evaluate the efficacy and safety of nivolumab + paclitaxel + bevacizumab therapy as a first-line treatment in patients with metastatic or recurrent HER2-negative breast cancer. **Methods:** This is a Phase II, multi-center, single-arm study to evaluate the efficacy and safety of nivolumab + paclitaxel + bevacizumab combination therapy as a first-line treatment for HER2-negative advanced metastatic or inoperable recurrent breast cancer. Patients will receive nivolumab 240 mg/body on day 1, 15, paclitaxel 90 mg/m^2 on day1, 8, 15, and bevacizumab 10 mg/kg on day1, 15 every 4 weeks until the protocol treatment is determined to be ineffective or may not be continued. The primary endpoint is the objective response rate (ORR) and key secondary endpoints include progression free survival, overall survival, and the toxicity of the protocol treatment. The threshold and expected ORR are 55% and 70%, respectively, and 47 patients are needed to ensure a statistical power of 80% (α = 0.10). A total of 51 patients will be enrolled and duration of enrollment will be one year. Tumor tissue will be evaluated for the amount and phenotypes of TILs, PD-L1 expression, and gene expression analysis. Peripheral blood will be evaluated for immune status and cytokine profiling. This trial opened to accrual in February 2018. Clinical trial information: UMIN000030242.

TPS1111 Poster Session (Board #186b), Sat, 8:00 AM-11:30 AM

ATTAIN: Phase 3 study of etirinotecan pegol (EP) vs. treatment of physician's choice (TPC) in patients (pts) with metastatic breast cancer (MBC) who have stable brain metastases (BM) previously treated with an anthracycline, a taxane, and capecitabine (ATC). *First Author: Debu Tripathy, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EP is a next-generation topoisomerase I inhibitor-polymer conjugate that provides continuous exposure to SN-38, the active metabolite. A BM mouse model showed high penetration and retention of SN-38 in CNS lesions, resulting in decreased size of CNS lesions and improved survival at concentrations achieved at the recommended dose in pts (Adkins BMC Cancer 2015). Although a phase 3 trial (BEACON) of EP vs TPC in 852 pts with advanced BC did not meet its primary endpoint of overall survival (OS) (HR 0.087; P = 0.08), a subset of 67 pts with stable BM showed improved OS (HR 0.51 [95% CI 0.30-0.86]; $P < 0.01$) (Perez Lancet Oncol 2015). The current phase 3 trial (ATTAIN) was designed for this subpopulation of pts having high unmet medical need. **Methods:** Pts with MBC with locally treated stable BM will be randomized 1:1 to EP or TPC in an open-label phase 3 study. Eligibility includes: ECOG PS 0 or 1; adequate organ function; prior ATC therapy (neo/adjuvant or locally advanced/MBC setting); $\geq$1 prior cytotoxic regimen for pts with triple negative MBC; $\geq$2 prior cytotoxic regimens for pts with HR+ or HER2+ BC (pts with HR+/HER2+ BC must have received prior hormone therapy/HER2 targeted therapy); prior definitive local therapy of BM (whole brain radiation [RT], stereotactic RT or surgical resection as single-agent or combination); and stable signs/symptoms of BM with steroids (ie, unchanged or decreasing $\geq$7 days prior to randomization). Primary endpoint is OS. Key secondary endpoints are ORR and PFS by RECIST v1.1 and RANO-BM, clinical benefit rate (ORR+SD $\geq$ 6 months) and QoL. Pts randomized to TPC will receive 1 of 7 cytotoxic IV agents. Pts are stratified by region, PS and receptor status. 350 pts will be randomized to obtain the number of events required at 90% power to detect a statistically significant improvement in OS (hypothesizing HR = 0.67); 1 interim analysis is planned at 50% of deaths (130 events). PK sampling and UGT1A1 testing will be performed in the EP arm; plasma ctDNA will be assessed for potential predictive markers of efficacy. Enrollment began early 2017. Clinical trial information: NCT02915744.

TPS1112 Poster Session (Board #187a), Sat, 8:00 AM-11:30 AM

An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity. *First Author: Anne Patsouris, Institute of West Cancerology Paul Papin, Angers, France*

Background: Rucaparib, a potent oral PARP-1, -2 and -3 inhibitor, has shown activity in a phase 3 study in patients (pts) with ovarian carcinoma (ARIEL 3) harbouring a *BRCA* mutation or an homologous recombination deficient (HRD) profile defined by high percentage of genome-wide loss of heterozygosity and in a phase 1 study that included breast cancer pts with germline *BRCA* mutation (Kristeleit *et al*, *Clin Can Res*, 2017). High genomic LOH score identified HRD tumors (also known as BRCAness tumors), including both known *BRCA1* methylation and unknown genetic/epigenetic mechanisms and somatic *BRCA1/2* mutations. This single arm, open-label, multicenter phase II RUBY study (NCT02505048) is evaluating the efficacy and safety of rucaparib in pts with HER2- metastatic breast cancer (MBC) associated with a "high tumor genomic LOH" score and/or a somatic *BRCA* mutation (excluding *BRCA1* and/or *BRCA2* germline mutation). **Methods:** Women with HER2- MBC with a HRD phenotype who received at least 1 prior chemotherapy regimens are eligible. ECOG PS 0-1 and adequate organ function is required. HRD phenotype is defined by a "high tumor genomic LOH" score, generated from the CytoScan HD SNP array, which is available from the SAFIR02 (NCT02299999) or SAFIR-TOR (NCT02444390) protocols. Pts received oral rucaparib 600 mg BID continuously in 21-day cycles until disease progression. The primary endpoint is clinical benefit rate (CBR), defined by complete and partial response and stable disease lasting for at least 16 weeks. If CBR is significant the objective response rate (ORR) will be considered as well. Secondary endpoints include progression-free survival, overall survival, safety, and the prognostic value of the HRD signature. This trial design is intended to establish proof-of-concept that rucaparib can improve ORR in HER2- MBC with HRD. Targeted enrollment is 41 pts using a Simon two-stage design, 19 pts in the first step and 22 pts in the second one. The prespecified goal of the first step was achieved; enrollment into the second step is ongoing. Clinical trial information: NCT02505048.

TPS1113 Poster Session (Board #187b), Sat, 8:00 AM-11:30 AM

A randomized phase II study of pembrolizumab, an anti-PD (programmed cell death) 1 antibody, in combination with carboplatin compared to carboplatin alone in breast cancer patients with chest wall disease, with immunologic and genomic correlative studies. *First Author: Neelima Vidula, UC San Francisco, San Francisco, CA*

Background: Chest wall disease from breast cancer has limited treatments. Given the inflammatory nature of this disease and the increased expression of PD-1 seen with lymphocytic infiltration, we hypothesize that pembrolizumab may be effective. Combining immunotherapy with platinum chemotherapy may facilitate anti-tumor immunity, as demonstrated in lung cancer. This study is evaluating the combination of pembrolizumab and carboplatin in breast cancer patients with chest wall disease. **Methods:** This is a randomized phase II multicenter trial in the Translational Breast Cancer Research Consortium. Eighty-four patients with breast cancer (hormone resistant, triple negative, or refractory HER2+) with chest wall disease will be enrolled. Patients may have had prior surgery but prior radiation is not required, and patients may have distant metastases. Patients will be randomized 2:1 to treatment with pembrolizumab 200 mg IV and carboplatin AUC 5 every 3 weeks for at least 6 cycles followed by pembrolizumab 200 mg IV alone (n = 56, Arm A) or carboplatin AUC 5 every 3 weeks (n = 28, Arm B) until progression. Patients in Arm B may cross over to pembrolizumab 200 mg IV every 3 weeks (Arm Bx) on progression. After 18 patients are enrolled in Arm B, an interim analysis for futility will be performed, to allow for early closure if lack of efficacy. The primary objective is to determine the disease control rate in both arms at 18 weeks of treatment; the study is powered to detect a 20% difference between arms, with a hazard ratio of 0.52 (α = 0.10, β = 0.20). The secondary objectives are to determine toxicity, progression free survival, and response based on irRECIST and PD-L1 expression. Exploratory objectives, using tumor biopsy and peripheral blood testing before and after treatment, include correlations of response with biomarkers including tumor PD-L1 expression, tumor and peripheral blood immune composition, circulating tumor cells, circulating tumor DNA, soluble PD-L1 and tumor MYC expression. This study is open to accrual; the first patient was enrolled in 11/17. Clinical trial information: NCT03095352.

TPS1114 Poster Session (Board #188a), Sat, 8:00 AM-11:30 AM

A phase II clinical trial to analyze olaparib response in patients with *BRCA1* and/or *BRCA2* promoter methylation with advanced breast cancer (GEICAM/2015-06 COMETA-Breast study). *First Author: Juan De La Haba, Biomedical Research Institute Maimonides.Hospital UniversitarioReina Sofia,Universidad de Cordoba, Spain.Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII. GEICAM, Spanish Breast Cancer Group, Spain, Cordoba, Spain*

Background: Identification of targeted therapies for advanced triple negative breast cancer (TNBC) remains as an important clinical challenge. TNBC frequently shows BRCA dysfunction and 80% of germline *BRCA1* mutation (g*BRCA*m) carriers with BC diagnosis are TNBC patients (pts). In addition to germline mutations, epigenetic silencing by aberrant methylation of *BRCA1/2* promoters can be responsible for a dysfunctional BRCA protein. Methylation of *BRCA1* promoter occurs in 15-57% of TNBCs. Interestingly, *BRCA1*-methylated sporadic breast tumors display pathologic features and gene expression profiles similar to those of g*BRCA*m carriers, a phenotype called "*BRCA*ness". Olaparib (O) is an oral poly (ADP-ribose) polymerase (PARP) inhibitor approved by the FDA for treatment of g*BRCA*-mutated HER2-negative metastatic BC. Tutt et al. have shown antitumor activity in g*BRCA*-mutated advanced TNBC (54% Objective Response Rate [ORR]). We report an ongoing phase II clinical trial to analyze the O efficacy in advanced TNBC pts with *BRCA1/2* promoter methylation (NCT03205761). **Methods:** Eligible pts are advanced TNBC cases with $\geq$ 1 prior treatment for advanced disease, without germline *BRCA1*/2 mutations and centrally confirmed somatic *BRCA1/2* promoter methylation in metastatic lesions. Pts receive O 300 mg b.i.d. orally. Primary objective is to analyze O efficacy in terms of ORR according to RECIST 1.1 by investigator assessment. Secondary objectives include safety, other efficacy endpoints, and biomarker analyses. Sequential tumor and blood samples are collected to a) explore changes in methylation status, b) correlate *BRCA*-methylation status both in blood vs. tumor and in primary vs. metastatic counterpart lesions, and c) correlate methylation status with *BRCA1/2* expression and outcome. Thirty-four evaluable pts are required based on an optimal two-stage Simon model (α error = 0.05, power = 80%, dropout rate = 10%). Recruitment started in October 2017, with 17 pts screened for methylation status, 3 pts enrolled by 31th January 2018, and 14 active sites out of 16 participants. Primary endpoint analysis is planned for Q2 2020. Clinical trial information: NCT03205761.

TPS1115 Poster Session (Board #188b), Sat, 8:00 AM-11:30 AM

IMpassion132: A double-blind randomized phase 3 trial evaluating chemotherapy (CT) $\pm$ atezolizumab (atezo) for early progressing locally advanced/metastatic triple-negative breast cancer (mTNBC). *First Author: Rebecca Dent, National Cancer Center, Singapore, Singapore*

Background: Atezo blocks the interaction of PD-L1 with receptors PD-1 and B7.1, restoring anti-tumor immunity. PD-L1 pathway inhibitors may be synergistic with CT. In a phase 1b study in mTNBC, atezo + nab-paclitaxel showed durable confirmed responses [Adams 2016]. The IMpassion130 and 131 randomized phase 3 trials are evaluating atezo combined with nab-paclitaxel and paclitaxel, respectively, as 1st-line therapy for mTNBC. Both exclude patients (pts) with disease progression (PD) within 12 mo of CT for early breast cancer (eBC). IMpassion132 (NCT03371017) compares atezo + CT vs placebo + CT in pts with PD $\leq$12 months after completing CT for eBC, and combines atezo with 2 commonly used non-taxane CT regimens. **Methods:** In this multinational placebo-controlled randomized phase 3 trial, pts with recurrent (inoperable locally advanced/metastatic) TNBC treated with standard (neo)adjuvant anthracycline and taxane CT and relapsing $\leq$12 months after the last treatment with curative intent for eBC are eligible if they have received no prior CT for advanced/metastatic TNBC. PD-L1 status (for stratification) and TNBC status are confirmed centrally before randomization. Investigators select CT (gemcitabine 1000 mg/m^2 + carboplatin AUC 2, d1 & 8 q21d [GC] or capecitabine 1000 mg/m^2 bid d1–14 q21d [X]) before randomization. All pts with prior platinum for eBC must receive X. At least 30% of ~350 planned pts will receive X. Stratification factors are: visceral (lung and/or liver) metastases (yes vs no); tumor PD-L1 status (IC 0 vs 1/2/3); and selected CT (GC vs X). Pts are randomized to either atezo or placebo 1200 mg q21d with the chosen CT, continued until PD, unacceptable toxicity or pt/physician decision. Tumors are assessed q8w for the 1st year and q12w thereafter until PD. The primary endpoint is overall survival (OS). Secondary endpoints include 12- and 18-mo OS rates, progression-free survival, objective response rate (RECIST v1.1), duration of response, clinical benefit rate, pt-reported outcomes (PROs; EORTC QLQ-C30) and safety. Exploratory endpoints include further PROs, pharmacokinetics and translational research. Clinical trial information: NCT03371017.

TPS1116 Poster Session (Board #189a), Sat, 8:00 AM-11:30 AM

VIOLETTE: A randomized phase II study to assess DNA damage response inhibitors in combination with olaparib (Ola) vs Ola monotherapy in patients (pts) with metastatic, triple-negative breast cancer (TNBC) stratified by alterations in homologous recombination repair (HRR)-related genes. *First Author: Andrew Tutt, Breast Cancer Now Toby Robins Research Centre The Institute of Cancer Research, and Breast Cancer Now Research Unit, King's College London Division of Cancer Studies, King's Health Partners Academic Health Sciences Centre, London, United Kingdom*

Background: Invasive BC is diagnosed in > 255,000 pts in the US annually, and TNBC comprises ≈15% of cases. Alterations in *BRCA1/2* are associated with ≈5% of all BCs. Ola (a poly ADP-ribose polymerase inhibitor [PARPi]) is approved in the US for treating pts with HER2-negative metastatic BC with germline *BRCA* mutation (g*BRCA*m). Pts treated with Ola had significant and clinically meaningful improvements in progression-free survival (PFS) vs pts treated with "physician's choice" of chemotherapy. Similarly, alterations in other non-*BRCA1/2* HRR genes (non-*BRCA* HRRm) may confer sensitivity to Ola therapy in pts with TNBC. Ola, AZD1775 (a WEE1 checkpoint inhibitor) and AZD6738 (an ataxia telangiectasia and Rad3-related protein inhibitor) target DNA damage repair and cell cycle regulation. Both Ola + AZD1775 and Ola + AZD6738 had synergistic antitumor effects vs Ola monotherapy in preclinical studies, supporting the clinical evaluation of these combinations vs Ola monotherapy in pts with TNBC. **Methods:** In this global, multicenter, open-label, phase II study (NCT03330847), 450 pts with advanced TNBC will be randomized (1:1:1) to 3 treatment arms 1) Ola 200 mg bid + AZD1775 175 mg bid, 2) Ola 300 mg bid + AZD6738 160 mg qd, or 3) Ola 300 mg bid. All pts will undergo centralized tumor molecular testing to detect mutation(s) in 15 HRR genes and ≈150 pts will be assigned to each of the 3 biomarker strata (A: *BRCA*m; B: non-*BRCA* HRRm; C: non-HRRm). All pts will be stratified by prior platinum exposure. Eligible pts will have received ≤2 prior lines of chemotherapy for metastatic disease, including an anthracycline or taxane. Exclusion criteria include prior PARPi therapy. The primary endpoint is PFS (each combination vs Ola alone) analyzed by blinded, independent central review (RECIST v1.1). Secondary endpoints are objective response rate, duration of response, change in tumor size, and overall survival for comparisons between combinations and for each combination vs Ola alone; drug exposure; and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT03330847.

TPS1117 Poster Session (Board #189b), Sat, 8:00 AM-11:30 AM

IPATunity130: A pivotal randomized phase III trial evaluating ipatasertib (IPAT) + paclitaxel (PAC) for *PIK3CA/AKT1/PTEN*-altered advanced triple-negative (TN) or hormone receptor-positive HER2-negative (HR+/HER2–) breast cancer (BC). *First Author: Rebecca Dent, National Cancer Center, Singapore, Singapore*

Background: In the LOTUS trial in advanced TNBC, adding IPAT to first-line PAC improved progression-free survival (PFS; primary endpoint), particularly in patients (pts) with *PIK3CA/AKT1/PTEN*-altered tumors [Kim, Lancet Oncol 2017]. The pivotal double-blind placebo (PBO)-controlled randomized phase III IPATunity130 trial (NCT03337724) aims to confirm and build on findings from LOTUS. **Methods:** Eligible pts have ECOG performance status 0/1 and RECIST-measurable locally advanced/metastatic BC not amenable to resection with curative intent. Pts are allocated to either cohort A (TNBC; n≈249) or cohort B (HR+/HER2– not suitable for endocrine therapy; n≈201) according to their most recent locally assessed receptor status (in recurrent/metastatic tumor if available). In cohort A, any prior systemic therapy for advanced TNBC is prohibited, whereas cohort B pts may have received prior systemic therapy except chemotherapy for advanced BC. Tumor *PIK3CA/AKT1/PTEN* eligibility is tested centrally by next-generation sequencing (Foundation Medicine). Stratification factors are prior (neo) adjuvant chemotherapy, geographic region, and either tumor *PIK3CA/AKT1*-activating mutation status (cohort A) or prior PI3K/mTOR inhibitor therapy (cohort B). Pts in both cohorts are randomized 2:1 to 28-day cycles of PAC 80 mg/m^2 (d1, 8, & 15) combined with either oral IPAT 400 mg/day (d1–21) or PBO until disease progression, intolerable toxicity, or withdrawal. Crossover to IPAT after progression on PAC + PBO is prohibited. The primary endpoint is investigator-assessed PFS by RECIST v1.1. Secondary endpoints include overall survival (key secondary), objective response rate (RECIST v1.1), duration of response, clinical benefit rate, EORTC QLQ-C30 global health status/health-related quality of life, and safety. Cohorts A and B will be analyzed separately. For each cohort, PFS will be compared between treatment arms using a stratified log-rank test. The trial is actively accruing pts. Clinical trial information: NCT03337724.

TPS1118 Poster Session (Board #190a), Sat, 8:00 AM-11:30 AM

A randomized phase II trial of carboplatin with or without nivolumab in first- or second-line metastatic TNBC. *First Author: Ana Christina Garrido-Castro, Dana-Farber Cancer Institute, Boston, MA*

Background: Triple negative breast cancer (TNBC) has an aggressive clinical course with higher relapse rates and shorter overall survival compared to patients with hormone receptor-positive or HER2-positive disease. Increasing data suggest that interaction with the immune system is critical for outcomes in TNBC. Tumor infiltrating lymphocytes (TIL) correlate with improved prognosis and response to several PD-1/-L1 inhibitors. However, response rates with single agent checkpoint inhibitors reach only ≈ 25% in first-line TNBC. Platinum agents are DNA crosslinkers that cause accumulation of genotoxic stress, which stimulates immune activation via IFN-γ signaling. In preclinical models, platinum has been shown to generate CD8-driven anti-tumor immune response, making the combination with nivolumab (PD-1 antibody) an attractive strategy to enhance the benefit of either agent alone. **Methods:** This Phase II open-label, multicenter trial will enroll 132 patients with metastatic TNBC randomized 1:1 to receive carboplatin (AUC 6) with or without nivolumab (360 mg) IV every 3 weeks. Eligible patients must have unresectable locally advanced or metastatic TNBC treated with 0 to 1 prior line of chemotherapy in the metastatic setting. Prior platinum exposure is allowed in the neo/adjuvant setting if ≥12 months elapsed since the end of adjuvant therapy to the development of metastatic disease. The primary objective is to compare the efficacy, defined as progression-free survival (PFS) per RECIST 1.1, of carboplatin in combination with nivolumab versus carboplatin alone. Key secondary objectives include objective response rate, overall survival, clinical benefit rate, and duration and time to objective response. Patients must be willing to undergo mandatory paired research biopsies, one at baseline and one after 2 cycles of therapy, if safely accessible, to assess the correlation between TIL and PFS, and to explore pharmacodynamic changes in TIL and other biomarkers of response and resistance to treatment. Additional correlative studies, including analyses of circulating tumor DNA, peripheral blood mononuclear cells and intestinal microbiome, are planned. Clinical trial information: NCT03414684.

TPS1119 Poster Session (Board #190b), Sat, 8:00 AM-11:30 AM

A phase II study of nivolumab in combination with cabozantinib for metastatic triple-negative breast cancer (mTNBC). *First Author: Romualdo Barroso-Sousa, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients with mTNBC have a poor prognosis, and new therapies are needed. Vascular endothelial growth factor (VEGF)-A and myeloid-derived suppressors cells (MDSCs) have been recognized as critical players of tumor immune suppression of T-cell mediated responses. We hypothesize that cabozantinib, a multikinase inhibitor that blocks the VEGF receptor 2, and reduces MDSCs while increasing the number of T cells, will enhance the activity of the anti-PD-1 checkpoint blocker nivolumab in mTNBC. **Methods:** This is a phase II, single arm, single-center study assessing the efficacy of nivolumab (480 mg intravenously on day 1, every 28 days) plus cabozantinib (40 mg daily by mouth) in patients with mTNBC (NCT03316586). Eligibility Criteria include patients with mTNBC, or estrogen and progesterone receptor low positive (< 10%) breast cancer, with measurable disease, and who have received 0-3 prior lines of chemotherapy in the advanced setting. The primary aim is to evaluate the efficacy of the combination, as defined by ORR according to RECIST 1.1. Secondary objectives include to determine the ORR according to immune-related criteria, the progression-free survival, the clinical benefit rate, the safety and the tolerability of the combination. Tumor biopsies and peripheral blood will be obtained at baseline, on treatment and at disease progression for immunoprofiling and to examine biomarkers of treatment response. Using the Simons "optimal" method, in the first stage, 18 patients will be enrolled. If there are least 3 responses, accrual will continue to the second stage where up to 17 additional patients will be enrolled. If at least 7 of these 35 patients have an objective response the regimen will be considered worthy of further study. With this design, if the true response rate is 10%, the chance the regimen is declared worthy of further study is less than 5% (exact alpha = 0.047). If the true response rate is 30%, the chance that the regimen is declared worthy of further study is 90%. The trial opened in December 2017 and has accrued 5 patients with a target accrual of 35 patients. Accrual should be completed in 12 months. Clinical trial information: 03316586.

1500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Low-fat dietary pattern and all cancer mortality in the Women's Health Initiative (WHI) randomized trial. *First Author: Rowan T. Chlebowski, City of Hope National Medical Center, Duarte, CA*

Background: In the Women's Health Initiative randomized (WHI) Dietary Modification (DM) primary prevention trial, after 16.1 years median follow-up, implementation of a low-fat dietary pattern significantly reduced deaths after breast cancer. Mortality from other cancer sites has not been reported. **Methods:** To determine low-fat dietary pattern influence on deaths from and after breast cancer and other cancers during 8.5 years (median) dietary intervention and now with 17.1 years (median) cumulative follow-up, 48,835 postmenopausal women with no prior cancer, aged 50-79, were randomized at 40 US clinical centers from 1993-1998 to dietary intervention (DM-I) (40%, n = 19,541) to reduce fat intake to 20% of energy and increase fruits, vegetables and grains intake, or usual diet comparison (DM-C) (60%, n = 29,294). DM-I influence on breast, colorectal, endometrium and ovarian cancers alone and as a composite were prospectively determined primary analyses. **Results:** During dietary intervention, deaths after breast cancer was the only statistically significant cancer mortality finding. During cumulative follow-up with 3,867 deaths after all cancers, significant reduction in deaths after breast cancer continued in the DM-I group (HR 0.85 95% CI 0.74-0.99, P = 0.03) especially in subgroup with waist circumference > = 88 cm (HR 0.78 95% CI 0.64-0.95). Deaths after pancreatic cancer were somewhat lower in the DM-I group (HR 0.89 95% CI 0.70 -1.13, not significant). In addition, in no other cancer or cancer composite group was a dietary intervention effect on death from or after cancer seen (see table). **Conclusions:** Adoption of a low-fat dietary pattern led to a lower incidence of deaths after breast cancer. No reduction in mortality from other cancer sites was seen. Clinical trial information: NCT00000611.

Deaths from cause after cancer	DM-I*	DM-C*	HR (95% CI)	P-value
Primary analysis				
Deaths after breast cancer	280(0.098)	507(0.12)	0.85(0.74,0.99)	0.03
Death after colorectal cancer	164 (0.057)	228(0.052)	1.10(0.90,1.35)	0.34
Death after ovarian cancer	92(0.032)	143(0.033)	0.98(0.75,1.27)	0.87
Death after endometrial cancer	69(0.042)	98(0.039)	1.07(0.79,1.46)	0.66

1501 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Pre- and post-treatment body weight and prognosis in a multiethnic cohort of breast cancer patients. *First Author: Lihua Shang, University of Chicago, Chicago, IL*

Background: Although pre-diagnosis obesity was found to be associated with worse outcomes in breast cancer patients, few studies have been conducted on weight change after diagnosis. African Americans have higher prevalence of obesity than other racial/ethnic populations, but it is unclear if obesity prevalence could explain mortality disparity between African Americans and whites. **Methods:** Data on body mass index (BMI) prior to, during, or after treatment were available in 3061 breast cancer patients enrolled in the Chicago Multiethnic Epidemiologic Breast Cancer Cohort (ChiMEC), including 1662 whites, 1183 African Americans and 216 other ethnicities. Multilevel random effects models were used to examine changes in body weight or BMI over time. Cox models were used to investigate the impacts of BMI on overall survival and disease-free survival. **Results:** At diagnosis, half of African Americans (51.5%) were obese, compared with 27.0% in whites. After 6 months, 1 year, 2 years, and 4 years from diagnosis, African Americans on average have lost 0.73 kg, 1.05 kg, 1.29 kg, and 2.47 kg, respectively ($P < 0.0001$), while there were only small weight changes in whites (< 0.31 kg). The impact of pre-treatment BMI on survival was stronger for estrogen receptor (ER) positive patients (hazard ratio [HR] 1.20 per 5 kg/m^2, 95% confidence interval [CI]: 1.06-1.36; p = 0.005) than for ER negative patients (HR 1.06 per 5 kg/m^2, 95% CI: 0.90-1.24; p = 0.52). African Americans had a 90% higher mortality risk relative to white patients after adjusting for age, stage and other clinical factors (HR 1.90, 95% CI: 1.41-2.55). Further adjusting for BMI at diagnosis, the HR for African Americans changed to 1.81 (95% CI: 1.34-2.43). In the landmark analysis of patients who were followed > 2 years, the multivariable HR for African Americans was 1.64 (95% CI: 1.05-2.58) without adjusting for post-treatment BMI and 1.55 (95% CI: 0.97-2.48) after adjusting for post-treatment BMI. Similar results were observed in the analysis of disease-free survival. **Conclusions:** African American patients had higher obesity prevalence but had substantial weight loss during and after treatment. The impact of BMI on survival differs by ER status.

1502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Cardiorespiratory fitness and incident lung and colon cancer: FIT-Cancer Cohort. *First Author: Catherine Handy, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Cardiorespiratory fitness (CRF), an objective measure of exercise tolerance, is a strong predictor of cardiovascular disease and mortality yet its relationship with cancer incidence is unclear. The goal of this analysis was to assess the relationship between CRF and lung and colon cancer in a large, multi-ethnic clinical cohort. **Methods:** From The FIT Project, a retrospective cohort of 69,885 consecutive patients who underwent physician referred treadmill testing using the Bruce protocol in the Henry Ford Health System (HFHS) between 1991 and 2009, we created the FIT-Cancer Cohort by linkage with the HFHS Tumor Registry. We included patients aged 40-70 years who were cancer free at baseline. Multivariable adjusted Cox proportional hazard models were used to evaluate the association between CRF (measured in peak metabolic equivalents [METs]) and incident lung and colon cancer. **Results:** 49,143 individuals (46% women, 64% White), with a mean age of 54 years, were included. During a median follow up of 8.3 years (IQR 7.1 years), there were 388 and 238 incident lung and colon cancers. Compared to those with the lowest level of CRF, individuals in the highest CRF category had a 77% (CI: 63-85%) decreased risk of developing lung cancer and a 60% (CI: 33-75%) decreased risk of colon cancer in multivariable adjusted models. There was a significant, inverse METs-incident cancer dose response relationship (Table 1, p trend for lung and colon < 0.01). Subgroup analyses in smokers, by sex and race showed similar results. **Conclusions:** In the largest study of its kind, CRF measured during exercise testing is a strong predictor of future lung and colon cancer risk. Our study provides another important reason for optimizing CRF.

Adjusted risk of incident lung and colon cancer, per category of CRF.

	Lung cancer				Colon cancer			
METS	**HR#**	**CI**	**HR***	**CI**	**HR#**	**CI**	**HR^**	**CI**
< 6	Ref		Ref		Ref		Ref	
6 -9	**0.70**	**0.55, 0.90**	**0.68**	**0.53, 0.87**	0.80	0.57, 1.11	0.80	0.57, 1.11
10 – 11	**0.50**	**0.38, 0.65**	**0.48**	**0.36, 0.63**	**0.49**	**0.34, 0.71**	**0.49**	**0.34, 0.71**
> = 12	**0.23**	**0.14, 0.36**	**0.23**	**0.15, 0.37**	**0.41**	**0.25, 0.66**	**0.40**	**0.24, 0.65**

#Adjusted for age, race, sex * Adjusted for age, race, sex, smoking, BMI ^ Adjusted for age, race, sex, smoking, aspirin & statin use, BMI

1503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Inherited mutations in breast cancer patients with and without multiple primary cancers. *First Author: Kara Noelle Maxwell, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Women with breast cancer have a 5-12% lifetime risk of a second primary cancer. Whether mutations in genes other than *BRCA1/2* are enriched in patients with breast and another primary cancer (MP-BC) over those with a single breast cancer (S-BC) is unknown. **Methods:** We identified pathogenic germline mutations in cancer susceptibility genes in *BRCA1/2* negative patients in two differently ascertained cohorts: Cohort #1, high risk breast cancer program (MP-BC, n = 551 vs S-BC, n = 464) and Cohort #2, familial breast cancer research study (MP-BC, n = 340 vs S-BC, n = 1464). Mutation rates in patients of European descent were compared to ExAC. **Results:** Overall pathogenic mutation rates for cancer panel testing genes were two-fold higher in patients with MP-BC versus S-BC in both cohorts (8.7% vs 4.1%, p = 0.003 and 8.2% vs 4.2%, p = 0.003, respectively). However, there were differences in individual gene mutation rates between cohorts (Table). In comparison to a race and ethnicity matched control group, mutations in *TP53* and *MSH6* were statistically significantly enriched in MP-BC but not S-BC patients. Mutations in *ATM*, *CHEK2* and *PALB2* were statistically significantly enriched in both MP-BC and S-BC patients relative to controls. **Conclusions:** These data demonstrate that mutations in high risk genes are typically found in patients with multiple primary cancers; whereas rates of moderate penetrance gene mutations are similar. Patients with multiple primary cancers should be offered multiplex panel testing.

Mutation rates in MP-BC vs S-BC patients in two cohorts.

	COHORT #1					COHORT #2				
	MP-BC		S-BC			MP-BC		S-BC		
Gene	**n**	**% of 551**	**n**	**% of 464**	**p**	**n**	**% of 340**	**n**	**% of 1464**	**p**
TP53	12	2.2%	1	0.2%	0.005	3	0.9%	6	0.4%	0.38
PALB2	3	0.5%	1	0.2%	0.63	5	1.5%	13	0.9%	0.36
CDH1	1	0.2%	0	0.0%	Nd	0	0.0%	2	0.1%	Nd
PTEN	1	0.2%	0	0.0%	Nd	0	0.0%	0	0.0%	Nd
STK11	0	0.0%	0	0.0%	Nd	0	0.0%	0	0.0%	Nd
CHEK2	14	2.5%	9	1.9%	0.67	9	2.7%	17	1.2%	0.07
ATM	5	0.9%	7	1.5%	0.40	8	2.4%	16	1.1%	0.11
NBN	0	0.0%	0	0.0%	Nd	0	0.0%	1	0.1%	Nd
MSH6	6	1.1%	0	0.0%	0.03	3	0.9%	1	0.1%	0.02
PMS2	3	0.5%	0	0.0%	0.25	0	0.0%	2	0.1%	1.00
MSH2	2	0.4%	0	0.0%	0.50	0	0.0%	3	0.2%	1.00
MLH1	0	0.0%	1	0.2%	Nd	0	0.0%	0	0.0%	Nd
CDKN2A	2	0.4%	0	0.0%	0.50	0	0.0%	0	0.0%	Nd
***MUTYH* monoallelic**	5	0.9%	6	1.3%	0.56	7	2.1%	21	1.4%	0.46
***CHEK2* Low Risk**	15	2.7%	5	1.1%	0.03	3	0.9%	17	1.2%	1.00

1504 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Frequency of actionable cancer predisposing germline mutations in patients with lung cancers. *First Author: Semanti Mukherjee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Most of the heritability for lung cancer, estimated at 18% in population studies, remains unexplained. Utilizing a tumor-normal screening, we determined the prevalence of clinically actionable germline cancer-susceptibility mutations in patients with lung cancer, and correlated findings with clinical, tumor associated, and family history characteristics **Methods:** Tumor/normal samples from lung cancer patients (pts) enrolled from 1/14 until 5/16 underwent sequencing analysis for 468 genes by MSK IMPACT [PMID: 28481359], with pathogenicity assessment for 76 cancer predisposition genes by ACMG guidelines. Selected patients with a strong family history of cancer, multiple primary tumors, or early age of diagnosis (≤50) were offered return of germline findings. As per IRB protocol, germline results were anonymized for all cases except those consenting to return of results. Frequencies of pathogenic/likely pathogenic (P/LP) germline mutations were compared to population databases. **Results:** 1118 pts consented to tumor-normal sequencing and 42 to return of germline findings; the median age of the two groups was 68 and 59 , respectively ($p < 0.05$). For the 42 pts receiving germline findings, 24% had early onset and 52% multiple cancer diagnosis, and 31% had P/LP mutations in 10 genes (3 *BRCA2*, 2 *MEN1*, 1 *APC*, 1 *ATM*, 1 *BAP1*, 1 *BLM*, 1 *CHEK2*, 1 *FH*, 1 *FLCN*, 1 *RAD51D*). Among 1118 pts, 8% had P/LP mutations in 16 genes (20 *APC*, 15 *CHEK2*, 13 *MUTYH*, 7 *BRCA2*, 6 *BRCA1*, 5 *FH*, 4 *ATM*, 4 FANCC, 4 *RECQL4*, 3 *FANCA*, 3 *TP53*, 2 *RAD50*, 2 *RAD51C*, 1 *BRIP1*, 1 *NBN*, 1 *PMS2*). 45% of the P/LP mutations of *CHEK2, APC, MUTYH, BRCA1* were population "founder" mutations. There was no statistically significant increase in burden of these pathogenic variants in the lung cancer cases studied. The 31% prevalence of germline variants in pts enriched for family history of cancer was greater than the 8% prevalence in patients unselected for family history ($p < 0.0002$). **Conclusions:** Our preliminary findings demonstrate an increased prevalence of clinically actionable germline mutations in patients with lung cancer with either a family history of other cancers, early age at onset, or multiple cancer diagnosis, compared to unselected lung cancer patients.

1505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Pathogenic somatic mutation (SM) of mismatch repair (MMR) genes and associations with microsatellite instability (MSI), tumor mutational burden (TMB) and SM in other DNA repair pathways in 24,223 tumor genomic profiles. *First Author: Joseph Nicholas Bodor, Fox Chase Cancer Center, Philadelphia, PA*

Background: SM disabling DNA repair mechanisms is common in cancer. SM in MMR genes (MLH1, MSH2, MSH6, PMS2) contribute to MMR deficiency and the MSI phenotype. Biallelic SM (bSM) of an MMR gene can cause MMR deficiency in colorectal (CRC) and endometrial cancers (EC), but the frequency of monoallelic SM (mSM) and bSM of MMR genes in other tumors is unknown. Clinical/molecular correlates of MMR gene mSM/bSM are not well described. **Methods:** The Caris Life Sciences database was queried for tumors with ≥1 SM of an MMR gene by NGS (Illumina NextSeq 592 gene panel). Association of mSM or bSM with clinical factors, MSI, TMB, and SM in non-MMR DNA repair pathways was examined. Associations were tested by Fisher's exact test and logistic regression. **Results:** Of 24,223 tumors queried, 470 had ≥1 SM, of which 80 had bSM in an MMR gene. MSH6 had the highest frequency of bSM (n = 46) primarily due to recurrent SM at F1088fs, a coding microsatellite. Tumors with bSM were more common in younger pts, median age 57.5 yrs bSM vs. 63 yrs mSM ($p = 0.003$). bSM was associated with high TMB ($p < 0.001$), and with SM in nucleotide excision repair (NER) genes ($p = 0.003$), and homologous recombination (HR) genes ($p = 0.01$), e.g. ATM (62/470, 13.2%) and BRCA1/2 (n = 91/470, 19.4%). At the single gene level, mSM in MSH2 ($p = 0.001$) and MSH6 ($p = 0.01$) were positively associated with TMB, but inversely with PMS2 ($p < 0.001$). MSI was only associated with mSM in MLH1 ($p < 0.001$). Further, SMs in HR genes were associated with mSM in MLH1, MSH2, and MSH6 (all $p < 0.01$), but SM in NER were associated only with mSM in MSH6 ($p = 0.004$). By tumor type, mSM were common in EC (n = 84), CRC (n = 80) and lung (n = 45), but nearly all bSM (98%) were in LS-spectrum tumors. Differences in bSM frequency in left vs. right CRC (30.0% vs 12.5%) were not seen ($p = 0.10$). **Conclusions:** MMR gene mSM occur in diverse tumors, but bSM occur almost exclusively in LS-spectrum tumors. Younger age suggests germ-line mutations may precede some bSM events. Association of MMR mSM/bSM to high TMB, MSI, and SM in other DNA repair pathways suggests cascade effects of DNA repair deficiency and reveals possible treatment targets.

1506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A breast cancer risk model as a predictor of interval cancer rate and tumor characteristics. *First Author: Nickolas Dreher, University of California, San Francisco, San Francisco, CA*

Background: The Breast Cancer Surveillance Consortium (BCSC) Risk Calculator is a validated and widely used risk model that predicts five- and ten-year risk of developing invasive breast cancer for women age 40-75. However, little research has been conducted to determine if women with high BCSC risk are also more likely to develop any particular type of cancer. These women may be at elevated risk to develop interval cancers, those that present symptomatically following a normal screening mammogram and are often faster-growing. If this were the case, women with high BCSC risk (defined here as the top 2.5% by age) may merit increased screening frequency. **Methods:** We calculated BCSC 5-year risk scores for female breast cancer patients who completed an online intake survey distributed by the Athena Breast Health Network before being seen at the UCSF Breast Care Center, and whose BI-RADS density category was available. We reviewed charts of patients who were in the top 2.5% of risk for their age according to national averages estimated by the BCSC, and we compared them to an equal number of female breast cancer patients from the lower 97.5%. We then compared the proportion of interval, ER-negative, node-positive, and high-grade cancers between each group using a Chi-squared test (two-sided alpha = .05). **Results:** Of 5253 female breast cancer patients who completed an intake survey, 1880 had BI-RADS data available. 131 of these patients fell in the top 2.5% of breast cancer risk for their age. Compared to 131 breast cancer patients from the lower 97.5% of risk, more high-risk patients developed an interval cancer within one year of a normal screening mammogram, with preliminary rates of 24.1% vs 4.1% respectively ($p = 0.003$). There was no significant difference between the rates of ER-negative, node-positive, or high-grade cancers between the two groups. **Conclusions:** Breast cancer patients in the top 2.5% of breast cancer risk according to the BCSC model are more likely to develop interval cancers, which may warrant tailored screening strategies.

1507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Validation of a combined residual risk score for healthy unaffected women presenting to breast cancer (BC) screening centers. *First Author: Kathryn Dalton, Cape Cod Healthcare, Mashpee, MA*

Background: Recent studies have identified single-nucleotide polymorphisms (SNPs) that individually confer modest risk but together explain genetic BC predisposition in many women testing negative for monogenic mutations. We have previously developed and validated an 86-SNP residual risk score (RRS) and a combined residual risk score (cRRS) that incorporates version 7.02 of the Tyrer-Cuzick (TC) model in large consecutive cohorts of women who tested negative for mutations in known BC predisposition genes during hereditary cancer testing. Here, we describe validation of the cRRS in a consecutive cohort of women enrolled from BC screening centers. **Methods:** This was a prospective, IRB-approved study conducted according to a case-control design. The primary objective was to demonstrate that cRRS offers significantly improved discriminatory accuracy compared to TC alone. A consecutive series of unaffected controls and recently diagnosed BC-affected cases of European ancestry who presented to screening centers were enrolled. Consented patients provided blood or saliva samples for SNP and multi-gene panel testing, and clinical information for the TC model. Discriminatory accuracy of cRRS and TC were evaluated with age-adjusted weighted logistic regression models. P-values were based on likelihood ratio chi-squared test-statistics, and reported as two-sided. **Results:** 518 patients (256 BC cases; 262 unaffected controls) who met study eligibility criteria were enrolled from 4 screening centers: Elizabeth Wende Breast Care (123); The Breast Center of NWA (145); Bethesda Health (113); CUDA/CCHC (137). Patients with mutations in BC genes were excluded from analysis. Both cRRS and TC significantly discriminated BC cases from unaffected controls in terms of remaining lifetime (cRRS $p < 10^{-11}$; TC $p < 10^{-5}$) and 5-year (cRRS $p < 10^{-10}$; TC $p < 10^{-4}$) risk estimates. The cRRS showed significantly improved discriminatory accuracy compared to TC alone (lifetime $p < 10^{-7}$; 5-year $p < 10^{-7}$). **Conclusions:** The cRRS offers superior risk stratification compared to TC alone, and may improve prevention and screening strategies for unaffected women testing negative for monogenic BC mutations. Clinical trial information: NCT03067389.

1508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Polygenic risk score for breast cancer in high-risk women. *First Author: Mary Helen Black, Ambry Genetics, Aliso Viejo, CA*

Background: While assessment of genetic contribution to breast cancer (BC) risk was once limited to high-penetrance genes such as *BRCA1/2*, additional genes conferring two- to five-fold increased risks of BC, as well common SNPs with relative risks ranging 1.03-1.57, have recently been identified. Although several reports suggest that a score based on combined genotypes across a large number of SNPs may have substantial predictive value for risk stratification in the general population, few studies have examined the performance of such a score in high-risk women. **Methods:** We genotyped 102 BC-associated SNPs using next-generation sequencing in order to examine whether a risk score based on these SNPs was predictive of BC in 2,910 women (1,758 cases with no other cancer primaries and 1,152 controls unaffected with any cancer) referred for genetic testing at a single diagnostic laboratory. All women were self-reported Caucasian, 18-85 years of age and provided family history information at the time of testing, and tested negative for pathogenic variants in BC-related genes (mean$\pm$SD age at testing 52$\pm$13 years). We constructed a polygenic risk score (PRS), with each SNP weighted by per-allele relative risks in Caucasians from large genome-wide association studies and population-specific allele frequencies, and tested PRS association with BC using logistic regression. **Results:** The PRS was significantly higher in cases than controls (mean$\pm$SD 1.41$\pm$0.86 vs. 1.06$\pm$0.66, $p < 0.0001$). Compared to women in the 1st quartile of PRS, those in the 2nd, 3rd and 4th quartile were 1.65 (95% CI: 1.34-2.05), 2.12 (95% CI: 1.71-2.64) and 2.75 (95% CI: 2.20-3.44) times as likely to have BC (all $p < 0.0001$). PRS predictive performance was consistent with prior literature (AUROC = 0.61). **Conclusions:** These data suggest that a 102-SNP PRS assessed in high-risk patients performs similarly to risk scores reported in the broader population, and has direct implications for their clinical management. Our ongoing analysis of the ability of the PRS to discriminate among specific pathologic subtypes, as well as validity and utility of a PRS combined with clinical models to estimate residual lifetime risk, has the potential to further inform screening guidelines and improve patient care.

LBA1509 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Pan-cancer microsatellite instability to predict for presence of Lynch syndrome. *First Author: Alicia Latham Schwark, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

1510 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Disclosure of secondary germline findings from clinical tumor-normal paired somatic mutation profiling. *First Author: Molly S. Daniels, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Accurate identification of cancer somatic mutations is facilitated by tumor-normal subtractive analysis. Tumor-normal paired testing (TNPT) can also lead to significant secondary germline findings. We report the secondary germline outcomes from clinical TNPT of 4923 patients at a single institution. **Methods:** TNPT via the Oncomine platform was performed in-house when ordered by patients' clinicians. Potential secondary germline findings were flagged and sent to clinical cancer genetics (CCG) for review. Pathogenic germline mutations in high penetrance hereditary cancer genes were selected by database and literature review. Medical records were reviewed to determine whether standalone germline testing (SGT) had already identified the mutation. If not, CCG contacted the patient and offered confirmatory SGT via outside reference laboratory. **Results:** From January 2016 to January 2018, 62/4923 (1.3%) of TNPTs were flagged for CCG review. 41/62 (66%) mutations were selected for follow-up (see table). 16/28 (57%) of patients with previously unknown mutations returned for confirmatory SGT. In 28/29 (97%) cases where both TNPT and SGT results were available, they were concordant. The exception was an *MSH2* mutation found on TNPT but not on SGT; further analysis revealed that the TNPT result had been a low confidence call. **Conclusions:** Clinical TNPT identified germline mutations in 0.8% of tested patients, many of which were not already known to patients and/or occurred in cancers outside the typical spectrum for that gene. Effective communication between pathology and CCG facilitates classification of mutations as well as patient notification. Offering secondary germline findings from clinical TNPT to patients is feasible and affords families the opportunity to benefit from predictive genetic testing.

Gene	Mutation previously found on SGT (13)	Mutation newly identified on TNPT (28)
BRCA1	Ovary (4)	Sebaceous(1), ovary (1), lung (2), colon (1)
BRCA2	Breast (1), ovary (3), prostate (2), lung (1), pancreatic (1)	Ovary (1), colon (5), lung (4), prostate (3), glioma (1), ampullary (1)
TP53	0	Sarcoma (2), colon (1), thymoma (1), pancreatic (1)
EGFR T790M	0	Lung (1), colon (1)
MSH2	Ovary (1)	Kidney (1)

1511 Clinical Science Symposium, Mon, 8:00 AM-9:30 AM

Genetic counseling (GC) and germline (GL) testing rates after adoption of an integrated clinical cancer genetics (CCG) approach to genomics tumor board (GTB). *First Author: Stefan Klek, Cleveland Clinic, Cleveland, OH*

Background: The clinical impact of addressing potentially GL alterations (PGA) from somatic next-generation sequencing (NGS) is not well characterized. We hypothesize that the addition of screening for PGA by genetics professionals at GTB increases GL findings in those who underwent NGS. **Methods:** In a prospectively accrued cohort with tumor NGS via FoundationOne (F1), we quantified (1) patients with $\geq$1 GC visit, (2) whether GC occurred pre- or post-F1 testing, (3) GC referrals due to F1 reports, (4) which had GL testing, and (5) results of GL testing. We analyzed these variables across 4 sub-cohorts: patients whose F1 reports were presented at GTB (C1) before and (C2) after the addition of screening for PGA by genetics professionals at GTB. C2 was further subdivided: (C2A) after the addition of GL screening at GTB and (C2B) after the addition of GL screening at GTB plus a formal CCG workflow to coordinate post-GTB GC. P-values were determined using a 2-sample, one-tailed z-test. **Results:** 907 F1 reports were reviewed at GTB from 2013 to 2017 ($n_{C1} = 281$, $n_{C2} = 626$, $n_{C2A} = 493$, and $n_{C2B} = 133$). Overall, the number of GC visits showed an increasing trend from C1 to C2A (14.6 to 19.9%, $P = .066$) with significance from C1 to C2B (14.6 to 33.1%, $P = .0012$). Incidence of GC visits post-F1 rose from C1 to C2 (7.3 to 41.6%, $P < .0001$) with visits specifically due to F1 increasing from C1 to C2A (7.3 to 32.7%, $P < 0.0001$) and even more from C1 to C2B (7.3 to 40.9%, $P < 0.0001$). Incidence of GL testing showed an increasing trend from C1 to C2A (11.0 to 14.4%, $P = 0.091$) with significance from C1 to C2B (11.0 to 27.8%, $P < 0.0001$). Finally, the number of pts found positive for GL mutation showed an increasing trend from C1 to C2A (1.4% to 2.2%, $P = .22$) with significance from C1 to C2B (1.4% to 6.0%, $P = .0046$). **Conclusions:** Integrating CCG with somatic NGS testing review significantly increased not only GC utilization but also the discovery of positive GL results. Although this approach should not substitute for documentation of a detailed family history, positive GL findings can be a direct consequence of somatic NGS and should be considered an independent clinical benefit of somatic NGS testing apart from therapeutic uses.

1512 Poster Discussion Session; Displayed in Poster Session (Board #83), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Implementing universal genetic counseling (GC) and multigene germline testing (MGT) for pancreatic cancer (PC) patients (pts). *First Author: Matthew B. Yurgelun, Dana-Farber Cancer Institute, Boston, MA*

Background: MGT will identify cancer susceptibility gene variants in 4-10% of unselected PC pts. Such data have prompted calls for universal GC and MGT of all PC pts, but the real-world benefits and barriers to implementing such systematic testing are unknown. This study's aim was to study the implementation of universal hereditary cancer risk assessment for all PC pts seen in an academic oncology practice. **Methods:** All gastrointestinal medical oncologists at the Dana-Farber Cancer Institute (DFCI) were recommended to refer all PC pts for GC and MGT beginning 12/2016. A special referral sheet was placed in new PC pt charts to remind providers and streamline GC referral workflows. Clinical and germline data were collected on a consecutive cohort of PC pts undergoing GC and MGT from 3/1/2017-1/31/2018. **Results:** Over the 11-month study period, 443 (43.9/month) PC pts were seen for medical oncology new patient visits at DFCI, 114 (10.4/month) were referred for GC, and 92 (8.4/month) eligible PC pts underwent GC and consented to MGT and study enrollment. Among the 92 participants, median time from first DFCI appointment to GC was 44 days (IQR 23-142 days), 33 (35.9%) underwent MGT within 30 days of their first DFCI appointment, and 4 (4.3%) died within 30 days of receiving MGT results. 8/92 (8.7%; 95% CI 2.9-14.5%) were found to carry germline mutations (2 *BRCA1*, 2 *BRCA2*, 1 *ATM* and *PALB2*, 1 *NBN*, 1 *PMS2*, 1 *STK11*) on MGT. There were no significant differences in patient age, sex, race, personal cancer history, family history of PC, or family history of other cancers between mutation carriers and non-carriers. 4/8 (50%) carriers received targeted therapy (eg, PARP inhibitors) based on MGT results (2 remain on 1st line chemotherapy; 2 died without undergoing targeted therapy) and 5/8 (63%) have family members who are actively pursuing cascade testing for the identified mutation. **Conclusions:** Clinical implementation of universal GC/MGT in PC pts is potentially feasible and results in the detection of mutations that are actionable for PC pts and their at-risk family members. In spite of streamlined workflows, lack of oncologist referral is a critical barrier to the real-world efficacy of universal GC/MGT in PC. Clinical trial information: NCT03060720.

1513 Poster Discussion Session; Displayed in Poster Session (Board #84), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Long-term (7-year) outcomes of universal mismatch repair screening (uMMR) of 1156 colorectal (CRC) and endometrial cancers (EC) in an academic setting. *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: uMMR of CRC/EC for Lynch syndrome (LS) is recommended to identify the 2-3% of incident CRC/EC with germline MMR mutations in MLH1, MSH2, MSH6, and PMS2. Many US centers use a positive immunohistochemical (IHC+) tumor test to prompt further evaluation such as genetic counseling (GC). Efficacy of uMMR is established, but real-world performance is not. W/recent Blue Ribbon Panel recommendations for broad implementation, we reviewed uMMR effectiveness in an academic cancer center. **Methods:** Outcomes of all CRC/EC undergoing uMMR from 9/2011 (start of uMMR at Fox Chase Cancer Center) to 12/2017 were reviewed. uMMR results are reported in the surgical pathology report and by email to providers w/a PDF test report meant for pts. Results [IHC, MSI, BRAF, MLH1 promoter methylation, gene testing] and clinical data were extracted from a clinical genetics database and the EMR. Associations were tested by chi-square and T-test (2-sided). **Results:** From 1156 screened tumors, 278 (24.0%) had +IHC: 112 (40.3%) CRC vs 166 (59.7%) EC. Mean age was 64.7 yrs, and 117/278 (42.4%) reported family history (FamHx) of a LS cancer. After BRAF V600E testing, 91.0% (253/278) warranted GC. Only 98/253 (38.7%) pts warranting GC have to date completed GC (mean follow-up 3.0 yrs)—most common pt-reported reason for non-compliance w/GC was low interest (46.7%). Pts who completed GC were younger (47.9% vs 29.6% were $<$ 60 yrs, p = 0.004), and had stronger FamHx (55.1% vs 34.8%, p = 0.006), while differences in GC uptake by race (40.6% White vs 28.2% non-White, p = 0.14) were not significant. Of the 67 pts who sought counseling and warranted a germline test, 91.8% completed testing. LS was diagnosed in 20.9% (14/67) or 1.1% of the uMMR population—nearly 1 in 4 tested (24.6%, 17/67) were clinically suspicious for LS but test results were inconclusive. **Conclusions:** uMMR effectiveness is limited by low uptake of GC as well as high rates of non-diagnostic test results. Among uMMR IHC+ pts, low interest is the foremost patient barrier to GC uptake, and is strongly influenced by personal (age) and familial risk factors. Molecular testing alone (IHC+ screen) may be insufficient to achieve desired uMMR outcomes.

1514 Poster Discussion Session; Displayed in Poster Session (Board #85), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Identification and referral of women at risk for *BRCA* mutations. *First Author: Cecelia Bellcross, Emory University, Atlanta, GA*

Background: It is estimated that less than 10% of *BRCA*1/2 mutation carriers have been identified, despite well-documented evidence of reduced cancer morbidity and mortality with targeted screening and prevention. The United States Preventive Services Task Force endorsed the Breast Cancer Genetics Referral Screening Tool (B-RST) as one of several validated screening tools to assist clinicians in identifying women appropriate for cancer genetics referral. The purpose of this study was to implement B-RST in mammography clinics to determine the most effective means of follow-up for screen positive women. **Methods:** Women undergoing routine screening mammography at one of four Emory clinics were approached to complete the B-RST. Participants were given written information about their results and appropriate resources. Those who screened positive, indicating increased risk for a *BRCA1/2* mutation, were randomized to one of three follow-up groups: self-referral (Group 1), electronic health record (EHR) messaging (Group 2), or direct contact (Group 3). We compared genetic counseling (GC) appointment scheduling and completion rates by group. Those who did not schedule an appointment were invited to participate in an online survey. **Results:** Of 2,422 participants, 610 (25.2%) screened positive. Demographic factors did not differ between the three groups. GC appointments were scheduled by 9.2% of Group 1 participants, 19.7% of individuals in Group 2, and 12.5% of Group 3 participants (p = 0.001). Challenges to scheduling included lack of physician response to EHR messages and unsuccessful direct contact. Among those scheduled (n = 76) 69.7% completed the appointment. with no difference in completion rate between the three groups. The most common barriers to scheduling reported by survey respondents (n = 97) were lack of physician recommendation (71%), health insurance concerns (67%) and indecision about GC (66%). However, 52% reported interest in future GC contact. **Conclusions:** B-RST can be used effectively in mammography settings to identify high-risk women for cancer genetics referral. While follow-up via EHR was the most effective, additional strategies are needed to facilitate completion of the GC process in routine clinical practice. Clinical trial information: NCT02786147.

1515 Poster Discussion Session; Displayed in Poster Session (Board #86), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Inherited defects in checkpoint kinase 2 (CHEK2) to confer increased susceptibility to testicular germ cell tumors. *First Author: Saud H. Aldubayan, Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA*

Background: Although up to 50% of testicular germ cell tumor (TGCT) risk is predicted to be inherited, no Mendelian TGCT predisposition genes have been so far identified. Recently, we showed that TGCTs are uniquely enriched for somatic DNA double-strand breaks. We hypothesized that inherited DNA repair gene (DRG) defects may drive TGCT susceptibility. **Methods:** A case-control germline mutation enrichment analysis was first used to screen 56 Mendelian DRGs in 205 unselected TGCT patients and 27,173 ancestry-matched cancer-free adults. Significant findings were then validated in independent cohorts of 448 unselected and 221 familial TGCT patients and matched controls. **Results:** Of 205 unselected TGCT patients in the discovery cohort, 24 pathogenic germline DRG mutations were identified in 22 patients (10.7%; 95% CI = 6.85-15.8). Unexpectedly, one-third of detected DRG mutations involved *CHEK2,* which ranked first as the most commonly mutated gene in TGCT patients. Unselected TGCT patients from the discovery cohort were almost four times more likely to carry a germline loss-of-function (LOF) mutation in *CHEK2* compared with ancestry-matched controls (OR = 3.87; P = 0.0055). A similar degree of enrichment was also seen in an independent cohort of 448 unselected Croatian TGCT patients *vs.* 442 matched controls (OR $>$ 1.4; P = 0.03) and a cohort of 221 familial TGCTs probands *vs.* 3,090 matched controls (OR = 6.12; P = 0.0014). In addition, the low-penetrance *CHEK2* mutation (p.Ile200Thr) was found to be a Croatian founder TGCT risk mutation (OR = 4.03; P = 0.001). Finally, *CHEK2* mutation carriers developed TGCTs at an earlier age compared with mutation-negative patients (8.43 years; P = 0.017). **Conclusions:** Our multicenter case-control analysis of 874 TGCT patients and matched controls provides validated evidence for *CHEK2* as a novel moderately-penetrant TGCT susceptibility gene, making it the first clinically informative molecular biomarker that can be offered to TGCT patients and their at-risk relatives. In addition to providing an important insight into potential mechanisms driving TGCT susceptibility, our analysis also provides new avenues to explore TGCT preventive strategies in high risk patients.

1516 Poster Discussion Session; Displayed in Poster Session (Board #87), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

DNA damage repair (DDR) germline mutations in patients (Pts) with urothelial carcinoma (UC). *First Author: Maria Isabel Carlo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We previously reported on germline mutations in cancer predisposition genes in 113 pts with UC, with a 19% rate of pathogenic or likely pathogenic (P-LP) variants in DDR genes. Here we report on an expanded cohort of 176 pts and on a separate cohort of 327 anonymized specimens devoid of clinical annotation. **Methods:** Pts with UC malignancies were prospectively enrolled to a matched tumor-germline DNA sequencing protocol from 3/2013 to 9/2017; starting in 2014, patients could opt in to receive germline results. Germline analysis was done with an institutional, CLIA-certified next generation sequencing (NGS) platform (IMPACT) and analyzed for germline mutations. This analysis includes pts seen in medical oncology clinics who consented to receive germline results (Cohort 1), and additional pts seen in urology and medical oncology clinics who had anonymized germline testing (Cohort 2) with an extended DDR panel. **Results:** Cohort 1 consisted of 176 pts, 90% with muscle invasive or metastatic disease, median age 63 (31-87), 76% male. Primary sites were bladder (B) (70%), upper tract (UT) (28%), or unknown (2%). 8% had early onset (≤45 yrs at diagnosis), 9% had a family history of UC, 19% had documented non-UC cancers. 30 P-LP DDR gene mutations were identified in 28 patients. The most frequent mutations are shown in the Table. P-LP mutations were present in 29% of pts with UT and 13% of pts with B primaries. Of pts with DDR germline mutations, 29% did not have additional somatic DDR mutations. Cohort 2 consisted of 327 anonymized pts. 32 P-LP DDR germline mutations, including in *ERCC2* and *ERCC3*, were identified in 30 pts. Including both cohorts, 77% of mutations were of high or moderate penetrance. **Conclusions:** Germline predisposition genes are common in UC pts and may be greater in higher stage disease, further investigation into mutation frequency by stage is warranted. Most mutations are highly penetrant and have profound implications for both pts and family members. Clinical trial information: NCT01775072.

Gene	Mutations Cohort 1 (%) Total n = 176	Mutations Cohort 2 (%) Total n = 327
Total DDR	30 (17)	32 (9.8)
MSH2	5 (2.8)	4 (1.2)
BRCA1	5 (2.8)	3 (0.9)
CHEK2	4 (2.2)	3 (0.9)
BRCA2	3 (1.7)	5 (1.5)
MSH6	2 (1.1)	0
MLH1	2 (1.1)	0
MUTYH	2 (1.1)	3 (0.9)
ERCC2	*	4 (1.2)
ERCC3	*	4 (1.2)

*Not analyzed

1517 Poster Discussion Session; Displayed in Poster Session (Board #88), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Clinical factors associated with urinary tract cancers (UTCs) among Lynch syndrome (LS) patients (Pts). *First Author: Jonathan W. Wischhusen, Beth Israel Deaconess Medical Center, Boston, MA*

Background: LS is the one of the most common inherited causes of cancer and predisposes to a wide variety of cancers. UTCs (kidney, renal pelvis, ureter, and bladder cancer) are collectively the second- and fourth-most common LS-associated cancers in male and female LS pts, respectively. This study's aim was to identify clinical factors associated with UTC among LS pts. **Methods:** The study population was a cohort of 52758 consecutively ascertained patients undergoing germline LS testing from 6/2006-7/2013 at a commercial laboratory. Clinical data, including age at genetic testing, personal history (PHx) of cancer, and family history of cancer in first- and second-degree relatives (FDRs and SDRs, respectively) were obtained from test request forms completed by the ordering provider. Multivariable logistic regression was performed to identify clinical factors associated with PHx of UTC among LS carriers. **Results:** Data from 51086 pts was analyzed after excluding 1672 pts without clinical data (N = 1664) or > 1 LS mutation (N = 8). Of these, 3828 carried pathogenic LS mutations (1346 *MLH1*, 1639 *MSH2*, 670 *MSH6*, 145 *PMS2*, and 28 *EPCAM*). 158/3828 (4.1%; 95% CI 3.5-4.8%) LS pts had a PHx of UTC (49 kidney; 62 ureter/renal pelvis; 67 bladder; 21 multiple UTCs) and 369 (9.6%; 95% CI 8.7-10.6%) had any family history of UTC. Compared to non-carriers, LS pts were significantly more likely to have a PHx of any UTC (4.1 vs 1.2%; $P < 0.0001$), kidney cancer (1.3% vs 0.7%; $P = 0.0003$), ureter/renal pelvis cancer (1.6% vs 0.1%; $P < 0.0001$), bladder cancer (1.8% vs 0.4%; $P < 0.0001$), and any family history of UTC (9.6% vs 6.5%; $P < 0.0001$). By multivariable logistic regression, PHx of UTC among LS pts was significantly associated with male sex (OR 2.04; 95% CI 1.73-2.41), age at genetic testing (OR 1.97 per 10 years; 95% CI 1.86-2.09), *MSH2* mutation carriage (OR 4.03; 95% CI 3.29-4.94; ref: non-*MSH2* LS mutations), and family history of UTC (OR 2.07 for each FDR/SDR with UTC; 95% CI 1.80-2.40). **Conclusions:** Increasing number of FDR/SDR with UTC, male sex, age, and *MSH2* mutations are each independently associated with PHx of UTC among LS pts. LS pts with these clinical features should be considered for UTC screening/prevention strategies.

1518 Poster Discussion Session; Displayed in Poster Session (Board #89), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Adapted physical activity and recommendations for second cancers prevention for adolescents and young adults with cancer. *First Author: Julien Carretier, Centre Léon Bérard, Lyon, France*

Background: While long term survival is about 80%, adolescents and young adults (15-25 years old) with cancer (AYAC) are at increased risk of second primary cancer (SPC). Risk depends on first cancer type, treatment and prevalence of risk factors (smoking, overweight, sedentary lifestyle, environmental exposures...). AYAC have reduced physical activity (PA) and decreased motivation for PA. The objective of this study is to implement a supervised program based on adapted PA (APA) and cancer prevention for AYAC. **Methods:** AYAC attended supervised APA sessions during the treatment period (4-6 months). Physical activity (IPAQ), quality of life (QLQ-C30) and physical functioning (six-min walk test) were assessed at baseline (T1) and at the end of treatment (T2). They then participated in individual information meetings on SPC risk prevention. At 1 year (T3), they were questioned by phone on pursuit of physical activity and adoption of cancer prevention behaviors. **Results:** 63 AYAC (39 boys, 24 girls; median age = 19 years) completed T1 and T2; 37 AYAC completed T3. On average, they participated in 4 supervised sessions at the hospital and 16 unsupervised sessions at home during 3.5 months [min 2-max 6]. Preliminary results indicate an increase in the PA level between T1 and T2 (median scores of 360 and 1059 MET-min/week, respectively; $P < .0001$) and in the six-min walk test from T1 to T2 (median distances of 391 and 464 m, respectively; $P < .0001$). Median sedentary time decreased from 53.3 h/week at T1 to 37.5 h/week at T2 ($P < .01$). Global QOL score significantly increased between T1 and T2 ($P < .001$). **Conclusions:** This APA program responds to AYAC's needs for support and information regarding PA and SPC prevention and shows increased PA, physical functioning and QOL for AYAC undergoing cancer treatment. Results will be validated in a multicenter study. Clinical trial information: NCT03336905.

1519 Poster Discussion Session; Displayed in Poster Session (Board #90), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Nutrition assessment among men undergoing genetic counseling for inherited prostate cancer: A teachable moment. *First Author: Veda N. Giri, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: Genetic counseling (GC) for men with or at-risk for prostate cancer (PCA) is growing with advancements in genetic testing (GT). GC provides a unique opportunity to promote a healthy lifestyle and is understudied in men. We conducted a targeted dietary analysis of men with or at-risk for PCA who have undergone GC and GT in the Genetic Evaluation of Men (GEM) study at two academic centers. **Methods:** GEM participants completed a structured lifestyle questionnaire (QA) which included dietary behaviors. QA included frequency of consuming six different types of foods (rich in vitamins C, A and D, cruciferous vegetables, rich in lycopene, smoked and/or salted meats) and daily servings for specific food groups (red meat, seafood, chicken, legumes/other protein sources, vegetables, fruit, grains, milk products, foods high in saturated fat) and alcohol. Diet intake was compared to USDA's dietary recommendations for cancer survivorship. Distributions of dietary consumption were assessed by PCA status, PCA aggressiveness (Gleason > 7, T3, or metastatic disease), family history (FH), and body mass index (BMI) with Chi-Square contingency analyses and adjusted residuals (adj resid). Alpha levels were set *a priori* at $p < .05$. **Results:** Self-reported dietary data among men with PCA (n = 239) and at-risk for PCA (n = 81) who underwent GC was included. Overall, 84% were overweight/obese per CDC guidelines. Consumption of Vitamin C 1-2 times per week was significantly lower among men with aggressive PCA (adj resid = -1.9) vs. less aggressive PCA (adj resid = 1.9). Men with aggressive PCA also reported eating more red meat vs less aggressive PCA ($p = 0.011$). A higher percentage of men with aggressive PCA and higher weight did not meet the recommended guideline for vegetables ($p = 0.047$) and red meat ($p = 0.015$) than expected per contingency analyses. **Conclusions:** In this sample, specific dietary patterns were associated with aggressive PCA. A high proportion of men receiving GC for inherited PCA were overweight and/or obese, affording a teachable moment for lifestyle intervention. Key focus areas to develop diet intervention include consumption of less red meat and more vegetables among men at-risk or in survivorship.

1520 Poster Discussion Session; Displayed in Poster Session (Board #91), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Risk of second primary HPV-associated cancers after index HPV-associated cancers. *First Author: Ryan Suk, University of Florida, Gainesville, FL*

Background: For the HPV-associated index cancer survivors, persistent HPV infection may remain a risk factor for preventable HPV-associated second primary cancer (HPV-SPC). However, the risk of HPV-SPCs among HPV-associated index cancer patients has not been well documented. **Methods:** Longitudinal data from 9 cancer registries of the Surveillance, Epidemiology, and End Results (SEER) database were used to identify cases of HPV-associated cancers diagnosed from 1973 to 2014. The HPV-SPC risk was quantified using standard incidence ratios (SIRs) and excess absolute risk (EAR) per 10,000 person-years at risk (PYR). **Results:** The SIRs for second primary HPV-related cancers after index HPV-related cancers among women and men were 3.3 (95% CI 3.2 to 3.4) and 15.8 (95% CI, 15.0 to 16.7), respectively; the EAR was 6.0 and 51.4 for women and men, respectively. When the same site second primary cancers were excluded, the risk remain significant both among women (SIR = 2.7) and men (SIR = 2.3). The risk of HPV-SPC was highest for oropharyngeal cancer both among women (SIR = 20.6; EAR = 83.8) and men (SIR = 18.8; EAR = 64.3), and lowest for cervical (SIR = 2.0; EAR = 2.4) and penile (SIR = 7.0; EAR = 20.7) cancer. **Conclusions:** The risk of developing HPV-SPC among HPV-related cancer survivors is significant, implying that HPV might be a cause for developing HPV-SPC. Our findings have the potential to inform surveillance recommendations among HPV-related cancer survivors.

SIRs for HPV-SPCs after index HPV-related cancers.

	Women				Men			
	All HPV-SPC		All HPV-SPC (same site excluded)		All HPV-SPC		All HPV-SPC (same site excluded)	
Index HPV Cancers	SIR (95% CI)	EAR	SIR (95% CI)	EAR	SIR (95% CI)	EAR	SIR (95% CI)	EAR
All HPV-related cancers	3.3 (3.2-3.4)	6.0	2.7 (2.5-2.8)	2.3	15.8 (15.0-16.7)	51.4	2.3 (1.8-2.9)	1.6
Cervical	2.0 (1.9-2.1)	2.4	2.5 (2.3-2.7)	1.8	NA	NA	NA	NA
Vaginal	6.6 (5.2-8.3)	20.5	3.9 (2.8-5.3)	10.0	NA	NA	NA	NA
Vulvar	9.5 (8.7-10.3)	28.0	4.1 (3.6-4.7)	8.5	NA	NA	NA	NA
Oropharyngeal	20.6 (19.1-22.2)	83.8	1.7 (1.2-2.3)	1.9	18.8 (17.7-19.9)	64.3	1.7 (0.9-2.7)	0.4
Anal	6.1 (5.0-7.4)	20.8	3.5 (2.6-4.6)	9.0	10.4 (8.5-12.5)	26.6	2.1 (1.3-3.3)	2.9
Penile	NA	NA	NA	NA	7.0 (5.7-8.7)	20.7	2.9 (2.0-4.0)	5.8

1521 Poster Discussion Session; Displayed in Poster Session (Board #92), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Dietary inflammatory index and breast cancer risk by menopausal status and histological subtype. *First Author: Adela Castello, National Center for Epidemiology, Instituto de Salud Carlos III, Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP). Instituto de Salud Carlos III.Faculty of Medicine, University of Alcalá, Madrid, Spain*

Background: Inflammation plays an important role in cancer development. The Dietary Inflammatory index (DII) reflects the inflammatory potential of diet. We examined the association between the DII and breast cancer (BC) risk by menopausal status and histological subtype. **Methods:** Epi-GEICAM is a nation-wide case-control study that collected epidemiologic information, including diet, of 973 BC cases from 23 hospitals individually matched to 973 controls by age and residence. Cases were sub classified by tumor subtype: 1) Estrogen Receptor(ER)+ or Progesterone Receptor(PR)+ with Human Epidermal Growth Factor Receptor 2(HER2)-; 2) HER2+; and 3) ER-,PR-&HER2-. The association of the calorie density adjusted DII score (0-10) with BC risk was evaluated using conditional logistic regression models, adjusted by alcohol, body mass index, age at menarche, physical activity, smoking habit, education, history of breast alterations, family history of BC, age at first delivery and menopausal status. Heterogeneity of the effects by menopausal status was tested including an interaction term between this variable and the DII. Multinomial logistic regression models -adjusted for age, hospital, and the same set of potential confounders described above- were used to evaluate the association of the DII score with each of the intrinsic BC subtypes. In all cases associations were analyzed both, as categorical (grouping the DII into quartiles of its distribution among controls) and continuous (1-point increase) variables. **Results:** Women whose diet was more pro-inflammatory showed higher BC risk ($OR_{4th\ quartile(Q4)vs\ 1st\ quartile(Q1)}$= 1.39; 95%CI = 1.05-1.84; p-trend = 0.023). This effect seemed to be confined to premenopausal women (OR_{Q4vsQ1}= 1.52; 95%CI = 1.05-2.21; p-trend = 0.030) and it was stronger for HER2+ (OR_{Q4vsQ1}= 1.46; 95%CI = 0.92-2.32; p-trend = 0.050) and ER-,PR-&HER2- (OR_{Q4vsQ1}= 2.72; 95%CI = 1.45-5.10; p-trend = 0.006) tumors than for ER+/PR+&HER2- (OR_{Q4vsQ1}= 1.24; 95% CI = 0.92-1.67; p-trend = 0.145) tumors. **Conclusions:** A diet that promotes inflammation might be associated with higher BC risk, especially among premenopausal women and for the most aggressive tumors (HER2+ and ER-, PR-&HER2-).

1522 Poster Discussion Session; Displayed in Poster Session (Board #93), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Value of EGD for gastric cancer surveillance in patients with hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome (LS). *First Author: Swetlana Ladigan, Department of Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany*

Background: Gastric cancer (GC) is the second most common non-gynecologic malignancy in patients with LS. Due to an absence of prospective randomized data, the value of esophago-gastro-duodenoscopy (EGD) for GC surveillance in LS patients remains a controversial issue. According to German guidelines regular EGDs beginning at the age of 35 are recommended for LS patients. The focus of this study was to evaluate the effectiveness of EGD as an instrument for early GC detection. **Methods:** Data of HNPCC and LS patients diagnosed with GC was retrieved from the German Consortium for Familial Intestinal Cancer Registry. Individuals from 3 groups were included: pathogenic germline mismatch repair gene mutation carriers (n = 47), untested patients from families with known germline mutations (putative carriers; n = 8) and individuals fulfilling at least the revised Bethesda criteria without a mutation but with microsatellite instability (MSI group; n = 47). Statistics were calculated using Fisher's exact test. **Results:** Overall a total number of 107 GCs were observed in 102 patients (male/female: 60/42) with 71 (69%) having a negative family history of GC. Among germline mutation carriers, *MLH1* (n = 21) and *MSH2* (n = 24) mutations were the most prevalent; *EPCAM* and *MSH6* mutations were rare with only one case each. The median age at diagnosis was 54.4 years (28.9-81.4) for the whole cohort, with mutation carriers being diagnosed at a younger age (51.8 years) than individuals from the MSI group (63.1 years). Of all GC patients, two were diagnosed at an age younger than 35 years and 7 patients were younger than 40 years. The GCs in patients undergoing surveillance were diagnosed significantly more often with an early stage disease (UICC I) than GCs detected through symptoms (77.8% vs. 23.5%; p = 0.0046). **Conclusions:** To our knowledge this is the largest study investigating the effectiveness of EGD surveillance for early GC detection in HNPCC or LS patients. This study indicates a benefit for patients undergoing regular EGDs and supports the recommendation of regular gastroscopic surveillance for HNPCC and LS syndrome patients beginning not later than at the age of 35.

1523 Poster Discussion Session; Displayed in Poster Session (Board #94), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

"What if I keep my breasts?" Extended follow-up of unaffected *BRCA* mutation carriers diagnosed with breast cancer (BC) in the Toronto magnetic resonance imaging (MRI) screening study. *First Author: Ellen Warner, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

Background: The addition of MRI to mammography for screening *BRCA* mutation carriers detects significantly earlier stage BC but, with median follow-up of < 10 years in all reports to date, the long-term prognosis of these cancers is uncertain. Moreover, while the short-term risk of ipsilateral recurrence for carriers who opt for breast conservation (BCT) are reported to be similar to that of non-carriers, the risk of late new breast primaries may be substantially higher. We report the long-term ipsilateral, contralateral, and distant recurrence as well as survival results for the previously unaffected women with BC diagnosed in the Toronto MRI screening study. **Methods:** From 07/1997 to 06/2009, 380 *BRCA* mutation carriers with no history of BC or ovarian cancer completed 1 to 9 rounds of annual screening with MRI and mammography; 41 cancers (30 invasive) were detected (38 by MRI, 5 by mammography) in 40 women (20 *BRCA1, 20 BRCA2*), median age at diagnosis 48 (32 to 68), followed annually for recurrence and survival by mailed questionnaire. 10-year results were calculated using the Kaplan-Meier method. **Results:** As of 01/2018, median follow up was 13.5 (8 to 19) years with none lost to follow-up. Of the 27/40 (68%) who initially had BCT, 6 (22%) had an ipsilateral recurrence/new primary at 3, 3, 6, 15, 16 and 19 years, with 2 of the latter 3 opting for repeat lumpectomy and re-irradiation. Of the 34 who did not have bilateral mastectomy initially, only 1 developed a metachronous contralateral cancer at 1 year. Of the 40 women, 34 (85%) are alive with no evidence of disease, and 6 have died: 2 (5%) of peritoneal cancer, 1 of ovarian cancer, 1 of suicide, and only 2 (5%) of ER+ BC, with distant recurrences 6 and 7 years after diagnosis. 10-year BC-specific survival was 94.6% for all 40 patients and 92.6% for those with invasive disease. **Conclusions:** MRI-detected BC in *BRCA* mutation carriers has a 10-year BC-specific distant recurrence-free survival rate of 95%. Distant recurrences occur relatively early, likely due to the known faster growth rate of these cancers. MRI-based breast screening has proven to be a very reasonable alternative to risk-reducing mastectomy.

1524 Poster Session (Board #95), Sat, 1:15 PM-4:45 PM

Expanding *BRCA1/2* testing criteria to include other confirmed breast and ovarian cancer susceptibility genes. *First Author: Fergus Couch, Mayo Clinic, Department of Laboratory Medicine and Pathology, Rochester, MN*

Background: The National Comprehensive Cancer Network (NCCN) has expanded its breast and ovarian cancer (BC and OC) genetic testing and management recommendations to address the broader spectrum of cancer predisposition genes. However, management recommendations are pending for some candidate BC genes (e.g. *BARD1*, *RAD51D*) and OC genes (e.g. *ATM*, *NBN*) due to insufficient evidence of increased cancer risk, and indications for multi-gene panel testing (MGPT) remain vague overall. We aimed to further characterize BC and OC risks for 21 candidate susceptibility genes and explore the potential utility of *BRCA1/2* testing criteria as an indication for MGPT. **Methods:** Gene-specific pathogenic variant (PV) frequencies among Caucasian BC and OC patients (unadjusted for other personal/family cancer history) ascertained from a cohort of > 175,000 patients referred for MGPT were compared to non-Finnish European reference controls from the genome aggregate database (gnomAD). Clinical histories of BC and OC patients were also reviewed to assess whether NCCN *BRCA1/2* testing criteria were met (version 2.2017). **Results:** We confirmed the association of 15 genes with increased risk (> 2.0-fold) of BC (*ATM*, *BARD1*, *BRCA1/2*, *CDH1*, *CDKN2A*, *CHEK2 (excluding p.I157T)*, *MLH1*, *MSH2*, *MSH6*, *NF1*, *PALB2*, *PTEN*, *RAD51D*, *TP53*). The pooled frequency of PVs in these genes was 9.2% among BC patients of all ethnicities (3.5% in *BRCA1/2* and 5.7% in other genes) and 8.6% among BC patients meeting *BRCA1/2* testing criteria (3.4% in *BRCA1/2* and 5.2% in other genes). Eleven genes were associated with increased risk of OC (> 2.0-fold, *ATM*, *BRCA1/2*, *BRIP1*, *MSH2*, *MSH6*, *NBN*, *PMS2*, *RAD51C*, *RAD51D*, *TP53)*. PVs in these genes were detected among 13.0% of OC patients of all ethnicities (8.0% for *BRCA1/2* and 5.0% for other genes combined). Therefore, inclusion of additional risk genes increases detection rate for BC and OC patients meeting *BRCA1/2* testing criteria by 152.9% and 62.5%, respectively. **Conclusions:** These results further characterize gene-specific BC and OC risks, which can be used to refine management recommendations for at-risk patients. Current testing criteria fail to capture a substantial proportion of women with increased risk of BC and OC.

1526 Poster Session (Board #97), Sat, 1:15 PM-4:45 PM

Towards personalised risk assessment and clinical management: A worldwide study of age-, sex-, geographic region-, gene- and cancer-specific risks for Lynch syndrome. *First Author: Aung K. Win, The University of Melbourne, Parkville, Victoria, Australia*

Background: Lynch syndrome is a cancer predisposition caused by inherited mutations in mismatch repair genes *MLH1, MSH2, MSH6* and *PMS2,* or *EPCAM*. Accurate cancer risk estimates are required for mutation carriers and their family members to develop appropriate genetic counselling guidelines and targeted screening and clinical management. Cancer risks for Lynch syndrome may differ not only by age, sex and the gene mutated but also by the genetic variant and geographic region of the carrier. **Methods:** We analysed pedigree data (age, sex, cancer histories and mutation status of family members) of Lynch syndrome families that were submitted by researchers and clinicians from 23 countries to the International Mismatch Repair Consortium (IMRC) (http://www.sphinx.org.au/imrc). For each cancer, we estimated age-specific cumulative risk (penetrance) and hazard ratios for carriers compared with the general population. We estimated penetrance by: cancer site, sex, the gene mutated, type of mutation, and geographic region. **Results:** IMRC has already received pedigree data from 6651 families with a mismatch repair gene mutation (2214 *MLH1,* 2717 *MSH2,* 1118 *MSH6*, 558 *PMS2,* 44 *EPCAM*) throughout the world (2482 in North America, 101 in South America, 3307 in Europe, 431 in Asia, 330 in Australasia). Preliminary analyses suggest that the risk of colorectal cancer to age 70 is highest for both male and female carriers in Australasia and North America and lowest for carriers in South America and Asia. **Conclusions:** Preliminary results from this world's largest study on Lynch syndrome penetrance suggest that cancer risks for people with Lynch syndrome differ by geographic region, which is consistent with existence of environmental modifiers for the disease and might justify region-specific screening guidelines.

Gene	Region	Hazard ratio	Risk to age 70 males	Risk to age 70 females
MLH1	Europe	19 (14–26)	50%	32%
	North America	32 (26–38)	61%	48%
	Australasia	32 (22–46)	68%	55%
	South America	6 (1.5–22)	12%	10%
	Asia	7 (4.5–15)	20%	14%
MSH2	Europe	14 (11–16)	39%	24%
	North America	33 (28–40)	61%	50%
	Australasia	36 (24–54)	73%	59%
	South America	70 (10–490)	82%	75%
	Asia	8 (4.8–17)	21%	15%

1527 Poster Session (Board #98), Sat, 1:15 PM-4:45 PM

Evaluation of whole body MRI for early detection of cancer in TP53 mutation carriers: Final results of the LIFSCREEN study. *First Author: Olivier Caron, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Li Fraumeni syndrome (LFS) is a rare cancer predisposition caused by TP53 germline mutation associated with a broad tumor spectrum making surveillance very complex. Whole body MRI (WBMRI) is an attractive strategy. The LIFSCREEN nation-wide trial was designed to evaluate the impact of adding WBMRI as a screening tool on the overall survival (OS) of LFS patients. **Methods:** Participants (pts) were TP53 mutation carriers, > 5 and < 71 y, with/without cancer personal history. Pt were randomized in standard surveillance arm ("A": clinical exam, brain MRI, abdomino-pelvic US, CBC, and breast MRI/US and breast US for women over 20), or in "B" arm (A + WB diffusion MRI). Each pt repeated annually the process for at least 3 years. Acceptability and psychological impact were evaluated throughout the study. **Results:** 105 pts (mean age 33y [5-67]) were randomized in one of the 19 French centers. In 318 screening rounds, 24 pts presented 31 new primary cancers (NPC): 20 in A arm and 11 in B arm. 12 NPC were diagnosed at the first round. Cancer-free survival (NPC and relapses) was similar at 3 years in both arm (p = 0.23). 27 Biopsies were carried out in A arm and 20 in B arm. 157 WBMRI were performed, with a sensitivity and specificity of 0,8 and 0,89, respectively (10% false positive). Their centralized review showed a 31% discordance rate (44/141). The 3 years OS was 90% [81-95], with no difference between the 2 arms (p = 0.58). The 3- years OS with NPC was 54.8% [32-75]. 10 pts voluntarily left the study. Psychological impact was similar in both arms, with low screening-related distress. **Conclusions:** This first randomized study performed on one of the largest TP53 carrier series did not show WBMRI efficiency on OS. Nevertheless, it displayed correct sensitivity and specificity, with few biopsy generation. Long-term follow-up was acceptable and feasible in each participating center. Despite its tricky interpretation, WBMRI was the only modality to detect lung cancer, whose incidence was surprisingly high. TP53 mutation carrier surveillance might be completed with WBMRI, in a multimodality setting. The very high short-term mortality in pt with new cancer makes prevention and treatments improvement mandatory. Clinical trial information: NCT01464086.

1529 Poster Session (Board #100), Sat, 1:15 PM-4:45 PM

Differences between screen-detected and interval breast cancers among BRCA mutation carriers. *First Author: Melissa Louise Pilewskie, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: BRCA mutation carriers have an elevated lifetime and interval breast cancer risk. We sought to compare BRCA mutation carriers with screen-detected versus clinically detected, interval breast cancers. **Methods:** Women with a known BRCA mutation prior to a breast cancer diagnosis were identified. Clinical and pathologic factors, and imaging within 18 months of diagnosis were compared among screen-detected vs clinically detected/interval cancers. Clinically detected tumors were those detected by physical exam regardless of screening history, whereas interval cancers were those detected by physical exam among women undergoing regular screening. **Results:** Of 115 breast cancers, 93 were screen and 22 clinically detected, of which 11 were interval cancers among regular screeners. Women with clinically detected/interval cancers were younger, had lower BMIs, and were more likely to be Black than those with screen-detected cancers ($p < 0.05$). Clinically detected/interval cancers were all invasive, were larger, more likely to be node positive and to have lymphovascular invasion, and were more likely to require axillary lymph node dissection and chemotherapy ($p < 0.05$). No significant differences were seen by BRCA mutation, mammographic density, MRI background parenchymal enhancement, tumor grade, or receptor status between cohorts. Women screened with both mammogram and MRI had significantly lower rates of clinically detected/interval cancer rates compared to women screened with only mammogram or MRI alone ($p < 0.05$)(Table). **Conclusions:** Clinically detected/interval breast cancers among BRCA mutation carriers have worse clinicopathologic features than screen-detected tumors, and require more aggressive medical and surgical therapy. Imaging with mammogram and MRI is associated with lower interval cancer development and should be utilized among this high-risk population.

Imaging	Screen-Detected	Clinically Detected	P value	Screen-Detected	Interval Cancers	P value
	All Women			Regular Screeners		
Alternating q6 Month Mammo/MRI	34 (89%)	4 (11%)	0.003	32 (91%)	3 (9%)	0.014
Synchronous Mammo/MRI	38 (90%)	4 (10%)		25 (93%)	2 (7%)	
Mammo Only	18 (58%)	13 (42%)		7 (58%)	5 (42%)	
MRI Only	3 (75%)	1 (25%)		1 (50%)	1 (50%)	

1530 Poster Session (Board #101), Sat, 1:15 PM-4:45 PM

Effect of breastfeeding on the risk of breast cancer in Li-Fraumeni syndrome. *First Author: Payal Khincha, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Li-Fraumeni syndrome (LFS) is an autosomal dominant inherited cancer predisposition syndrome associated with germline pathogenic variants in *TP53*. It is characterized by early-onset cancer and a high lifetime risk for multiple cancers. Although women with LFS are at very high risk of pre-menopausal breast cancer some women will perhaps never develop the disease. This may be due to non-genetic factors that may modify the risk. **Methods:** The aim of this retrospective cohort study was to evaluate the impact of female reproductive factors such as age at menarche, parity, breastfeeding (BF) and use of oral hormonal contraceptives (OCP) on the risk of breast cancer (BC) in LFS patients. **Results:** We enrolled 154 *TP53* mutation-positive women from the NCI's LFS protocol, 86 of whom had at least one breast cancer. Median age at first breast cancer diagnosis was 32 years (range 20-54 years), 32 women had a second BC. Sixty percent of first breast cancers were ER/PR+; and 57% were HER2/neu+. Our data showed that breastfeeding (BF) reduced the risk of breast cancer in LFS, most notably reduced in patients with over 6 months of BF (Odds Ratio (OR) 0.36, $p = 0.04$, OR at 12 months of BF 0.32, $p = 0.02$). The association was strongest in ER+ BC *versus* BC-free women, but was not significant when comparing odds of developing ER+ to ER- BC. Controlling for age and parity, women with BF $>$ 12 months had a lower risk of BC *versus* BF $<$ 12 months ($p = 0.02$). Neither parity nor OCP independently altered BC risk significantly, a finding limited by limited sample size of the comparator group of OCP non-user LFS women. **Conclusions:** Our data show that while BF for any duration reduces risk of BC, the risk is significantly reduced with BF for at least 6 months, a protective effect similar to previous studies of BF and BC risk in the general population and *BRCA1* cohorts. Neither parity nor OCP independently altered BC risk significantly. This is the first study to evaluate BC reproductive risk modifiers in LFS patients. Larger, prospective case-control studies are needed to validate these findings. If confirmed, women with LFS would warrant education regarding BF's protective effect to inform management decisions.

1531 Poster Session (Board #102), Sat, 1:15 PM-4:45 PM

Interest in and outcomes with web-based education for return of genetic research results for inherited susceptibility to breast cancer. *First Author: Angela R. Bradbury, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: How frequently research participants are interested in receiving genetic individual research results (IRR) and the best method for returning IRR remains unknown. **Methods:** Woman at three centers with a personal or family history of cancer, who provided a bio-sample for research, were offered the opportunity to receive IRR for 25 cancer susceptibility genes. Participants could complete pre-disclosure education by a self-directed web-education (WebED) or by telephone with a genetic counselor (GC). All participants received IRR by phone with a GC. Participants completed surveys at baseline, after pre-disclosure education and disclosure. We used t-tests and multiple linear regressions of change scores. **Results:** 1277 participants were contacted. Mean age was 61.4 years, 68% were white, 68% had a history of cancer and 56% had a college education. 393 (31%) enrolled to receive IRR, 120 (9%) actively declined, and 764 (60%) have not responded to multiple contacts. Age, education and race/ethnicity were not significantly associated with interest in IRR. To date, 211 (81%) completed pre-disclosure education by WebEd and 50 (19%) by GC. Younger age was associated with completing WebEd v GC. 250 (95%) received IRR; 12 (4%) declined. 12 (5%) received a positive result and 56 (22%) a VUS. Knowledge increased significantly after pre-disclosure education and disclosure of IRR, and was not associated with WebEd v. GC pre-disclosure. Depression, anxiety, cancer specific distress and perceived utility declined significantly after pre-disclosure education and disclosure. Change in knowledge, anxiety, cancer-specific distress and uncertainty did not differ from baseline to post-disclosure between WebEd v. GC education. After IRR, having WebEd and receiving a positive result were associated with greater reduction in depression as compared to GC pre-disclosure. **Conclusions:** Among participants interested in receiving genetic IRR, there was high interest in a web-based pre-disclosure education. Web-education was not associated with negative outcomes after receipt of IRR with a genetic counselor, suggesting a potential alternative resource reducing model for return of IRR.

1532 Poster Session (Board #103), Sat, 1:15 PM-4:45 PM

Development of HOPE-Genomics: An IT platform for patient-directed cancer genome sequencing education and return of results. *First Author: Ilana Solomon, City of Hope, Duarte, CA*

Background: Profiling of somatic/germline tissue has the potential to improve outcomes for patients with cancer. However, the realization of precision medicine is hindered by patients' limited understanding of genetics and their own tumor/germline results. Innovations to improve patient education and care engagement are urgently needed. **Methods:** We recruited patients at a comprehensive cancer center to help develop a web-based, patient-directed cancer genomic sequencing education and reporting tool: HOPE-Genomics. We obtained clinical data through patient surveys and chart reviews. We obtained feedback on the tool from patients, family members, and clinicians via focus groups. **Results:** 40 patients (mean age 40, 92% White, 8% Asian, 15% Hispanic, 15% $\leq$ high school) completed the survey; 93% had advanced disease and 30% had lung, 25% breast, 10% ovarian, 18% colon, and 17% other cancers. Although 98% had tumor and/or germline profiling on chart review, 33% of patients were unaware this tested occurred. All breast and gastric cancer patients knew they had *HER2* testing whereas only 20% of CRC patients knew they had *KRAS* testing. The majority of participants wanted to see, or their patients to see, "patient-friendly" reports. When presented with HOPE-Genomics, themes identified in patient/family focus groups included the opinion that the tool could help patients prepare questions, a desire for all types of information (e.g., prognostic, uncertain), and favorable attitudes about including genetic counseling information. Themes identified in clinician focus groups included the opinion that the tool could help patients share information with family and decrease patient confusion. Clinicians had mixed feelings about tool implementation (e.g., provider control vs. time-dependent release of report, concern over disclosure of some types of information). **Conclusions:** Many patients do not recall having molecular/genomic testing but are interested in learning their results. Early development of a web-based education and reporting tool appears to be acceptable to patients, family members and clinicians. We plan to refine the tool and develop processes for optimal clinical integration.

1533 Poster Session (Board #104), Sat, 1:15 PM-4:45 PM

Genomic profiling of tumors from patients with germline *BRCA* mutations. *First Author: Anne-Vibeke Laenkholm, Department of Surgical Pathology, Zealand University Hospital, Slagelse, Denmark*

Background: Gene expression profiling assays are not commonly used for therapy selection for breast cancer patients with germline *BRCA* mutations but a complete molecular characterization could lead to identification of novel subgroups where therapy modification may be considered. We hypothesized that the PAM50 intrinsic subtypes and ROR score in combination with characterization of the immune response could provide biological insights to guide the next generation of treatment strategies for *BRCA*-mutated tumors. **Methods:** The Danish Breast Cancer Group database was used to identify a cohort of 584 *BRCA*-mutated breast cancer patients diagnosed between 1977 and 2011. Tumor RNA from archived FFPE tissue samples was analyzed on the NanoString platform using a 770-gene Breast Cancer Panel and the PAM50 intrinsic subtypes were determined using the Prosigna gene signature algorithm. The immune response was evaluated with the Tumor Inflammation Signature (TIS) score. **Results:** Of the 532 samples assessable for PAM50 subtype, 54% were Basal-like, 7% Her2-Enriched, 23% Luminal B, and 16% Luminal A, with significant heterogeneity between *BRCA1* and *BRCA2* tumors. *BRCA1* tumors were primarily Basal-like while *BRCA2* tumors were enriched for Luminal subtypes. There was a wide range of Prosigna ROR scores with 15% of the Luminal tumors identified as low-risk (ROR$\leq$40). Similarly, there was a broad spectrum of immune response with *BRCA1* tumors demonstrating a higher average TIS score ($P < 0.001$). However, the heterogeneity of TIS by *BRCA* mutant was explained by intrinsic subtype with basal-like tumors exhibiting higher inflammation. **Conclusions:** To our knowledge, this is the largest study of a prognostic signature on *BRCA*-mutated tumors presented to-date. We observed heterogeneity in the intrinsic subtypes and a wide range of inflammation response with differences between *BRCA1* and *BRCA2* tumors being explained by intrinsic subtype. Additional analyses are ongoing including evaluation of signatures associated with DNA Damage, immune profile, and HRD as well as association of expression signatures with outcomes.

	Intrinsic Subtypes: N (%)			
	Basal-like	**Her2-Enriched**	**Luminal B**	**Luminal A**
BRCA1	241 (73)	19 (6)	38 (12)	30 (9)
BRCA2	48 (24)	18 (9)	84 (41)	54 (26)

1535 Poster Session (Board #106), Sat, 1:15 PM-4:45 PM

Risk of pediatric malignancy in families known to carry *BRCA1/2* mutations. *First Author: Kevin Thomas Nead, University of Pennsylvania Perelman School of Medicine Hospital, Philadelphia, PA*

Background: Inherited mutations in cancer predisposition genes typically associated with adult-onset cancers, including *BRCA1/2*, have been found in children with cancer. However, it is unknown whether such mutations are causative. Our objective is to determine whether there is an increased risk of pediatric malignancy in families known to carry *BRCA1/2* mutations. **Methods:** We utilized the Cancer Risk Evaluation Program (CREP), a registry of high-risk breast and ovarian cancer families undergoing *BRCA1/2* testing. We compared the proportion of pediatric malignancies (age $\leq$ 18 years) among families tested positive vs negative for *BRCA1/2* mutations in 1) the proband's siblings and 2) other potential at risk relatives of the proband (siblings, children, nieces and nephews). We used generalized estimating equations to account for familial clustering. We compared pediatric malignancy rates in *BRCA1/2* mutation positive families from CREP to the general population from SEER (Surveillance, Epidemiology and End-Results) using an incidence rate ratio (IRR). **Results:** We compared 1,313 *BRCA1/2* mutation negative and 1,402 *BRCA1/2* mutation positive families. 3,168 siblings had 10 pediatric malignancies (0.3%) in *BRCA1/2* negative families and 3,185 siblings had 9 pediatric malignancies (0.3%) in *BRCA1/2* positive families. When examining at-risk family members there were 30 *BRCA1/2* negative families (2.3%) with a pediatric malignancy (31 malignancies) and 24 *BRCA1/2* positive families (1.7%) with a pediatric malignancy (25 malignancies). We found no evidence for an increased risk of pediatric malignancy in *BRCA1/2* positive vs *BRCA1/2* negative families in the sibling (OR = 0.69, 95% CI, 0.25-1.92; p = 0.482) or family based (OR = 0.76; 95% CI, 0.42-1.35; p = 0.342) multivariable adjusted analyses. The pediatric malignancy rates (per 100,000 person-years) among *BRCA1/2* positive families in CREP (incidence rate [IR] = 16.1, 95% CI, 10.9-23.9) and SEER (IR = 16.1, 95% CI, 16.0-16.3) were similar (IRR = 1.00; 95% CI, 0.65-1.48). **Conclusions:** We find no evidence for an increased risk of pediatric malignancy in *BRCA1/2* mutation positive families. Our data supports delaying *BRCA1/2* testing in *BRCA1/2* mutation positive families until adulthood.

1536 Poster Session (Board #107), Sat, 1:15 PM-4:45 PM

Feasibility of perioperative multi-gene panel testing (MGPT) in cancer patients eligible for hereditary genetic evaluation (GE): The PROTECT pilot. *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: Uptake of genetic evaluation (GE) remains limited in cancer pts. MGPT is recommended for GE of women with ovarian cancer (OC), but many will never be tested. For pts w/incident colorectal (CRC) and endometrial cancer (EC), universal mismatch repair screening (uMMR) for Lynch syndrome (LS) precedes GE and is also standard of care, but the limited scope of uMMR screening may obscure actionable mutations in non-LS genes, which are more prevalent than LS. We hypothesized that the opportunity to receive MGPT as part of GE would be favorably received by pts having cancer surgery, when relevance is highest. Additionally, to explore variation in timing/approach, we examined completion of a modified GE approach beginning w/MGPT immediately post-op (i-MGPT) vs completion of GE/MGPT when offered via a usual care (UC) pathway (MD- or self-referral). **Methods:** Women (F)/men (M) w/CRC (n = 20), women w/EC (n = 28) or ovarian cancer/OC (n = 6) were recruited 1-3 days pre/postop (6/2017-1/2018). Interested pts consented and were randomized to i-MGPT vs UC. Those on i-MGPT arm watched a brief pre-testing video about MGPT w/standard genetic counseling available at request. Results were phoned to i-MGPT pts; in-person counseling was encouraged for pathogenic (PV) and uncertain variants. Feasibility was measured by study consent rate (goal $>$ 50%). **Results:** 56/110 (50.9%) eligible pts consented. Most (89%) reported family history (FHx) of cancer. All pts on i-MGPT arm completed GE: 11% (3/27) had actionable PVs—a BRCA2 PV in a 60F w/EC and FHx pancreas cancer; a BRIP1 PV in a 70F w/OC and FHx breast cancer; a MUTYH PV in a 52M w/CRC. On UC arm, only 40.7% (11/27) have completed GE—PVs in MSH6 (70M w/CRC) and BRCA1 (44F w/OC) were found. Another 29.6% (8/27) on the UC arm with strong cancer risks have not sought GC, including 3 pts with cancer $<$ 50 yrs, a 54F w/OC, and a 70F w/IHC+ CRC and a strong FHx cancer. **Conclusions:** Perioperative I-MGPT lead to 100% completion of GE while uptake of GE on the UC arm was lower (40.7%). Of the 5 PVs discovered by MGPT, 4 were in non-LS genes. Peri-op MGPT to evaluate hereditary cancer risk is feasible in CRC, EC, and OC pts.

1537 Poster Session (Board #108), Sat, 1:15 PM-4:45 PM

Importance of genetic counseling referrals for high-risk women with endometrial cancer despite intact mismatch repair immunohistochemistry. *First Author: Jessica Lee, New York University School of Medicine, New York, NY*

Background: Lynch syndrome (LS) accounts for most inherited endometrial cancers (EC). The identification of probands presents a chance to prevent other cancers and enable cascade testing. Professional organizations have released guidelines for genetic counseling referrals (GCR) based on high-risk (HR) criteria including loss of mismatch repair (MMR) protein expression on tumor immunohistochemistry (IHC). **Methods:** All women diagnosed with EC from 2012 to 2017 were retrospectively identified and evaluated. Comparative analyses were performed with appropriate two-sided statistical tests. HR criteria were defined as age $\geq$50 at diagnosis, significant family or personal histories of LS-related cancers or positive MMR IHC. **Results:** A total of 716 women were diagnosed with EC and of these, 230 (32%) had at least one HR criteria. Of the HR women, 51% were given GCR and 13 (19%) were found to have LS. Mid-2015, we implemented universal MMR IHC. GCR rates among HR women were higher after January 2016 (72% vs 52%, $p = 0.01$). Among women with positive MMR IHC, there were higher rates of GCR after January 2016 that trended towards significance (94% vs 67%, $p = 0.08$). Table 1 lists GCR and LS rates. Of the 13 women with LS, 11 underwent MMR IHC. Of the 11 women, six (55%) had loss of MMR expression and one (9%) had intermediate MSH6 expression. Three (27%) had retained expression and one (9%) had loss of MLH1 and PMS2 expression but positive MLH1 promoter methylation; these four women all had significant family histories. All LS women had $\geq$ one HR criteria to warrant GCR Table 1. **Conclusions:** The initiation of universal MMR IHC correlates with a time of increased awareness for GCR among HR women, resulting in higher GCR rates. Although retained MMR expression is regarded as an indication to forgo GCR, almost 40% of LS women had MMR IHC findings which were not suggestive of LS. It is important to consider all HR characteristics even with intact MMR IHC to capture all LS cases.

Cohort	GCR / Cohort	LS / GCR women
All HR women	118 / 230 (51%)	13 / 118 (11%)
Before 2016	69 / 133 (52%)	8 / 69 (12%)
After 2016	49 / 68 (72%)	5 / 49 (10%)
+ MMR IHC women	39 / 52 (75%)	8 / 39 (21%)
Before 2016	24 / 36 (67%)	5 / 24 (21%)
After 2016	15 / 16 (94%)	3 / 15 (20%)

1538 Poster Session (Board #109), Sat, 1:15 PM-4:45 PM

Investigation of discordant sibling pairs from hereditary breast cancer (HBC) families. *First Author: Kara Landry, University of Vermont, Burlington, VT*

Background: Women who undergo testing for hereditary breast cancer (HBC) may be offered a panel of up to 40 genes but the majority of women tested have no mutation identified on these panels. This implies the existence of additional genes associated with HBC. Using a family-based design, our goal is to identify novel gene(s) or variants associated with HBC. **Methods:** We enrolled discordant sister pairs (one with and one without breast cancer) from families with $\geq$3 breast cancers (one diagnosed $\leq$50) on an IRB approved study. Germline DNA was extracted and whole exome sequencing performed. In order to highlight variants identified by our sequencing analysis as putative risk alleles, we used publicly available bioinformatics tools and genomic databases. By combining information across these resources, we generated a list of candidate risk alleles. Discordant allele scores were calculated for each of the variants (from genes with known cancer associations, and variants likely to alter function) seen in $\geq$1 case but no controls. Variants were flagged for further study if they were 1. predicted to alter function (using publicly available data bases), 2. located in a cancer associated gene, and 3. seen at low frequency ($<$ 1%) in the general population. **Results:** We enrolled 22 sister pairs with a mean age of diagnosis for sisters with breast cancer being 44 (range 34-60, only 1 $>$ 55). More than 50% of families have $>$ 3 cases of breast cancer. We have sequence data from germline exomes from 14 sib-pairs. Analysis has revealed several rare variants in genes not previously associated with HBC (ECO1, RECQL4, PMS1, MYC, UBE2D4). Additionally, 8 rare variants in three known HBC genes (BRCA1, CTNNA1, PMS2), but not reported in current databases (i.e. ClinVar), were identified. Co-segregation analysis of these families is underway. **Conclusions:** Using a family-based design we have identified both novel genes and novel variants in known HBC associated genes, in affected sisters from HBC families. These findings may represent private variants associated with HBC or support emerging hypotheses that accumulation of variants in cancer risk associated genes may account for HBC. Future studies will evaluate the functional significance of these variants.

1539 Poster Session (Board #110), Sat, 1:15 PM-4:45 PM

Genetic testing and clinical management practices for variants in non-*BRCA1/2* breast (and/or ovarian) cancer susceptibility genes: An international survey by the Enigma Clinical Working Group. *First Author: Sarah Nielsen, The University of Chicago Medical Center, Chicago, IL*

Background: Advances in massively parallel sequencing technologies have made multigene panels affordable and have revolutionized genetic testing for hereditary breast and ovarian cancer. Through the Evidence-Based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) consortium, we conducted a survey regarding non-*BRCA1/2* genes to assess international testing practices and risk management approaches for breast cancer (BC) and ovarian cancer (OC) susceptibility. **Methods:** Data were collected via in-person and paper/electronic surveys. ENIGMA members from around the world were invited to participate. Additional information was collected via country networks in the UK and in Italy. **Results:** Responses from 61 cancer genetics centers across 20 countries showed that 16 genes were tested by more than 50% of the centers, but only 6, *PALB2, TP53, PTEN, CHEK2, ATM,* and *BRIP1,* were tested regularly. US-based centers tested those genes most often, while UK and Italian centers (not directly affiliated with ENIGMA at the time of the survey) were the least likely to regularly test them. Most centers tested the 16 genes through multigene panels; some centers tested *TP53, PTEN* and other cancer syndrome-associated genes individually. The majority of centers reported pathogenic variants to patients and would test family members for such variants. Gene-specific guidelines for BC/OC risk management were limited and differed between countries, especially with regard to starting age and type of imaging techniques and risk-reducing surgery recommendations. **Conclusions:** Only a few genes beyond *BRCA1/2* are currently routinely analyzed and related management guidelines are limited and largely based on expert opinion. To achieve clinical application of multigene panel testing through evidence-based management practices, clinicians and patients should be encouraged to participate in international initiatives aimed at sharing information from panel testing, interpreting sequence variants, and collecting prospective data to underpin risk estimates and evaluate the outcome of risk intervention strategies.

1540 Poster Session (Board #111), Sat, 1:15 PM-4:45 PM

Non-BRCA hereditary gene mutations and breast cancer phenotype: An ISC-RAM Consortia study. *First Author: Banu Arun, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The use of multi-gene panel testing (MGP) for hereditary breast cancer has been increasing. Currently, the indications for MGP depend on personal and/or family history of cancer, as tumor phenotype and patient characteristics for non-BRCA related cancers are not well described. The present study analyzed tumor characteristics of breast cancers associated with non-BRCA hereditary mutations. **Methods:** Institutional IRB-approved prospective databases from the International Society of Cancer Risk Assessment and Management (ISC-RAM) members were queried for patients with invasive breast cancer who underwent MGP between 2013-2017. Clinical and tumor characteristics for mutation carriers were analyzed using descriptive statistics and Pearson's and Fisher's Chi-Square analyses. **Results:** Of a total of 1,854 patients with invasive breast cancer who underwent MGP, 374 (20%) had a positive pathogenic gene mutation. Median age at diagnosis was 46 years (range: 22-85). Positive testing results were as follows: BRCA1: 77 (21%); BRCA2: 76 (20%); ATM: 45 (12%); CHEK2: 47 (12.5%); PALB2: 32 (8.5%); TP53: 16 (4.3%); MUTYH: 13 (3.5%); 68 (18.2%) patients tested positive for other genes (APC, BRIP1, BARD1, PTEN, STK11, CHD1, MLH, MSH, PMS, CDKN2A, NBN, NF1, RAD50, RAD51, SDHD, AXIN2, MITF, GALNT12, XRCC2). As expected, BRCA1 mutation was associated with triple negative breast cancer ($p < 0.0001$). The tumor characteristics of all other carriers were similar to those seen in BRCA2 carriers with two exceptions: MUTYH carriers were more likely to have invasive lobular cancers ($p < 0.0001$) and TP53 carriers were younger at diagnosis ($p < 0.001$) and more likely to have HER-2/neu positive cancers ($p = 0.006$). **Conclusions:** Our collected series of patients with non-BRCA hereditary breast cancers demonstrates specific tumor characteristics associated with TP53 and MUTYH mutations. Further exploration is warranted to expand this data set and further characterize cancers that are associated with low frequency genetic mutations. The frequency of ER positive tumors in these patients suggests that chemoprevention may be an important strategy in this population.

1541 Poster Session (Board #112), Sat, 1:15 PM-4:45 PM

Integrative clinical genomics of early-onset breast cancer. *First Author: Lixi Li, National Cancer Centre/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Cancer Hospital, Beijing, China*

Background: The peak onset age of breast cancer in China is about 10 years ahead of Europe and the United States. Early-onset breast cancer has more aggressive clinicopathological characteristics and worse prognosis. The spectrum of germline mutation among unselected patients with early-onset breast cancer is largely uncertain, and it has never been studied among women under 25 years old. Exploring the mutation spectrum of early-onset breast cancer can help identify molecular markers and provide therapeutic targets for clinical treatment. **Methods:** About 20,000 women with breast cancer visited National Cancer Center between 2000 and 2015, and nearly 5% of those patients were 35 years old or younger, of whom 242 women were included in this study. Peripheral blood samples were collected and germline DNA was sequenced with a 139-gene panel using next generation sequencing. Clinicopathological characteristics were assessed by age at diagnosis and mutation status. **Results:** In this study, 58 of the 242 (24.0%) women with early-onset breast cancer had at least one pathogenic germline mutation. The cumulative frequency of pathogenic germline mutations increased with decreasing age at diagnosis ($P < 0.001$). In addition to most of genes previously implicated in breast cancer (BRCA1, BRCA2, CHEK2, TP53, PALB2, MSH2, MSH6, MLH1, RAD51D, RAD51B, ATM), a number of novel mutated genes were identified, including APC, SLX4, TSC2, TGFBR2, RET, SBDS and FANCE. Germline mutation differed according to clinicopathological characteristics. Similar to the association between BRCA1 and TNBC, BRCA2 germline mutation was enriched in luminal B subtype and predicted worse prognosis, and CHEK2 p.H371Y mutation predicted HER2 negativity. **Conclusions:** The cumulative frequency of germline mutations increased with decreasing age at diagnosis. Hereditary susceptibility could account for 50% of breast cancer in ultra-young patients ($\leq$25 years). Germline mutation could predict clinical characteristics and prognosis in early-onset breast cancer. Because of the high frequency and wide spectrum of pathogenic mutations, early-onset breast cancer should be offered genetic testing with a multigene panel.

1542 Poster Session (Board #113), Sat, 1:15 PM-4:45 PM

Beyond *BRCA1* and *BRCA2*: Implementation of a multigene panel for the upfront testing of germline mutations in ovarian cancer. *First Author: Maria Beatriz Mira, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal*

Background: Germline mutations impacting homologous recombination repair have been associated with predisposition to breast (BC) and ovarian cancer (OC). OC, even if no family history (FH) confers a 10% combined probability of *BRCA1/2* mutations, being a criteria for testing. *BRCA1/2* detection rate may vary FH and pathology. Besides *BRCA1/2,* other genes have also been associated with hereditary OC. **Methods:** all index, consecutive, OC patients (pts) counselled between September 2016-December 2017 were tested upfront for a panel testing (PT) including *BRCA1*, *BRCA2*, *RAD50*, *RAD51C*, *RAD51D* and *BRIP1 (*BRCA Hereditary Cancer MASTER Plus methodology). All pts were required to have a pathology confirmation of OC (mucinous cases excluded). In here, we analyze the molecular results and discuss the clinical potential of PT for OC. **Results:** 109 female pts consented to PT (108 OC pts and 1 BC pt with a first degree relative with OC). Medium age at testing was 58.1 years (26-83). Pathogenic variants were found in 20 pts (18.3%): *BRCA2* – 8 (40%), *BRCA1* – 5 (25%), *RAD51C* – 3 (15%), *RAD51D* – 2 (10%), *RAD50* – 1 (5%), *BRIP1* – 1 (5%). Of the 8 *BRCA2* pts, 2 were diagnosed with the c.156_157insAlu mutation. 13 pts (65%) had high grade serous OC and 4 pts endometrioid OC (20%). 2 pts had low grade OC, both stage III at diagnosis – one with a *RAD51C* mutation (c.404G > A, p.C135Y) and other with a pathogenic *BRCA2* variant (c.156_157insAlu). All of these pts (except the one with *BRIP1* mutation) had a personal history of OC and 3 of them had had BC and OC (1 *BRCA1,* 2 *BRCA2*). The pt with the *BRIP1* mutation (c.484C > T; p.Arg162Ter) was the only one without OC: she was as BC survivor with a FH of OC. **Conclusions:** With this panel, and without restrictions relating to non-mucinous pathology, we observed a high (18%) germline mutation detection rate for OC. Adding 4 genes to *BRCA1/2* testing increased the mutation detection rate by 53.8%. Even if counselling is complex in families harbouring variants in moderate penetrance genes, our results suggest clinical utility for OC prevention. Other genes will be included in our upfront OC panel.

1543 Poster Session (Board #114), Sat, 1:15 PM-4:45 PM

Prospective Registry of Multiplex Testing (PROMPT): Feasible and sustainable. *First Author: Heather Symecko, Basser Center for BRCA, University of Pennsylvania, Philadelphia, PA*

Background: Prospective Registry of Multiplex Testing (PROMPT) is an online registry for individuals who completed multiplex panel testing for cancer susceptibility. The overall objective of this registry is to ascertain families to allow penetrance calculations for mutations in less characterized genes. **Methods:** Since September 2014, health care providers and commercial laboratories have provided PROMPT information to eligible participants and ordering providers with the test results. The PROMPT registry has self-enrolled those with pathogenic mutations and variants of unknown significance (VUS) in cancer susceptibility genes. Registrants consent to full participation (FP), permitting study investigators to have contact information, or partial participation (PP), with de-identified information only. In 2016, we expanded to Phase II, targeting enrollment by genes of interest for family co-segregation, and collecting additional risk factor data and saliva samples. **Results:** Over 4500 individuals have enrolled into PROMPT. Using initial recruitment goals, to date we have reached 250% of our initial recruitment. 94% of enrollees are women, representing 33 countries (96% from the United States). 63% of participants reported at least one cancer (67% breast cancer) and 23% reported two or more cancers. 29% report likely pathogenic/pathogenic alteration, 25% VUS, and the remaining are in the process of being verified. The most frequently reported genes are ATM (13%), CHEK2 (12%), PALB2 (7%), BRIP1 (4%), and BARD1 (4%). 58% of participants have participated more than 1 year, and of those, 28% completed the first annual follow-up survey. A gene-specific survey sent to participants with CDH1 genetic alterations had a 61% response from FP and a 32% response rate from PP. **Conclusions:** The continued linear enrollment since the inception of PROMPT and the willingness of participants to respond to survey studies, annual follow-up, and PROMPT II enrollment, supports the feasibility and sustainability of a prospective registry for the collection of genetic epidemiology data. Strategies to increase follow up participation are underway, including gene-specific surveys and transitioning PP to FP, for those who are willing.

1544 Poster Session (Board #115), Sat, 1:15 PM-4:45 PM

Treatment failure: Why patients with BRCA mutations are declining risk-reducing surgery. *First Author: Olivia R Khouri, New York University Medical Center, New York, NY*

Background: The NCCN guidelines recommend risk-reducing bilateral salpingo-oophorectomy (RRBSO) for patients with BRCA mutations by age 35-40 or upon completion of childbearing. We previously reported high rates of non-compliance with these guidelines, with many women pursuing RRBSO after 40, if at all. We sought to evaluate patients' reasons for declining RRBSO to identify areas for improvement in counseling and prevention. **Methods:** We conducted a retrospective chart review to identify patients with BRCA mutations (diagnosed 2006–2017). Data were abstracted from electronic medical records and analyzed using descriptive and two-tailed statistics. **Results:** There were 345 women with BRCA mutations identified (57% BRCA1, 43% BRCA2), with median age 32(16–49) at the time of diagnosis. Eighty-seven percent (303) were Caucasian and 50% (172) were of Ashkenazi descent. A majority (87%, 287) had a family cancer history and 25% (88) had a personal cancer history. Thirty-eight percent (132) underwent risk-reducing mastectomy (RRM) and 32% (102) underwent RRBSO. Among those noncompliant with RRBSO, 21% cited menopausal symptoms, 56% fertility preservation, 15% "other," and 8% were lost to follow up. Undergoing RRBSO was associated with age > 40 ($p < 0.0001$), personal cancer history ($p = 0.02$), family cancer history ($p < 0.0001$), and previous RRM ($p = 0.04$). Patients > 40 more often cited menopausal symptoms in declining RRBSO ($p < 0.0001$), while patients < 40 were more likely to cite fertility preservation ($p < 0.0001$). **Conclusions:** Patients with a personal or family history of cancer, history of RRM, or age > 40 were more apt to undergo RRBSO. The majority of women who declined RRBSO reported fertility or menopause as primary concerns. As the age of childbearing increases, counseling of BRCA patients should address early childbearing, assisted reproductive technology, and hormonal therapy to facilitate timely RRBSO for prevention of ovarian cancer and mortality reduction.

1545 Poster Session (Board #116), Sat, 1:15 PM-4:45 PM

Identification and characterization of germline pathogenic variants using matched tumor-normal next-generation sequencing in 7363 pan-cancer patients in China. *First Author: Yuting Yi, Geneplus-Beijing Institute, Beijing, China*

Background: Comprehensive NGS panel based genetic testing is becoming more common to help clinicians provide personalized cancer care. Matched tumor-normal sequencing is recommended primarily to detect tumor-specific variants. Previously under-explored, it could also detect pathogenic germline alterations in cancer patients. Using targeted matched tumor-normal NGS, we identified and characterized germline variants in a large pan-cancer patient cohort in China. **Methods:** We surveyed the germline variants in 7363 Chinese patients across more than 18 diverse cancer types. Germline variants in 62 cancer-susceptibility genes were called from a 1021 gene NGS panel analyzing matched normal DNA. Following AMCG guidelines, variants were classified into pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign. **Results:** 385 germline pathogenic and likely pathogenic variants (GPVs) were identified in 374/7363 (5.1%) patients. Ovarian cancer (27.6%, 37/134) represented the highest prevalence. Breast cancer (11.3%, 92/813), colorectal cancer (8.3%, 66/791), pancreatic cancer (6.2%, 8/130), renal cell cancer (6%, 5/84), and gastric cancer (5.1%, 14/273) displayed relatively high rates of GPVs in line with expectations. Interestingly, NSCLC (2.5%, 88/3572) and hepatocellular cancer (2.3%, 5/214) also showed such events. In total, only 192/385 (49.9%) participants presented with GPVs in cancer-susceptibility genes in the expected cancer types. *BRCA2* and *BRCA1* were the top two common genes, which were found in 146 patients across 15 cancer types including 27/3572 (1%) NSCLC and 3/214 (1.4%) hepatocellular cancer patients. 285/385 (74%) of the GPVs were actionable for targeted therapy. **Conclusions:** Germline variants can be identified on routine targeted matched tumor-normal NGS and commonly exist in patients with cancers of diverse tissue origin. Recognition of germline variants may be valuable in therapeutic interventions and genetic risk analysis. We are currently performing retrospective family history analysis and genetic counseling for those patients with unreported GPVs.

1546 Poster Session (Board #117), Sat, 1:15 PM-4:45 PM

Population health and cancer testing pilot protocol (PHACT). *First Author: Mallika Sachdev Dhawan, University of California San Francisco, San Francisco, CA*

Background: There is considerable uncertainty on cancer risk and recommendations for genetic testing in various populations. The purpose of this study is to test types and frequencies of cancer risk mutations in large, unaffected multiethnic populations, as well as feasibility and acceptance of general population germline testing. **Methods:** After consent, germline genetic testing via Color Genomics Multigene Cancer Risk panel with personal and family cancer history assessment, was offered to at least 500 participants residing in the San Francisco Bay Area. Participants were older than 21 and without a known personal history of a cancer risk mutation. Recruitment occurred at random and by various community events. Genetic counseling through a genetic counselor at UCSF was offered to all participants. **Results:** 457 total samples have been submitted by 535 consented participants. 28 participants in 440 finalized tests were found to have a cancer risk mutation (6.4%). The majority of these have been in moderate risk cancer mutations including CHEK2 (1.4%), APC (0.9%), MUTYH (1.6%) and NBN (0.4%); higher risk mutations were found in BRCA1 (0.4%), BRCA2 (0.4%), BRIP1 (0.2%), PMS2 (0.2%) and PALB2 (0.2%). 4 additional participants were found to have mutations (3 BRCA1, 1 ATM) but had a known family history of a cancer risk mutation. Ancestry data via self-reporting and SNP testing via the Color Genomics platform was collected to contextualize these results. Rates of VUS (variants of uncertain significance) differed among the various ethnic groups ($p = 0.029$) with the lowest rates in Europeans (18% vs. 31% $p = 0.002$). **Conclusions:** The PHACT study demonstrates that large population screening of cancer risk mutations is feasible. The number of participants found to have mutations was greater than expected although the majority of these were in moderate risk genes. We found high rates of VUS in non-Europeans, which supports the need to broaden genetic testing in minority populations to better understand the significance of these variants. This is to our knowledge the largest study of cancer risk mutations in an unaffected multiethnic population and serves as a pilot to a much larger 10,000-person study of the prevalence of cancer risk mutations across California.

1547 Poster Session (Board #118), Sat, 1:15 PM-4:45 PM

Evaluating empowerment in genetic counseling using patient reported outcomes. *First Author: Suat Ying Lee, National Cancer Centre, Singapore, Singapore, Singapore*

Background: Despite the demand for cancer genetic services, patient-derived benefits remain poorly captured due to a paucity of validated tools. The Genetic Counselling Outcome Scale (GCOS-24), a genetics-specific Patient Reported Outcome Measure (PROM), has been adapted to evaluate our local cancer genetic service (CGS). We aim to evaluate the psychometric properties of GCOS-24 using Rasch analysis. **Methods:** 155 patients who attended CGS at National Cancer Centre Singapore (May 2016-2017) were recruited. The questionnaire was interviewer-administered pre- and post-counselling. Responses were subjected to Rasch analysis, comparing individual Rasch item scores pre and post. Multiple regression analysis was used to assess the association of baseline characteristics with changes in scores. **Results:** GCOS-24 questionnaire displayed good precision (person separation index > 2.0) and targeting (difference between person and item means < 1.0). Cognitive Control [post-intervention: median 1.23 (IQR -0.3-6.2); pre-intervention: median 0.46 (IQR -1.1-3.6)] and Emotional Control [post-intervention: median 0.99 (IQR -1.1-6.4); pre-intervention: median 0.61 (IQR -1.1-3.9)] scores showed significant improvement. All components of cognitive control consistently showed improvement. Notably, aspects of Emotional Control such as alleviating feelings of being upset ($p = 0.88$) and hopelessness ($p = 0.2$) did not reflect significant improvement. Family history ($p = 0.047$) and genetic testing ($p = 0.002$) were significantly correlated with cognitive control. As for emotional control, genetic testing ($p = 0.002$) and the female gender ($p = 0.033$) were also significantly correlated. **Conclusions:** This study shows that GCOS-24 is well adapted and validated in our population. Significant improvements in cognitive and emotional control are concordant with previous adaptations, demonstrating the value of empowerment through genetic counselling. This study highlights the need for further emphasis to be placed on improving hope and addressing emotions, through hope-based interventions and a systems-based approach to identifying and alleviating negative emotions associated with genetic conditions and testing.

1548 Poster Session (Board #119), Sat, 1:15 PM-4:45 PM

The effect of Genetic Cancer Risk Assessment (GCRA) on the uptake of risk-reducing surgeries (RRS) in Hispanic women with breast cancer (BC). *First Author: Yanin Chavarri Guerra, Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán, Mexico City, Mexico*

Background: The management of women with BC includes GCRA for those at risk of carrying deleterious *BRCA* mutations. GCRA can aid decisions regarding RRS, including contralateral risk reducing mastectomy (CRRM) and risk reducing salpingoophorectomy (RRSO). The uptake of RRS among Hispanic women with BC is unknown, partly due to disparities in access to GCRA. We hypothesized that these disparities may be accentuated in Latin America (LA). **Methods:** Hispanic women from the US & LA (Mexico, Colombia, Peru & Puerto Rico) with history of BC who underwent GCRA, enrolled in the Clinical Cancer Genomics Community Research Network registry from 1997-2016 were included. Demographic characteristics and data regarding RRS were obtained from chart reviews and self-reported surveys. Data was analyzed using Fisher's and x2 tests. An adjusted logistic regression model including a set of selected factors was used to predict the likelihood of undergoing RRS. **Results:** RRS data was collected on 1,517 Hispanic women with BC. 270 (17.7%) were *BRCA* carriers and 1247 (82%) non-*BRCA* carriers. Median age at GCRA was 44 years (y)(range 17-87). Median follow-up was 2.6 y. RRS were more common among *BRCA* carriers (34% CRRM and 27.7% RRSO) compared to non-*BRCA* carriers (18.6% CRRM and 4.1% RRSO). Of those that had CRRM, it occurred after GCRA for 79% of *BRCA* carriers and 50% of non-*BRCA* carriers. Factors associated with CRRM in *BRCA* carriers were: $\geq$1 pregnancies (OR 0.3, p 0.01), and living in the US (OR 5.2, $p < 0.01$). Factors associated with CRRM among non-carriers were: older age (OR 0.9, $p < 0.01$), $\geq$1 pregnancies (OR 1.4, p 0.4), family history of cancer (OR 1.9, $p > 0.1$), living in the US (OR 30.6, $p < 0.01$) and previous ipsilateral mastectomy (OR 2.9, $p < 0.01$). **Conclusions:** RRS uptake among Hispanic women with BC in LA was lower than previously reported in other populations. GCRA may influence risk appropriate RRS uptake, especially for *BRCA* carriers. CRRM and RRSO can prevent new primary cancers, and RRSO can improve survival for *BRCA* carriers, so a better understanding of behavioral factors is needed to inform interventions to improve risk appropriate uptake of RRS among Hispanics.

1549 Poster Session (Board #120), Sat, 1:15 PM-4:45 PM

Influence of vitamin D (Vit D) on mammographic density (MD) and insulin like growth factor 1 (IGF1): Results of CALGB (Alliance) 70806. *First Author: Marie Wood, University of Vermont, Burlington, VT*

Background: Vitamin D is safe and has breast cancer prevention properties. CALGB 70806 was a randomized phase II trial evaluating the effect of vit D on several breast cancer biomarkers (including MD and serum IGF1). **Methods:** Premenopausal women were assigned to receive either 2000IU of Vit D or placebo for 12 months, stratified by baseline (BL) vit D level (sufficient vs insufficient). Eligible women were premenopausal, age < 55, with at least 25% dense breast tissue. Biomarker specimens were collected at baseline and 12 months. MD was determined using the Breast Imaging Reporting and Data System (BIRADS), semi-automated and automated methods. Serum IGF1 was determined by ELISA. Biomarkers were compared between arms using Wilcoxon and t-tests. **Results:** 300 women were recruited from 41 institutions across the US between 1/11 -12/13. The mean age was 42.6 years with 14% Hispanic, 12% African American, 74% European. 62% of participants were vitamin D deficient at enrollment and 49% of women had MD between 25-50% with only 12% over 50% dense. 216 (72%) of participants completed treatment, 8 withdrew due to side effects, and 76 for other reasons (28% withdrawal rate). A significant increase in Vit D was seen with treatment with 99% and 72% of experimental and control subjects having sufficient levels at 12 months($P < 0.0001$)). MD decreased 2.2% over 1 year for the entire cohort, with no significant difference between arms (Table 1). Similarly, no significant change in IGF1 levels was seen with Vit D. **Conclusions:** Vit D supplementation resulted in a significant increase in serum Vit D (from a mean of 35.5 to 49.7 ng/mL, $p = < 0.0001$). However, no significant change in MD was observed with treatment; potentially due to small change in MD seen at 1 year, the low percentage of high MD or that Vit D works by another mechanism. Further study with longer Vit D exposure is warranted. Support: UG1CA189823, U24CA196171. Clinical trial information: NCT01224678.

Biomarker changes over 12 months.

Biomarker	Placebo	Vit D	P-value
25(OH)D (ng/mL)	-0.9 (12.5)	+14.3 (12.9)	< 0.0001
IGF1 (ng/mL)	-0.1 (0.6)	-0.1 (0.6)	0.3699
MD	-2.4% (7.9%)	-1.9% (9.8%)	0.7048

1550 Poster Session (Board #121), Sat, 1:15 PM-4:45 PM

Randomized double-blind placebo-controlled biomarker modulation study of vitamin d in premenopausal women at high risk for breast cancer (SWOG S0812). *First Author: Katherine D Crew, Columbia University Medical Center, New York, NY*

Background: Observational studies have reported an inverse association between vitamin D status and breast cancer risk. We examined whether high-dose vitamin D supplementation among high-risk premenopausal women reduces mammographic density (MD), a strong predictor of breast cancer risk. **Methods:** We conducted a multicenter randomized double-blind placebo-controlled trial among premenopausal women at high risk for breast cancer [5-year Gail risk score $\geq$1.67%, lobular carcinoma *in situ*, prior stage 0-II breast cancer, hereditary breast cancer syndrome, or high MD (heterogeneously/extremely dense)] and with a baseline serum 25-hydroxyvitamin D [25(OH)D] $\leq$32 ng/mL. Subjects were randomized 1:1 to 1 year of vitamin D3 20,000 IU/week or matching placebo. All received standard-dose vitamin D 600 IU/day. The primary endpoint was change in MD from baseline to 1 year as assessed by the Cumulus technique. Secondary endpoints were serial blood biomarkers [25(OH)D, 1,25(OH)D, parathyroid hormone, insulin-like growth factor (IGF)-1, IGF binding protein-3] and MD change at 2 years. **Results:** Among 208 subjects registered from December 2011 to April 2014, median age was 44.6 years (range, 21-50); 84% were white; 33% had a baseline serum 25(OH)D < 20 ng/mL; 78% had a high baseline MD. At 1 year, we observed a significant mean change in serum 25(OH)D in the active vs. placebo group (+18.9 vs. +2.8 ng/mL, $p < .01$), but non-significant change for IGF-1 (-9.8 vs. -1.8 ng/mL, $p = 0.28$). Mean absolute change in MD at 1 year and 2 years after randomization was -0.3% and -1.2%, respectively, in the active arm and +1.5% and +1.6%, respectively, for the placebo arm ($p > 0.05$). At 1 year, MD correlated with serum IGF-1 and IGF-1/IGFBP-3 ($p < .01$). High-dose vitamin D3 was well-tolerated. **Conclusions:** Changes in MD at 1-2 years were small and did not significantly differ between high-dose and standard-dose vitamin D. Longer exposure may be required to detect a difference. The relationship between vitamin D, IGF-1, and MD are hypothesis-generating. Understanding the relationship between vitamin D and biomarkers of breast cancer risk may inform future clinical trials. Clinical trial information: NCT01097278.

1551 Poster Session (Board #122), Sat, 1:15 PM-4:45 PM

Case-only analyses for identifying genotypes that modify the effect of finasteride in the Prostate Cancer Prevention Trial (PCPT): SWOG S9217. *First Author: James Dai, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The Prostate Cancer Prevention Trial (PCPT) reported decreased risk of all prostate cancers but increased risk of high-grade prostate cancer in the finasteride arm. The aim of the present analysis was to identify genotypes that modify the effect of finasteride using case-only methods for estimating gene-treatment interactions. **Methods:** Germline genetic data from 1157 prostate cancer cases in the Prostate Cancer Prevention Trial (PCPT, NCT00288106) were analyzed by case-only methods. Genotypes included 357 single nucleotide polymorphisms (SNPs) from 83 candidate genes in androgen metabolism, inflammation, circadian rhythm and other pathways. Univariate case-only analysis was conducted to evaluate whether individual SNPs modified the finasteride effect on the risk of high-grade and low-grade prostate cancer. Case-only classification trees and random forests, which are powerful machine learning methods with resampling-based controls for model complexity, were employed to identify a predictive signature for genotype-specific treatment effects. **Results:** Accounting for multiple testing, a single SNP in *SRD5A1* gene (rs472402) significantly modified the finasteride effect on high-grade prostate cancer (Gleason score > 6) in PCPT (p-value = 8×10^{-5}, family-wise error rate < 0.05). Men carrying GG genotype at this locus had a 55% reduction of the risk in developing high-grade cancer (RR = 0.45, 95% C.I. [0.27, 0.75]). Additional effect-modifying SNPs with moderate statistical significance were identified by case-only trees and random forests. A prediction model built by the case-only random forest method classified 36% of PCPT men to have reduced risk of high-grade prostate cancer when taking finasteride, while the others have increased risk. No SNP-finasteride interaction was found for low-grade prostate cancer. **Conclusions:** Case-only methods identified SNPs that modified the effect of finasteride on the risk of high-grade prostate cancer in PCPT and predicted a subgroup of men who had reduced cancer risk by finasteride. Clinical trial information: NCT00288106.

1552 Poster Session (Board #123), Sat, 1:15 PM-4:45 PM

Chest x-ray (CXR) screening to improve outcomes in lung cancer: Reanalysis of the lung cancer component of the Prostate-Lung-Colorectal-Ovary (PLCO) randomized controlled trial. *First Author: John Paul Flores, Virginia Mason Medical Center, Seattle, WA*

Background: CXR screening for lung cancer is considered ineffective because no randomized trial demonstrated a lung cancer mortality reduction. However, in the Mayo Lung Project, CXR screening has been reported to produce significant survival advantages not attributable to overdiagnosis or other screening biases (JCO: 20: 1973-83, 2002). PLCO compared CXR to no screening and reported no lung cancer mortality reduction after 13 years. Lung cancer survival was not reported. That analysis included all lung cancers diagnosed over 13 years, though active screening lasted only 3 years. Since screening is unlikely to benefit individuals diagnosed many years after screening is discontinued, we evaluated lung cancer outcomes among cases diagnosed only within 4 years of randomization. **Methods:** PLCO randomized 77,445 subjects to an experimental group (EG) undergoing a prevalence CXR and 3 annual incidence CXRs and 77,456 to an unscreened control group (CG). Lung cancer survival and mortality were calculated for all lung cancers diagnosed during the 13-year follow-up and those diagnosed only within 4 years of randomization. **Results:** After 13 years, 1,838 and 1,737 lung cancers were detected in EG and CG (RR = 1.06; 95%CI 0.99-1.13; p = 0.09). Five year survival was 24% vs. 19% in EG and CG ($p < 0.001$). There were 1,217 and 1,203 lung cancer deaths, indicating no mortality reduction (p = 0.77). Within 4 years of randomization, 658 and 582 lung cancers were detected in EG and CG (RR = 1.13; 95%CI 1.01-1.13; p = 0.030). Five-year survival was 27% vs. 18% in EG and CG ($p < 0.001$). Among these, there were 463 and 481 lung cancer deaths, a difference not statistically significant (p = 0.58). **Conclusions:** In PLCO, randomization to CXR screening produced a significant improvement in lung cancer survival, an advantage not attributable to any screening bias, including overdiagnosis as lung cancer incidence was not statistically different. The benefit is diminished when lung cancers diagnosed well beyond the active screening interval are included. This analysis supports that CXR screening did save lives in PLCO among patients diagnosed during the active screening period.

1553 Poster Session (Board #124), Sat, 1:15 PM-4:45 PM

Long-term effectiveness and immunogenicity of quadrivalent HPV vaccine in young men: 10-year end-of study analysis. *First Author: Stephen Goldstone, Laser Care Surgery, New York, NY*

Background: The quadrivalent human papillomavirus (qHPV) vaccine prevented HPV6/11/16/18-related persistent infection and external genital lesions in young men in an international, randomized, placebo-controlled pivotal efficacy study. We report the end-of-study analysis of a long-term follow up (LTFU) extension study that assessed the effectiveness and immunogenicity of the qHPV vaccine through 10 years after the first dose. **Methods:** In the 3-year base study, young men (16-26 years old) were randomized 1:1 to receive a 3-dose regimen of qHPV vaccine or placebo; we report results from those who received 3 doses of qHPV vaccine in the base study and participated in the LTFU. The entire study population was assessed annually in the 7-year LTFU for HPV6/11-related genital warts and HPV6/11/16/18-related external genital lesions (EGL), and a subpopulation was assessed for HPV6/11/16/18-related anal intraepithelial neoplasia (AIN) or anal cancer. Persistence of anti-HPV6/11/16/18 antibodies was evaluated from serum samples collected 48-72 months (first LTFU visit) and 10 years post-Dose 1. **Results:** A total of 917 participants were followed for effectiveness for up to 11.5 years (median: 9.5 years) post-Dose 3. There were no new cases of HPV6/11-related genital warts, HPV6/11/16/18-related EGL, or HPV6/11/16/18-related high-grade AIN during the LTFU (Years 3 to 10 of the study) in the per-protocol population. One case of low-grade AIN (AIN1) with positive PCR results for HPV6 and HPV58 was reported. Seropositivity rates assessed by competitive Luminex immunoassay (cLIA) were $> 97\%$ at Month 7 (1 month post-Dose 3); remained high over time for HPV6, 11, and 16; and decreased over time for HPV18 (40.2% at Month 120 by cLIA). Seropositivity rates at Month 120 assessed by IgG Luminex immunoassay (a more sensitive assay) were $> 90\%$ for all 4 HPV types. **Conclusions:** The qHPV vaccine provides durable protection from vaccine-type–related anogenital disease and elicits persistent HPV antibody responses through 10 years post-vaccination onset in 16-26–year-old men. Clinical trial information: NCT00090285.

1554 Poster Session (Board #125), Sat, 1:15 PM-4:45 PM

Breast cancer risk perception and adherence to u.s. cancer prevention guidelines. *First Author: Jillian Eckroate, Yale University, New Haven, CT*

Background: In the United States, nearly 300,000 cancer diagnoses each year are attributed to poor diet and physical inactivity. We sought to determine whether perceived personal breast cancer risk was associated with adherence to healthy lifestyle habits. **Methods:** The National Health Interview Survey (NHIS) is conducted annually by the CDC, designed to broadly represent the U.S. civilian population. We utilized data from the 2010 and 2015 NHIS adult and cancer supplements to evaluate fruit/vegetable intake, alcohol use, and exercise habits among women who perceived themselves to be at high risk of developing breast cancer, as compared to those women who perceived themselves to be at average or low risk. **Results:** In 2010 and 2015, 12,055 and 14,542 women without a history of cancer were surveyed, representing 94,990,140 and 98,404,285 people, respectively. In 2010, those who perceived themselves to be at higher risk of breast cancer were more likely to follow the fruit/vegetable and physical activity guidelines, but less likely to follow the alcohol intake guidelines than those at low to average risk, but these differences were not statistically significant (p = 0.57, 0.15, 0.31 respectively). In 2015, those who perceived themselves to be at high risk were significantly more likely to follow the fruit/vegetable guidelines (p = 0.02) as their low/average risk counterparts, but had similar rates of following alcohol and physical activity guidelines (p = 0.58 and 0.67 respectively). In general, guideline adherence did not improve from 2010 to 2015 (see table). **Conclusions:** Less than a third of women adhere to nutrition and physical activity guidelines regardless of self-perceived breast cancer risk, a trend that has remained stable over time and indicates a need to educate patients on healthy lifestyle habits.

	2010	2015	p-value
High Risk—% meeting guidelines			
Fruit/Veg Intake (³ 5 servings/daily)	4.90%	6.25%	0.25
Alcohol Intake (£ 7/week)	94.22%	95.80%	0.16
Physical Activity (75-150 min vig-mod activity/week)	30.11%	28.97%	0.64
Low/Avg Risk—% meeting guidelines			
Fruit/Veg Intake (³ 5 servings/daily)	4.42%	3.92%	0.11
Alcohol Intake (£ 7/week)	95.13%	95.35%	0.53
Physical Activity (75-150 min vig-mod activity/week)	27.74%	29.79%	0.01

1555 Poster Session (Board #126), Sat, 1:15 PM-4:45 PM

Clinical characteristics and EGD surveillance in Lynch-syndrome patients with small bowel/duodenal carcinomas. *First Author: Deepak B. Vangala, Department of Medicine, Knappschaftskrankenhaus, Ruhr-University Bochum, Bochum, Germany*

Background: Small bowel carcinomas (SBC) account for less than 5% of all gastrointestinal malignancies in the general population. However in patients with Lynch-Syndrome (LS) the life-time-risk for SBC is reported as high as 10%. The aim of this study was to evaluate the effectiveness of esophagogastro-duodenoscopy (EGD) surveillance for early detection of proximal SBCs. **Methods:** The *German Consortium for Intestinal Cancer* database was screened for patients with a diagnosis of SBC. General tumor characteristics such as mutational status and age specific incidence where analyzed. Tumor stage at diagnosis was used as a surrogate parameter for prognosis and correlated to patients being diagnosed by symptoms compared to patients diagnosed by EGD-surveillance. Furthermore, adherence to EGD-surveillance after SBC diagnosis was correlated to survival. Statistics were calculated using Fisher's exact test. **Results:** A total of 125 SBC in 112 patients were included in the study (45.6% duodenal, 32% jejunal, 10.4% ileal, 9.6% unclassified). The median age at diagnosis was 51.7 years (15.1 – 80.7) with 62% of patients being male. MLH1 and MSH2 germline mutations were most prevalent with 37 % each. Of all SBCs, 10.4% of patients were younger than 35 years at diagnosis (8.8 % of duodenal cancers). Duodenal cancer patients undergoing surveillance were diagnosed with early stage disease (UICC I-IIa) significantly more often than patients diagnosed because of symptoms (69.2 % vs 26.6%; $p = 0.0089$). In non-duodenal SBC there was no stage difference between these groups. Adherence to EGD surveillance was better after SBC diagnosis with significantly less cancer deaths among patients undergoing surveillance after SBC. **Conclusions:** To our knowledge, this is the largest study regarding the role of EGD surveillance for early detection of SBC in LS patients. Our data support the use of EGD as a surveillance instrument for duodenal cancer, which make up nearly half of SBC in LS patients. In contrast to current practice in Germany, the results of this study suggest an earlier beginning of EGD surveillance than at the age of 35.

1556 Poster Session (Board #127), Sat, 1:15 PM-4:45 PM

Effects of U.S. Preventive Services Task Force (USPSTF) guidelines on cervical cancer screening, incidence, and mortality. *First Author: Alexander Melamed, Massachusetts General Hospital, Boston, MA*

Background: To evaluate the consequences of USPSTF recommendation to stop pap testing in well-screened women age ≥65 years on cervical cancer incidence and mortality. **Methods:** In 2003, the USPSTF recommended that women age ≥65 years with prior normal cervical cancer screening could discontinue screening. Using nationally-representative survey data from the Behavioral Risk Factor Surveillance System, we constructed a joinpoint model to evaluate if the guideline affected pap smear discontinuation (defined as no pap for ≥5 years). We performed interrupted time-series to evaluate whether guideline-related pap-smear discontinuation affected stage-specific cervical cancer incidence and mortality in women ages ≥65, using women ages 30-64 as controls. Incidence and mortality rates were obtained from the Surveillance, Epidemiology, and End Result program, and adjusted for age and hysterectomy prevalence. **Results:** After declining from 1992 to 2004, the proportion of women reporting no pap smear for ≥5 years increased from 2004 to 2014 among women age ≥65 years and 30-64 years ($p < 0.001$ for both). However, the proportion of women who discontinued screening was greater in those age ≥65 years (10.7 versus 2.7 percentage points from 2004 to 2014, $p < 0.001$). Despite this, women age ≥65 had greater-than-expected declines in the incidence of localized (-2.3% per year, $p = 0.05$) and regional (-3.0% per year, $p = 0.03$) cervical cancer after 2004, compared with 30-64-year-old women. Incidence of distant cancer increased slightly in both groups, but the magnitude of the change did not differ between groups ($p = 0.23$). Cervical cancer mortality rates declined in both groups throughout the study period ($p < 0.001$), and there was no evidence that guideline-related pap-smear discontinuation led to excess mortality among women ≥65 compared to those 30-64 years. **Conclusions:** Compared to women unaffected by the USPTF guidelines, women age ≥65 years had larger declines in the incidence of locally- and regionally-confined cervical cancer, and no difference in the incidence of metastatic cancer. Recommendations to stop pap testing in women age ≥65 did not appear to have led to increased cervical cancer mortality.

1557 Poster Session (Board #128), Sat, 1:15 PM-4:45 PM

Profile of cancer-screening resistant individuals (EDIFICE 6). *First Author: Thibault De La Motte Rouge, Groupe Hospitalier Pitie Salpetriere, Paris, Cedex 13, France*

Background: The efficacy of cancer screening (cost effectiveness, reduced mortality) relies on a minimum threshold uptake rate. Target populations are asymptomatic with only average risk, and thus likely to avoid screening. We studied the characteristics of cancer-screening resistant individuals. **Methods:** The French nationwide observational survey, EDIFICE 6, was conducted online from 26 June-28 July 2017 on a core sample of 12 046 individuals (age 18-69 y). Representativeness was ensured by quota sampling on age, gender, profession, and stratification by geographical area and type of urban district. Multivariate stepwise logistic regression analyses were conducted with a common set of variables to identify factors likely to explain non-uptake of cancer screening. The analysis focused on individuals in the age range of target populations for organized programs: 50-69 y for breast (BC) and colorectal cancer (CRC) (N = 1954 and N = 4300, respectively) and 25-65 y for cervical cancer (CC) (N = 4499). **Results:** Of those who had never taken part in a screening program, 6% (N = 108) were in the target population for BC screening, 12% (N = 539) for CC, and 38% (N = 1625) for CRC screening. Items associated with not undergoing screening included: for BC, the statement "progress is accomplished through clinical research" rated as unimportant (OR = 2.14, 95% CI = [1.16-3.82]); social vulnerability (OR = 2.09, [1.36-3.25]); rating BC prevention programs as ineffective (OR = 1.60, [1.01-2.51]). For CC: living alone (OR = 2.31, [1.89-2.82]); manual worker (OR = 1.95, [1.21-3.05]); social vulnerability (OR = 1.83, [1.49-2.26]). For CRC: self-employed (OR = 1.83, [1.24-2.71]); rating CRC prevention programs as ineffective (OR = 1.76, [1.48-2.08]); current smoker (OR = 1.45, [1.25-1.68]); manual worker (OR = 1.40, [1.05-1.87]). **Conclusions:** Mistrust in clinical research—possibly linked to medical skepticism—and social vulnerability play major roles in resistance to BC screening. A disadvantaged socioeconomic profile has a negative impact on CC screening uptake and yet is an acknowledged risk factor for the disease. Self-employed people who mistrust cancer prevention are resistant to CRC screening. Our findings highlight the need for tailored education campaigns.

1558 Poster Session (Board #129), Sat, 1:15 PM-4:45 PM

A health system experience with an electronic medical record based application to increase lung cancer screening. *First Author: Brandon Weckbaugh, UMKC School of Medicine, Kansas City, MO*

Background: Screening high risk patients for lung cancer with Low Dose Computed Tomography (LDCT) reduces lung cancer-specific mortality, however its adoption in routine clinical care has been limited. We designed an Electronic Medical Record (EMR) based application to identify patients for screening in the primary care setting. **Methods:** A two-step screening application was created to identify patients meeting CMS criteria for LDCT screening in a visit to a primary care provider (PCP). First, the application directs medical assistants to complete a patient's smoking history. If the patient meets eligibility for LDCT screening, step-by-step direction for PCPs to complete the screening process, including reviewing smoking history, shared decision making and ordering the LDCT scan, is initiated. We compared the number of referrals for screening LDCT in the 12-month periods before and after implementation of the screening application. **Results:** During the 12-month period prior to implementation of the screening application in a 18-person PCP group, there were a total of 198 referrals for LDCT screening. Of these, 162 (81.8%) were negative (CAT 1 and 2), 20 (10.1%) required follow up CT (CAT 3), 16 (8.1%) were positive (CAT 4), 3 (1.5%) required an invasive diagnostic procedure (bronchoscopy with biopsy, endobronchial ultrasound, CT guided biopsy, thoracic surgery). Cancer was diagnosed in 2 patients (1.0%), both of whom received cancer treatment. In the 12 months after implementation, referrals increased by 40% to 278. Of these, 241 (86.7%) were negative, 19 (6.8%) required follow up CT, 18 (6.5%) were positive, 4 (1.4%) required an invasive diagnostic procedure, and 3 (1.1%) were diagnosed with cancer and are receiving treatment. Major challenges include variable user compliance in completing accurate smoking history and providers ignoring alerts to initiate lung cancer screening. **Conclusions:** To our knowledge this is the first report on the use of an EMR based application to identify patients at risk for lung cancer. Implementation of the EMR based application correlated with an increase in referrals for LDCT screening and led to the identification of high risk lung lesions including lung cancer.

1559 Poster Session (Board #130), Sat, 1:15 PM-4:45 PM

Attributable failure and costs associated with continued smoking by cancer patients. *First Author: Graham W. Warren, Medical University of South Carolina, Charleston, SC*

Background: Smoking by cancer patients causes adverse outcomes including increased cancer specific mortality, but there are no estimates of the effects of continued smoking in cancer patients on costs of continued medical care for cancer. **Methods:** Attributable failure (AF) was modeled across expected first-line cancer treatment failure in non-smoking patients (ns-FLF), prevalence of current smoking, risk for escalated first-line cancer treatment failure caused by smoking, and cost of subsequent treatment after failure of first-line cancer treatment. **Results:** As smoking prevalence increases, AF increases with peak AF in cancer treatment conditions where ns-FLF ranged from 30-50%. In disease sites with 90% ns-FLF, the AF caused by smoking was lower than in patients with 10% ns-FLF, supporting a more significant effect of continued smoking in patients with higher expected cure rates. Using a conservative 60% increased risk of treatment failure caused by smoking across all cancer patients and cancer treatments published from median cancer related mortality estimates of risk from the 2014 Surgeon General's Report, the conditions of 20% smoking prevalence and 30% ns-FLF resulted in 10.7 AF per 100 smoking patients. Cost per smoking patient per $100,000 incremental cost of ns-FLF cancer treatment was $10,675, Extending results to 1.6 million cancer patients, treatment of AF due to continued smoking by cancer patients cost $3.4 billion for every $100,000 increment of cost of cancer treatment per AF. **Conclusions:** Treatment of AF caused by continued smoking in cancer patients results in significant costs. Because estimates did not include costs associated with medical care not related to cancer progression, results are expected to underestimate the true costs of medical care caused by smoking in cancer patients.

1560 Poster Session (Board #131), Sat, 1:15 PM-4:45 PM

Overweight and breast cancer risk in the International Breast Cancer Intervention studies I and II. *First Author: Samuel G Smith, University of Leeds, Leeds, United Kingdom*

Background: Overweight increases breast cancer risk in population risk postmenopausal women. Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 and P2 chemoprevention trials indicate premenopausal overweight, but not postmenopausal overweight, increases breast cancer risk in high risk women. We estimated the relationship between overweight and breast cancer risk in the International Breast Cancer Intervention Studies (IBIS) I and II. **Methods:** The IBIS prevention trials compared tamoxifen (IBIS-I) and anastrozole (IBIS-II) vs. placebo in women at increased risk of breast cancer. Baseline body mass index (BMI) was calculated for premenopausal (n = 3138) and postmenopausal (n = 3733) women in IBIS-I and postmenopausal women in IBIS-II (n = 3783). BMI change ($<$ 5%, 5-9.9%, $>$ 10%) was available for 2504 IBIS-I women. There were 542 (IBIS-I) and 168 (IBIS-II) invasive breast cancer events and median follow-up was 19.6 years (IQR 17.8–21.1) and 9.3 years (IQR 7.2–11.4), respectively. We used Cox proportional hazards regression to calculate Hazard Ratios (HRs) for invasive breast cancer risk after adjusting for previous trial participation (IBIS-II only), age, diabetes, hormone therapy use, smoking and menopausal status (IBIS-I only). **Results:** Higher BMI was associated with increased invasive breast cancer risk in IBIS-I (HR = 1.02, 95% CI = 1.00-1.03, p = 0.044) and IBIS-II (HR = 1.06, 95% CI = 1.03-1.09, $p < 0.001$). In IBIS-I, the association between BMI and breast cancer risk was restricted to postmenopausal women (HR = 1.03, 95% CI = 1.01-1.05, p = 0.004). Among IBIS-I postmenopausal women, compared with healthy weight, HRs were 1.20 (95% CI = 0.92-1.56) for overweight and 1.29 (95% CI = 0.97-1.72) for obese women. In IBIS-II HRs were 1.15 (95% CI = 0.75-1.75) for overweight and 1.90 (95% CI = 1.27-2.84) for obese women. There was no interaction between BMI and treatment group in either trial. Weight gain did not affect breast cancer risk. **Conclusions:** Contrary to NSABP P1 and P2 data, we found no evidence for increased breast cancer risk among overweight premenopausal women. IBIS-I and IBIS-II data suggest higher BMI increases breast cancer risk in postmenopausal women with elevated breast cancer risk. Clinical trial information: ISRCTN91879928 and ISRCTN31488319.

1561 Poster Session (Board #132), Sat, 1:15 PM-4:45 PM

Smoking cessation after a cancer diagnosis and survival in cancer patients. *First Author: Graham W. Warren, Medical University of South Carolina, Charleston, SC*

Background: Extensive literature confirms that continued smoking by cancer patients and survivors increases overall mortality, but the benefits of smoking cessation specifically after a cancer diagnosis has not been well described. **Methods:** Comprehensive evaluation of all Pubmed studies identified using "smoking" and "cancer" published since 2000 was performed to identify all studies with at least 100 patients reporting on the effects of smoking cessation after a cancer diagnosis on overall mortality. Studies that evaluated the exclusive or combined effects of smoking cessation before a cancer diagnosis were not included. **Results:** Ten (10) studies were identified that met all inclusion criteria including 7 prospective and 3 retrospective studies. The effects of smoking cessation were evaluated for lung cancer patients in 4 studies, head/neck cancer patients in 3 studies, breast cancer patients in 1 study, and multiple cancers in 2 studies. In 3 prospective studies, continued smoking increased risk of overall mortality as compared with never smoking and quitting smoking had an intermediate risk between continued smoking and never smoking. In 7 studies comparing smoking cessation with continued smoking, the median risk of overall mortality in patients who quit smoking was 0.55 (range 0.19-0.92) as compared with continued smoking including 6 of 7 studies with statistically significant reductions in overall mortality risk. Only 1 study reported on overall mortality in cancer patients who were actively enrolled in a smoking cessation program after a cancer diagnosis, and quitting smoking was observed to reduce overall mortality by 44% (HR 0.56, 95% CI 0.36-0.89). **Conclusions:** Of larger contemporary studies evaluating the effects of smoking cessation after a cancer diagnosis on overall mortality, most demonstrate a significant benefit of quitting smoking.

1562 Poster Session (Board #133), Sat, 1:15 PM-4:45 PM

Community based lung cancer screening program: Evaluation of the initial lung cancer screening CT scan. *First Author: Tripurari Mishra, Advocate Lutheran General Hospital, Park Ridge, IL*

Background: Low-dose chest CT for lung cancer screening has shown to have a significant impact on the early diagnosis of lung cancer. In the initial trials, approximately a 20% decrease in lung cancer mortality was found. Patients enrolled in a community-based lung cancer screening program initiated in March 2013 at Lutheran General Hospital and Illinois Masonic Hospital were evaluated for initial outcomes. **Methods:** All patients who completed an initial consultation in oncology clinic from March 2013-June 2017 were included in the analysis. Eligibility criteria for the program included patients within the age range of 55-77, with a $>$ 30 pack year history, and that were current smokers or quit tobacco less than 15 years ago. Individuals between 50-55 years old were also included if they had $>$ 20 pack year smoking history and at least one additional risk factor. All patients with significant abnormalities were discussed at a multidisciplinary conference prior to embarking on any invasive procedures. Also, they underwent a low-dose chest CT for lung cancer screening and were subsequently seen in consultation by a thoracic surgeon. All patient data was entered into a REDCap database and subsequently evaluated. **Results:** 392 patients were enrolled during the study timeframe. Majority of the patients were caucasian (88%) and male (60%). They were referred by their primary physician (95%). The average age of the sample was 64 years ($\pm$6.6). 211 (53.8%) patients were found to have pulmonary nodules. A total of 506 pulmonary nodules were found with an average size of 4.9 ($\pm$ 4.3) mm. Of the 392 patients who underwent lung cancer screening, a total of 11 lung cancers were found (2.8%). Of the 11 patients, 6 (55%) patients were Stage I, 1 (9%) patient was Stage II, 2 (18%) patients were Stage III, and 1 (9%) patient was Stage IV. There was also 1 (9%) patient with limited stage small cell carcinoma. **Conclusions:** Of the 11 cancer patients identified, 64% presented with early stage lung cancer on initial lung cancer screening. In fact, 55% of the patients presented with Stage I lung cancer. These data suggest that lung cancer screening is a viable tool in discovering early stage lung cancer with the potential to improve lung cancer survival.

1563 Poster Session (Board #134), Sat, 1:15 PM-4:45 PM

Herpes zoster vaccine and varicella zoster virus infection among cancer patients having chemotherapy. *First Author: Lisa Y. Law, Kaiser Permanente, Davis, CA*

Background: Varicella zoster virus (VZV) infection is an opportunistic infection among immunocompromised patients. The herpes zoster (HZ) vaccine is a live vaccine not approved for administration to oncology patients receiving chemotherapy. We aimed to assess the association between HZ vaccine given prior to cancer diagnosis and VZV infection in this population. **Methods:** In this retrospective cohort study conducted in Kaiser Permanente Northern California (KPNC) we assessed the association between prior HZ vaccination and VZV infection in cancer patients age 60-89 years having chemotherapy January 1, 2010-December 31, 2014. Subjects were followed until death, loss of membership, or end of study (December 31, 2016). Multivariable analyses were performed using adjusted relative risk models. Variables controlled for included age, sex, hematological vs. non-hematological cancers, high dose steroid therapy, prior immunomodulation therapy, and antiviral prophylaxis. Subanalyses were performed for subjects with and without hematological cancers. **Results:** Our study consisted of 13,069 subjects having cancer and chemotherapy; of these 5090 (39.9%) had prior administration of the HZ vaccine. Median follow-up time was 26.0 months (IQR: 10.6-42.9). Of vaccinated subjects 198 (3.9%) developed VZV infection compared to 410 (5.1%) of unvaccinated subjects (Adjusted Relative Risk [ARR] 0.73, 95% CI 0.62-0.86). Hematological cancers were associated with VZV infection (referent: other cancers, ARR 2.76, 95% CI 2.32-3.29); antiviral prophylaxis was not (ARR 1.00, 95% CI 0.72-1.40). In subanalyses the HZ vaccine was more protective against VZV infection in subjects with hematological cancers (ARR 0.62, 95% CI 0.47 – 0.83) than in those with other cancers (ARR 0.81, 95% 0.66-0.99). There were 7965 deaths (60.9%) during follow-up. The HZ vaccine was protective against all-cause mortality in all subjects (ARR 0.76, 95% 0.74-0.79). **Conclusions:** The live HZ vaccine is protective against VZV infection in oncology patients receiving chemotherapy; this effect is greater in subjects having hematological cancers. The vaccine is also associated with decreased all-cause mortality.

1564 Poster Session (Board #135), Sat, 1:15 PM-4:45 PM

Occupational exposure to pesticides and prognosis of diffuse large B-cell lymphoma: A cohort study. *First Author: Sylvain Lamure, Department of Clinical Hematology, Montpellier University Hospital, Montpellier, France*

Background: Professional use of pesticides is a risk factor for non-Hodgkin lymphoma. The main biological mechanisms of both pesticides and chemotherapy are genotoxicity and reactive oxygen species generation. Cellular adaptation among patients exposed to low doses of genotoxic and oxidative compounds may hinder chemotherapy efficiency in lymphoma patients. We aim to determine the influence of occupational exposure to pesticides on response to immuno-chemotherapy and survival of patients treated for Diffuse Large B Cell Lymphoma (DLBCL). **Methods:** The ProLyPhy study is a retrospective cohort of patients treated between 2010 and mid-2015, for DLBCL, with a least 2-year follow-up. The study took place in 6 hospitals of central southern France. We screened 404 patients with newly-diagnosed DLBCL treated with anthracycline-based immuno-chemotherapy (R-CHOP like). Occupational history was reconstructed for 244 patients. Occupational data were analysed with the Pestipop French job-exposure matrix to determine probability of occupational exposure to pesticides. We have compared treatment failure rate, 2-year event-free survival (EFS) and overall survival (OS) between exposed and non-exposed patients, after adjustment. **Results:** Mean age was 61.3 years (range 19-90), 62.7% of patients were male, 67 had occupational exposure to pesticides, of which 38 from farming activities. Occupational exposure did not impact clinical and biological characteristics at diagnostic. We observed that exposed patients had significantly higher treatment failure rate: 22.4% versus 11.3% ($p = 0.027$), OR = 3.2 (1.8-11.5, $p = 0.007$); this difference was higher among farmers: 31.4% CR versus 12.8%, $p = 0.005$, OR = 4.6 (1.8-11.5, $p = 0.001$). Two-year EFS was 70% in the occupationally-exposed group versus 82%, HR = 2.1 (CI 95% 1.2-3.6, $p = 0.008$). Among farmers, the difference was more pronounced: 2-year EFS was 56% versus 83%, HR = 3.1 (CI 95% 1.7-5.6, $p < 0.001$). Similarly 2-year OS was lower in the farmer group: 81% versus 92%, HR = 3.9 (CI 95% 1.5-10.0, $p = 0.005$). **Conclusions:** This retrospective study suggests that agricultural occupational exposure to pesticides is an independent risk factor for treatment failure, EFS and OS in DLBCL.

1565 Poster Session (Board #136), Sat, 1:15 PM-4:45 PM

Risk of second malignancies in breast cancer patients who received chemotherapy: A SEER analysis. *First Author: Snigdha Nutalapati, Morehouse School of Medicine, Atlanta, GA*

Background: Chemotherapy agents used in breast cancer have carcinogenic potential and can cause malignancies. Patients with breast cancer could also be at risk for a second malignancy as well. We aimed at determining the risk of after adjuvant chemotherapy for breast cancer. **Methods:** We did an observational study of women who received a diagnosis of breast cancer from 1990 to 2009 using Surveillance, Epidemiology, and End Results (SEER) registries database 9 registries. Second malignancy(SM) was defined as any malignancy diagnosed 6 months after initial diagnosis of breast cancer (includes both chemotherapy-related malignancies and second primary malignancies). hormone receptor (HR) status into estrogen receptor (ER) and progesterone receptor (PR), positive (+) and negative (-). Standardized incidence ratios(SIR) were calculated based on United States population in 2000. p-value of < 0.05 is considered statistically significant. **Results:** Total of 245,235 cases (2,409,502 person-years) were identified, 36.3% received chemotherapy. 66.2% were ER+PR+, 11.9% were ER+PR-, 2.5% ER-PR+ and 19.5% were ER-PR-. Median follow up was 11.3 years (range 1-22.9 years), 36,005 (14.7%) cases eventually developed SM. In patients who received radiotherapy (RT), risk of developing SM was increased by 43% (SIR 1.43 [95%CI 1.39-1.46] in those who received chemotherapy (CT) compared to only 22% (SIR 1.22 [95%CI 1.20-1.24]) in those who did not receive chemotherapy (non-CT). In patients who were not treated with radiotherapy, those who got chemotherapy (CT) had an increased risk of developing SM: SIR 1.27 [95%CI 1.23-1.31]. Breast cancers represented 37% of all SM followed by digestive system (16.6%), uterine (14.3%), bronchopulmonary (12.7%), colorectal (9.4%), urinary system (4.6%), lymphoma (3.4%) and ovarian cancers (3.0%). Acute myeloid leukemia (AML) and salivary gland tumors represented only 1.3% and 0.3% of all SM. **Conclusions:** Risk of secondary malignancies, which includes second primary cancers is significantly higher for cases that received chemotherapy and the risk is increased irrespective of radiation status. Radiation therapy increases the risk for secondary malignancies.

1566 Poster Session (Board #137), Sat, 1:15 PM-4:45 PM

Impact of prophylactic bilateral salpingo-oophorectomy on bone health in *BRCA* mutation carriers: A prospective cohort study. *First Author: Elizabeth Hall, Women's College Research Institute, Toronto, ON, Canada*

Background: Women who inherit a deleterious mutation in *BRCA1* or *BRCA2* face a high lifetime risk of ovarian cancer. Prophylactic bilateral-salpingo oophorectomy (PBSO) is recommended prior to natural menopause; however, the impact of abrupt hormonal withdrawal on bone health in this high-risk population is not known. We conducted a longitudinal study to evaluate the impact of PBSO on bone mineral density (BMD) in *BRCA* mutation carriers. **Methods:** The study population included women who underwent PBSO at the University Health Network (Toronto, Canada) between January 2000 and May 2013. Eligibility criteria included having a *BRCA* mutation, at least one ovary prior to surgery, and no personal cancer history other than breast cancer. Information regarding medical history, medication use, and lifestyle factors was collected via questionnaire. BMD measurements using dual x-ray absorptiometry were collected at baseline (prior to surgery) and follow-up. The % change in BMD from baseline to follow-up was calculated for the lumbar spine, femoral neck, and total hip. **Results:** A total of 103 women had baseline and follow-up BMD measurements available. Mean age at PBSO was 49 years (range 37-52). Mean time to first follow-up was 2.04 years (range 0.98-4.74). Among women premenopausal at the time of surgery ($n = 58$), there was a significant change in BMD from baseline to first follow-up in the lumbar spine (-5.32%; 95% CI -7.17 to -3.48), femoral neck (-2.94%; 95% CI, -4.62 to -1.26), and total hip (-2.75%; 95% CI, -3.82 to -1.68) respectively. Among the women who were postmenopausal at the time of surgery ($n = 45$), there was a significant change in BMD across the lumbar spine (-2.41%; 95% CI, -4.41 to -0.41), and femoral neck (-2.73%; 95% CI, -4.86 to -0.60), but not for total hip (-0.78%; 95% CI, -2.40 to 0.85). **Conclusions:** These preliminary findings suggest significant post-operative bone loss, particularly among women who were premenopausal prior to PBSO. Targeted interventions as well as routine BMD measurements may be needed to improve management of bone health in this population. Additional analyses evaluating the impact of supplement use, body mass index, as well as hormone replacement therapy are underway.

1567 Poster Session (Board #138), Sat, 1:15 PM-4:45 PM

Comparing the prevalence of non-AIDS defining cancers by HIV status in the Ohio Medicaid population. *First Author: Siran M. Koroukian, Case Western Reserve Univ, Cleveland, OH*

Background: Persons living with human immunodeficiency virus (PLWHV) are over-represented in low income and minority populations. This makes Medicaid data particularly relevant for evaluating cancer care needs and outcomes among PLWHV. As a first step, we compare the prevalence of non-AIDS defining cancers (NADCs) between PLWHV and their non-HIV counterparts, hypothesizing that, adjusting for age, race, and sex, PLWHV are more likely than others to have been diagnosed with NADCs. **Methods:** This is a cross-sectional of Medicaid beneficiaries 18-64 years of age, using the 2012 Ohio Medicaid Analytic eXtract (MAX) file. Demographics included age, race (White, Black, and Other), and sex (male, female). We identified HIV status, as well as cancer for the different anatomic sites based on ICD-9 diagnosis codes documented in inpatient and outpatient claims data. We conducted descriptive analysis, and multivariable logistic regression analysis to evaluate the association between HIV status and NADCs after adjusting for age, race and sex. Given that a large percentage of Medicaid beneficiaries are enrolled in Medicaid for only part of the year, we also adjusted for the length of enrollment in Medicaid in our multivariable analysis. **Results:** Our study population included 1,061,471 individuals; 0.28% were PLWHV. Men and Blacks represented 55.2% and 58.9% of PLWHV, respectively, compared with 35.7% and 28.5% of their non-HIV counterparts. Adjusting for age, race, and sex, the two NADCs with which PLWHV were significantly more likely to have been diagnosed were rectal cancer (adjusted odds ratio: 4.03 (95% confidence interval: 2.31 - 7.03)), and anal cancer (34.19 (21.82-53.57)). **Conclusions:** For some cancers, the burden is significantly higher in PLWHV than among others. The higher prevalence of rectal and anal cancer highlights the importance of cancer prevention through screening and safe sex practice.

1568 Poster Session (Board #139), Sat, 1:15 PM-4:45 PM

Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 2006 to 2016: A systematic analysis for the Global Burden of Disease study. *First Author: Christina Fitzmaurice, University of Washington, Institute for Health Metrics and Evaluation, Division of Hematology, Seattle, WA*

Background: Increasing burden due to cancer poses a threat to human development, which has resulted in global political commitments reflected in the Sustainable Development Goals as well as the WHO Global Action Plan on NCDs. To determine if these commitments have resulted in improved cancer control, quantitative assessments of the cancer burden are required. In the Global Burden of Disease (GBD) study 2016 we assessed the cancer burden for 29 cancer groups in order to provide a framework for policy discussion, resource allocation, and research focus. **Methods:** Cancer incidence, mortality, years lived with disability, years of life lost, and disability adjusted life years were analyzed for 195 countries from 2006 to 2016 using the GBD estimation methods. Levels and trends were analyzed over time, and by Sociodemographic Index (SDI). Changes in incident cases were decomposed into changes due to the epidemiological versus the demographic transition. **Results:** In 2016, there were 17.2 million cancer cases worldwide and 8.9 million deaths. Incident cases increased by 28% between 2006 and 2016. The smallest increase was seen in high-SDI countries. Aging contributed 17%, population growth 12%, and changes in age-specific rates -1% to this change. The most common cancer globally for men was prostate cancer (1.4 million). The leading cause of cancer deaths and DALYs was tracheal, bronchus, and lung cancer (1.2 million deaths and 25.4 million DALYs). For women, the most common cancer and leading cause of cancer deaths and DALYs was breast cancer (1.7 million cases, 535 000 deaths and 14.9 million DALYs). Between 2006 and 2016, the average annual age-standardized incidence rates for all cancers increased in 154 of 285 countries. The average annual age-standardized death rates for all cancers decreased in 221 of 285 countries. **Conclusions:** Large disparities exist between countries in cancer burden. Scaling up cancer prevention and ensuring universal access to cancer care are required for health equity and to fulfill the global commitments for NCDs and cancer control.

1569 Poster Session (Board #140), Sat, 1:15 PM-4:45 PM

Milk intake and mammographic density in premenopausal women. *First Author: Yunan Han, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO*

Background: Mammographic density (MD), which reflects the amount of epithelial and stromal tissues in relation to adipose tissue in the breast, is a strong risk factor for breast cancer. Although diet is associated with breast cancer risk, studies evaluating the associations of adult diet with MD have mainly reported null associations. Few studies have, however, investigated the associations of dairy intake with MD, with conflicting results. Therefore, we investigated the associations of milk intake with MD in premenopausal women. **Methods:** We recruited 375 premenopausal women, with no history of cancer, who had routine screening mammography at the Breast Health Center, Washington University in St. Louis in 2016. We used Volpara to measure MD: volumetric percent density (VPD), dense volume (DV) and non-dense volume (NDV). In addition to known breast cancer risk factors, all participants completed a detailed questionnaire on milk intake (skim milk and 1%/2% milk were categorized into 4 groups: $<$ once/week, once/week, 2-6 times/week, $\geq$once/day; whole and soy milk were categorized into 2 groups: $<$ once/week, $\geq$once/week, because fewer women consumed them). We used multivariable linear regression models (adjusted for age, body mass index (BMI), parity, oral contraceptive use, family history of breast cancer, race) to evaluate the associations between milk intake and log transformed VPD, DV and NDV. Beta coefficients (β) were evaluated and back transformed for easier interpretation. **Results:** The mean age was 47.5 years (range: 32-58 years), mean VPD was 9.48%, mean DV was 80.69 cm^3, and mean NDV was 1079 cm^3. Compared with women who drank 1%/2% milk $<$ once/week, VPD was 20% (p-value = 0.003) lower in the once/week group, 14% (p-value = 0.047) lower in the 2-6 times/week group, and 12% (p-value = 0.144) lower in the $\geq$once/day group. NDV was 19% (p-value = 0.039) lower among women who drank soy milk $\geq$once/week compared with women who drank $<$ once/week. There were no associations of skim and whole milk with MD. **Conclusions:** We observed that 1%/2% milk intake was inversely associated with VPD, while soy milk intake was inversely associated with NDV. Further studies on how 1%/2% and soy milk intake impact MD are needed, as this could have implications in breast cancer prevention.

1570 Poster Session (Board #141), Sat, 1:15 PM-4:45 PM

Association between pesticides use and incidence of diffuse large B cell lymphoma (DLBCL). *First Author: Alaa Altahan, University of Tennessee Health Sciences Center, Memphis, TN*

Background: Some studies have linked pesticide exposure to risk of developing cancers. However, these studies were limited to single or few pesticides. We analyze association between incidence of DLBCL and all chemicals reported by The United States Geological Survey (USGS). **Methods:** Using International Classification of Diseases for Oncology (ICDO-3) code 9680, patients (pts) diagnosed with DLBCL in 2012 were extracted from Lymphoma-leukemia dataset from The Surveillance, Epidemiology, and End Results (SEER) database. Pts were grouped by Federal Information Processing Standards (FIPS) code. United States Census data (www.census.gov) was used to obtain population estimates for each FIPS code in 2012. USGS data (www.usgs.gov) was used to extract quantitative pesticides use in the year of 1992 per FIPS code*. Incidence of DLBCL per FIPS code was calculated then matched to USGS data. SPSS software was used for statistical analysis. Association between level of pesticides use and incidence of DLBCL was analyzed using linear regression. Two tailed P value of <0.05 on Pearson correlation was used for statistical significance. **Results:** A total of 2258 pts with DLBCL in 167 counties were identified. Of the 290 chemicals reported by USGS, 65 were excluded due to lack of data. Of the remaining 225, forty showed statistically significant correlation (30 positive and 10 negative) with incidence of DLBCL. Of these chemicals, 8 have moderate or strong correlation with R coefficient $>$ 0.4 (table). **Conclusions:** Some agriculture chemicals have significant correlation with incidence of DLBCL. This warrants further evaluation of these chemicals as potential carcinogens or protective agents. Analysis of the underlying mechanisms may reveal some common mechanisms.

Chemical	R coeff	P - value	Median	Range	N**
BARIUM POLYSULFIDE	0.997	0.049	8.3	3.1-12.2	3
PEBULATE	0.67	0.003	16.7	0.2-188.8	17
FERBAM	0.655	0.011	87.9	0.5-891.9	14
CHLORETHOXYFOS	0.478	0.038	201.4	114.2-451.1	19
MSMA	0.441	0.010	70.2	0.4-241.2	33
MONOCROTOPHOS	-0.616	0.044	0.4	0.2-1.0	11
DICROTOPHOS	-0.558	0.038	11.2	0.1-65.1	14
CHINOMETHIONAT	-0.548	0.043	0.55	0.1-1.3	14

* Data reported by high use estimate ** N is number of counties included in analysis i.e. have data available

1573 Poster Session (Board #144), Sat, 1:15 PM-4:45 PM

The role of adiposity in the association between type 2 diabetes and the risk of breast cancer. *First Author: Maria Bota, University of Strathclyde Institute for Global Public Health at iPRI, Ecully, France*

Background: Studies have shown an increased risk of breast cancer (BC) among women with type 2 diabetes (T2D). This association could be causal, related to hyperglycaemia or hyperinsulinaemia, or could be triggered by other factors such as obesity and physical inactivity which are known risk factors for T2D and for BC in post-menopausal women. **Methods:** A meta-analysis was performed to assess the risk of BC in T2D patients compared to non-diabetic women, with special attention to changes in the risk of BC when the body mass index (BMI) was included in multivariate analyses. Studies were selected if they had a prospective design. Studies that compared BC incidence in T2D women to the incidence in the general population were excluded. Summary relative risks (SRR) and 95% confidence intervals (CI) were computed using random-effects models. **Results:** Eighteen studies were included in the meta-analysis, based on 28,230,143 person-years of follow-up and 320,111 BC cases. Compared to non-diabetic women, the SRR of BC among T2D women was 1.13 (95% CI: 1.04, 1.24). There was a large amount of unexplained heterogeneity of results across studies (I^2 = 95%), but no indication of publication bias. Three studies reported the risk of BC by BMI category, with a consistently higher risk of BC associated with increasing BMI. In the 9 studies that adjusted for adiposity, the SRR decreased to 1.05 (95% CI: 0.97, 1.14) while the heterogeneity of results across studies reduced to I^2 = 21%. Only two studies reported data by menopausal status. In contrast, in the 9 studies that did not adjust for adiposity, the SRR increased to SRR = 1.19 (95% CI: 1.01, 1.39), while the heterogeneity remained high (I^2 = 98%). Five studies reported data for post-menopausal women only, with a SRR of 1.13 (95% CI: 0.89; 1.44) and high heterogeneity (I^2 = 94%) with one study representing 82% of the weight in the meta-analysis. **Conclusions:** This analysis provides evidence for a moderately increased risk of BC in T2D women. The effect of the adjustment for BMI on the SRR and on the heterogeneity suggests that the higher risk of BC among women with T2D may not be due to the diabetes itself but to adiposity. New studies should examine the relationship between BC, T2D and adiposity in premenopausal women.

1574 Poster Session (Board #145), Sat, 1:15 PM-4:45 PM

Nasopharyngeal cancer in Alaska Native people: A cancer health disparity. *First Author: Matthew J. Olnes, Alaska Native Tribal Health Consortium, Anchorage, AK*

Background: Cancer is a leading cause of death in Alaska Native (AN) people. Significant cancer health disparities exist in both incidence and mortality between AN people and the US Whites. Nasopharyngeal cancer (NPC) is the leading cancer disparity among AN people, with an incidence rate 17.3 times higher (2009-2013) and a mortality rate that is 21 times higher (1992-2011) than those in US whites. The etiologic basis for these disparities has not been identified. **Methods:** To better understand this health disparity, we created an Alaska Native NPC patient database derived from the Alaska Native Tumor Registry and Alaska Native Medical Center Tumor Registry to characterize all cases of NPC in AN people over the last forty years. We identified 186 cases of NPC in AN people from 1976 to 2016 by merging electronic data sets from the Alaska Native Medical Center Tumor Registry and the Alaska Native Tumor Registry, and analyzed, baseline demographics, clinical and pathologic features, patterns of care, and treatment outcomes for this disease for which data were available for analysis. **Results:** The median age of AN NPC patients was 60 years, and 68% of patients were male. The regions with the highest numbers of NPC were Anchorage/Mat-Su, followed by Yukon-Kuskokwim and Norton Sound regions of Alaska. The histologic subtype of NPC by World Health Organization category were 55% of tumors type 3, 25% type 1, and 15% type were type 2. Most AN patients with NPC presented at advanced AJCC TNM clinical stages at the time of diagnosis with 2% diagnosed at stage I, 10% at stage II, 9% at stage III, and 43% at stage IV. Patients were treated with chemotherapy (62%), radiation (69%), and combinations of chemotherapy and radiation (58%). Median survival for all patients was 2.5 years (95% Confidence Interval 1.9-3.0). **Conclusions:** This study represents the first characterization of NPC in AN people that includes treatment and clinical outcome data, and it may serve as a useful database to develop treatment guidelines and future translational studies to better understand this cancer health disparity.

1575 Poster Session (Board #146), Sat, 1:15 PM-4:45 PM

Prevalence of HIV infection among cancer patients in a Haitian hospital. *First Author: Joseph Bernard, Université Notre Dame d'Haiti, Faculté de Médecine et des Sciences de la Santé, Port-Au-Prince, Haiti*

Background: Malignancies are nowadays among the main conditions affecting HIV-infected patients. The state of immunosuppression puts these patients at high risk of developing cancer in their lifetime. The objectives of this study were to determine the prevalence of HIV infection among cancer patients and compare the overall mortality rate between the HIV-positive and HIV-negative subpopulations. **Methods:** A two-year retrospective study was conducted in the cancer program of Innovating Health International (IHI). Were included all cancer patients with a known HIV status enrolled from January 1st, 2016 to December 31st, 2017. Date of admission, age, gender, cancer type, cancer stage, antiretroviral therapy status for HIV-infected patients and outcome were the main variables selected for this chart review. HIV infection was tested as a factor associated with mortality. **Results:** Among the 785 cancer patients selected for this study, 398 (50.7%) had a known HIV status. Thirty (7.5%) of them were HIV-infected, among them 19 women and 11 men. The mean age was 45.9 years [25-69] versus 49.5 years [16-87] for the HIV-negative patients (p = 0.15). There were 11 patients with AIDS-defining cancers (ADC) such as invasive cervical cancer (n = 8) and Non-Hodgkin lymphoma (n = 3). 18 patients had Non-AIDS-defining cancers (NADC) such as head and neck cancers (n = 8), among them 3 oral cancers and 3 ocular cancers, breast cancer (n = 4), penile cancer (n = 2), and one case each of Hodgkin's lymphoma, lung cancer, ovarian cancer and pancreatic cancer. 1 patient had a carcinoma of unknown primary (CUP). 22 of these 30 patients (73.3%) were already known HIV-infected before their admission and were on antiretroviral therapy. 75% of the staged patients were at stages III or IV of their cancer. The overall mortality rate was 33.3% [95% CI, 17.3% – 52.8%] versus 20.9% [95% CI, 16.9% – 25.4%] for the HIV-negative patients. HIV-infected cancer patients were more likely to die than HIV-negative ones. (Odds ratio = 1.9, p = 0.11). **Conclusions:** The prevalence of HIV infection among the cancer patients was 7.5% [95% CI, 5.1% - 10.6%], with a predominance of Non-AIDS-defining malignancies. HIV infection was not for this cancer cohort a significant factor associated with mortality.

1576 Poster Session (Board #147), Sat, 1:15 PM-4:45 PM

Non-AIDS defining malignancies among HIV-infected patients in a tertiary referral center in Hong Kong. *First Author: Daisy Wing-san Mak, Queen Elizebeth Hospital, Hong Kong, Hong Kong*

Background: Non-AIDS defining malignancy (NADM) is increasingly recognized as an important cause of death among human immunodeficiency virus (HIV)-infected individuals. This study describes the details and survival trend of NADM in this group of patients in a tertiary center in Hong Kong. **Methods:** We have investigated the occurrence of NADM in a retrospective observational study of 1,523 HIV-infected patients. Baseline demographics, immunological data, the use of highly-active anti-retroviral therapy (HAART), details of malignancy and their treatment were analyzed. Survival was analyzed by Kaplan-Meier and Cox proportional hazards model. **Results:** From November 1993 to March 2013, a total of 41 NADM was diagnosed in 39 HIV-positive patients. Lung cancer, anogenital cancer, head and neck cancer, and hepatocellular carcinoma were the most common malignancies among the NADM. Compared with the 65 patients diagnosed with AIDS-defining malignancy (ADM), patients with NADM were significantly older at cancer diagnosis (age 53 vs. 47, p = 0.01), had a significantly longer duration of HIV infection (94 vs. 2 months, $p < 0.0001$), were more likely to be recipients of HAART (92% of patients with NADM vs. 77% of patients with ADM, p = 0.028), and had a significantly higher CD4 count at cancer diagnosis (257 vs. 76 cells/ul, $p = < 0.0001$). Median survival of patients with NADM was 9 months (95% CI, 4.3-13.8 months), and was not dependent on age, CD4 count at diagnosis of malignancy, and treatment with HAART. **Conclusions:** This retrospective, observational study describes the pattern of NADM in a tertiary institution in Hong Kong. Together with the emerging body of literature on NADM, we have known that the general trend of NADM is rising in HIV-infected population, and the risk of these cancers is much beyond than seen in the general population. Frontline clinicians must recognize that these diseases strike a population at an age which still permits high functional capacity. The oncology community should add to the knowledge of how the immune system interplays with environmental factors and oncogenesis, work towards the goals of reducing the morbidity in these patients, and ultimately, prevent these diseases and revert the mortality.

1577 Poster Session (Board #148), Sat, 1:15 PM-4:45 PM

Prevalence of germline genetic alterations in colorectal cancer patients. *First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Although universal screening of all colorectal tumors for Lynch syndrome (LS) is recommended, the prevalence of other germline mutations, with potential clinical implications, in colorectal cancer (CRC) patients is less well-defined. We performed comprehensive germline testing (GT) in a prospective cohort of CRC patients in order to determine the proportion of clinically actionable germline mutations detected by universal tumor-normal sequencing. **Methods:** Between 11/2015 to 1/2018, 427 unselected CRC patients were prospectively consented to GT in 76-genes associated with cancer susceptibility using an IRB-approved protocol. Prevalence of likely pathogenic and pathogenic genetic alterations (PGAs) were reported and correlated with clinical and somatic findings. **Results:** Of 427 CRC patients, the median age was 52 years (range, 18-88 years), 54% were male. PGAs were present in 55 (13%) of CRC patients including 24 PGAs in high-penetrance (MLH1, MSH2, MSH6, EPCAM, PMS2) and 23 PGAs in moderate-low penetrance (CHEK2, mono-MUTYH, APC I1307K) CRC-associated risk genes. The prevalence of moderate/high PGAs was 12.5% (20/160) versus 6% (17/267) in patients with CRC age $\leq$50 versus age $>$ 50, respectively (p-value = 0.045). LS accounted for 12 (60%) and 5 (30%) of high or moderate mutations in the age $\leq$50 versus age $>$ 50 groups. All LS-associated tumors exhibited concordant tumor findings with high-frequency microsatellite instability, deficient mismatch repair protein expression, or high mutational load. Seventeen (31%) of patients with PGAs did not meet current guidelines for GT. PGAs not traditionally associated with CRC-risk were identified in 14 cases, including 7 high- (4 BRCA2, 1 FLCN, 1 NF1, 1SDHA) and 7 moderate-penetrance (3 BRIP1, 3 ATM, 1 HOXB13) genes. Correlative tumor data, including assessment of somatic mutations and loss of heterozygosity in the gene(s) corresponding to these germline mutations will be presented. **Conclusions:** Although the prevalence of PGAs is higher in patients with young-onset CRC($\leq$ 50), LS accounts for the vast majority of germline mutations in these patients. Analysis of PGAs not traditionally associated with CRC to evaluate for causality versus incidental findings will be performed.

1578 Poster Session (Board #149), Sat, 1:15 PM-4:45 PM

Genetic testing and results in population-based breast cancer patients and ovarian cancer patients. *First Author: Allison W. Kurian, Stanford School of Medicine, Stanford, CA*

Background: Genetic testing for cancer risk has expanded rapidly, with more genes tested. Little is known about test use or pathogenic variant (PV) prevalence among population-based cancer patients. **Methods:** Women aged $\geq$20 years, diagnosed with breast or ovarian cancer in 2013-14 and reported to SEER registries covering the entire populations of Georgia and California, were included. Registry data were linked to clinical genetic testing results, performed from 1/1/2012 through 4/30/2016, by 4 laboratories that did nearly all cancer genetic testing in these states. **Results:** There were 77,085 breast cancer and 6,001 ovarian cancer patients, with almost 30,000 patients of racial groups other than non-Hispanic (NH) White. One-quarter (24.1%) of breast and one-third (30.9%) of ovarian cancer patients had genetic test results. While test use was similar across racial groups for breast cancer, testing in ovarian cancer patients was lower in NH Blacks (21.6%, CI 18.2-25.4%, vs NH Whites: 33.8%, CI 32.3-35.4%). The most prevalent PVs in breast cancer patients were *BRCA1* (3.2%), *BRCA2* (3.1%), *CHEK 2* (1.6%), *PALB2* (1.0%), *ATM* (0.7%), *NBN* (0.3%) and *TP53* (0.3%); and in ovarian cancer patients were *BRCA1* (8.7%), *BRCA2* (5.8%), *CHEK2* (1.4%), *BRIP1* (0.9%), *MSH2* (0.8%), *ATM* (0.6%) and *RAD51C* (0.6%). Racial differences in PVs included *BRCA1* (ovarian cancer: NH Whites, 7.2%, CI 5.9-8.8%; Hispanics, 16.1%, CI 11.8-21.2%) and *CHEK2* (breast cancer: NH Whites, 2.3%, CI 1.8-2.8%; NH Blacks, 0.2%, CI 0-0.8%). Among those tested for all genes designated by the National Comprehensive Cancer Network as associated with their cancer type (breast: *ATM, BRCA1, BRCA2, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, STK11, TP53*; ovarian: *BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PMS2, STK11, RAD51C, RAD51D*), 7.7% of breast and 14.5% of ovarian cancer patients had a PV. **Conclusions:** Clinically tested, population-based breast cancer patients and ovarian cancer patients had 8-15% PV prevalence in guideline-designated cancer risk genes. *CHEK2* and *ATM* PVs were relatively prevalent in ovarian cancer patients: this merits further study because *CHEK2* and *ATM* are not known to be ovarian cancer risk genes. Racial testing disparities are targets for improvement.

1579 Poster Session (Board #150), Sat, 1:15 PM-4:45 PM

Impact of pre-surgical germline multigene panel testing on choice of surgery for breast cancer. *First Author: Elena Zarcaro, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Knowledge of hereditary risk-associated mutations may impact primary surgical decision-making for breast cancer(BC) patients (pts). Since 2015, all new pts seen in the Massachusetts General Hospital (MGH) multidisciplinary BC clinic have been screened by genetic counselors (GCs) for rapid GC consultation and multigene panel testing. We sought to determine the impact of pre-surgical BC multigene panel testing on the timing and type of surgery. **Methods:** All pts screened and tested by the MGH GCs from July, 2016 through December, 2017 were identified, and only those who had surgery at MGH were included. Pts may have had genetic testing prior to initial visit at our institution. Screening criteria for rapid GC consultation included personal or family history of BC with the following features: age $<$ 45, triple negative age $<$ 60, male, bilateral, Ashkenazi Jewish descent, or ovarian ca. Surgical and genetic testing outcomes were collected by retrospective chart review and Fishers exact test was used for statistical analysis. **Results:** During our study period, 1341 eligible pts were screened in the MGH multidisciplinary BC clinic. Of 628 pts who met genetic testing criteria, 588 (93.6%) were tested and 50 (8.5%) were positive for a germline mutation including 16 BRCA1, 10 BRCA2, 8 ATM, 8 CHEK2, 5 PALB2 and 1 each of TP53, BRIP1, and RAD51C. In 24 pts with BRCA1/2 mutations who had genetic results prior to surgery, 21 (87.5%) had upfront bilateral mastectomies (BM). In 21 pts who tested positive for other germline mutations before surgery, 14 (66%) had upfront BM. In a cohort of 120 pts with negative test results before surgery, only 37 (30.8%) had up front BM ($p < .05$ compared to BRCA1/2 and other germline mutations). **Conclusions:** Screening newly diagnosed BC pts for rapid GC consultation and testing prior to surgery successfully identified pts with germline mutations in our population. Pts with BRCA1/2 mutations had a higher rate of BM than gene-negative pts and pts with other germline mutations also had a higher rate of BM. Further studies should explore factors influencing pre-operative decision-making in the context of non-BRCA1/2 germline mutations to assess concordance with guideline recommendations.

1580 Poster Session (Board #151), Sat, 1:15 PM-4:45 PM

Mosaic *TP53* pathogenic variants on multi-gene hereditary cancer panel testing: Clinical characteristics and follow-up testing. *First Author: Sarah A. Jackson, GeneDx, Inc., Gaithersburg, MD*

Background: Li-Fraumeni Syndrome (LFS) is an autosomal dominant cancer susceptibility syndrome due to germline pathogenic variants in *TP53* and is associated with a significant risk for sarcomas, female breast, and other cancers. A subset of individuals undergoing germline *TP53* analysis will have a variant with an allele fraction (AF) less than that in heterozygous individuals, consistent with mosaicism. *TP53* mosaicism may be limited to hematopoietic cells, such as in age-related hematopoietic expansion, or may be constitutional, in which case the variant exists in additional tissues and may increase LFS-associated cancer risks. This study aims to characterize the clinical characteristics and follow-up results of cases with a *TP53* mosaic pathogenic or likely pathogenic variant (PV). **Methods:** We performed a retrospective review of all individuals undergoing multi-gene hereditary cancer panel testing at our diagnostic laboratory. Cases included those with mosaicism for one or more *TP53* PV, characterized as an AF of $<$ 35.0% on next-generation sequencing (NGS) on a blood or oral rinse specimen. Data were analyzed utilizing descriptive statistics and hypothesis tests, including Fisher s exact test. **Results:** We identified 117 *TP53* mosaic PV cases. Among 37 cases that had one or more relatives undergo testing for the mosaic PV, no relatives were positive. Among 21 cases that underwent subsequent fibroblast (FB) testing, 19.0% (4/21) correlated with the initial mosaic result, suggesting constitutional mosaicism. Of those that confirmed on FB, the mean AF for the original sample was 28.3% (n = 4; SD = 3.2%), whereas the mean for those negative on FB was 18.5% (n = 17; SD = 6.3%). Confirmation of mosaicism on FB was associated with an initial NGS AF $\geq$25.0% (p = 0.0276; FB Pos: 3/4, FB Neg: 2/17) and with a personal history of a breast cancer or sarcoma diagnosed $<$ 46 years (p = 0.0276; FB Pos: 3/4, FB Neg: 2/17). **Conclusions:** Although NGS is not purely quantitative, apparent constitutional mosaicism appears to correlate with higher AF on NGS. In addition, phenotypes of cases with *TP53* mosaicism confirmed via FB are more suggestive of LFS. Further studies are required to establish clinical correlation.

1581 Poster Session (Board #152), Sat, 1:15 PM-4:45 PM

Promoting breast cancer screening after multiplex genetic panel testing (MGPT) and genetic counseling. *First Author: Gregory Idos, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Cancer screening guidelines recommend that germline carriers with a pathogenic variant (PV) in a breast cancer susceptibility gene undergo more intensive breast screening including breast magnetic resonance imaging (MRI). We assessed the impact of genetic counseling and MGPT on adherence to recommended screening. **Methods:** In a prospective cohort study of 2000 patients undergoing MGPT, patients completed self-adminstered questionnaires to document breast cancer screening within one year of testing. Patients were surveyed at 3, 6, and 12 months after genetic results disclosure. Multivariable logistic regression was used to analyze an association between MGPT result and breast MRI after adjusting for study center, personal history of breast cancer and personal history of breast surgery. **Results:** 2000 patients completed MGPT and 1532 (77%) completed at least one follow-up survey. 242 (12%) tested positive for at least 1 PV in any one of 25 (or 28) genes. MGPT identified a PV in the following increased risk breast cancer genes: *BRCA1* (n = 41), *BRCA2* (n = 36), *CHEK2* (n = 17), *ATM* (n = 16), *NBN* (n = 2), *PALB2* (n = 9), *TP53* (n = 6), and CDH1 (n = 1). Within 1 year, patients with a PV (OR = 2.1 95% CI [1.45-3.15], $p < 0.001$) were more likely to undergo MRI versus those testing negative. Patients with a PV in *BRCA1/2* (OR = 3.5 95% CI [1.96-6.33], $p < 0.001$) or a moderate risk breast cancer gene (CHEK2, ATM, NBN) (OR = 3.3 95% CI [1.30-8.15], p = 0.012) were three times more likely to have MRI versus those testing negative. Patients with a PV in other high risk breast cancer genes (*PALB2*, *TP53*, or *CDH1*) were three times more likely to undergo MRI (OR = 3.5 95%CI [0.76-15.97], p = 0.107) versus those testing negative, but the results did not reach statistical significance. There was no difference in Breast MRI (OR = 1.0 95%CI [0.78-1.37], P = 0.814) use among those with a variant of uncertain significance (VUS) versus those with negative results. **Conclusions:** MGPT and genetic counseling prompted patients with a *BRCA1/2* PV to appropriate adoption and adherence to breast cancer screening. There was no difference in screening between those with VUS or negative results. Clinical trial information: NCT 02324062.

1582 Poster Session (Board #153), Sat, 1:15 PM-4:45 PM

Promoting colorectal cancer (CRC) screening after multiplex genetic testing and genetic counseling. *First Author: Gregory Idos, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Cancer screening guidelines recommend that germline carriers with a pathogenic variant (PV) in a CRC susceptibility gene should undergo more frequent colonoscopy screening. We assessed the impact of genetic counseling and multiplex genetic panel testing (MGPT) on adherence to colonoscopy screening. **Methods:** In a prospective cohort study of 2000 patients undergoing MGPT, patients completed-self-adminstered questionnaires to document colon cancer screening within one year of testing. Patients were surveyed at 3, 6, and 12 months after genetic results disclosure. Multivariable logistic regression was used to analyze an association between MGPT result and colonoscopy after adjusting for study center, personal history of colorectal cancer and personal history of colorectal surgery. **Results:** 2000 patients completed MGPT and 1622 (81%) completed at least one follow-up survey. 242 (12%) tested positive for at least 1 PV in any one of 25 (or 28) genes. High risk CRC gene mutations were in *PMS2* (n = 11), *MLH1* (n = 10), *MSH2* (n = 10), *MSH6* (n = 8), *EPCAM* (n = 1), *TP53* (n = 6), Biallelic *MUTYH* (n = 2), *APC* (N = 3). Moderate risk CRC mutations were in monoallelic *MUTYH* (n = 41), *CHEK2* (n = 17), and *APC* I1307K (n = 16). Within 1 year of testing, patients with a PV were twice more likely (OR = 2.0, 95% CI [1.33, 2.92], $p < 0.001$) and patients with a VUS were as likely (OR = 1.2, 95% CI [0.86, 1.62], p = 0.312) to have a colonoscopy as compared to patients with a negative test result. Patients identified to carry a PV in a mismatch repair gene were 4x (OR = 3.6 95% CI [1.66-7.91], p = 0.001) or a PV in *APC,* Biallelic *MUTYH, or TP53* were 10x (OR = 10.1, 95% CI [1.80-57.29], p = 0.009) more likely to undergo colonoscopy. Those with a mutation in a moderate risk gene were 3x (OR = 3.3, 95% CI [1.79-5.95], $p < 0.001$) more likely to undergo colonoscopy. **Conclusions:** MGPT and genetic counseling prompted patients with a PV in a high risk CRC gene to appropriate adoption and adherence to screening colonoscopy. In contrast, there was no difference in colonoscopy screening among those with a VUS or negative results. These findings demonstrate genetic testing and counseling can encourage appropriate CRC screening. Clinical trial information: NCT 02324062.

1583 Poster Session (Board #154), Sat, 1:15 PM-4:45 PM

Examining patients' medical and psychosocial experiences following detection of a *CDH1* variant with multiplex genetic testing. *First Author: Jada Hamilton, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Germline *CDH1* mutations are associated with hereditary diffuse gastric cancer and lobular breast cancer. We conducted a cross-sectional, self-report survey to understand genetic testing experiences, medical management, and psychosocial adaptation among patients with a *CDH1* variant. **Methods:** We recruited participants from the Prospective Registry of Multiplex Testing (PROMPT), an online genetic registry. We invited individuals with a *CDH1* variant to complete a survey of validated and investigator-designed items. We computed descriptive statistics, and used *t* tests and chi-square tests to compare responses of individuals with pathogenic variants (PV) or variants of uncertain significance (VUS). **Results:** Data were available from 55 individuals (96% female, 89% white, 75% college graduate, age 32-78) with a *CDH1* PV (n = 16; 3 with a family history of gastric cancer) or VUS (n = 39; 12 with a family history of gastric cancer). Overall, 82% had received genetic counseling, 73% felt sufficiently informed when they had genetic testing, and participants reported low decisional regret about testing ($M \pm SD$= 12.6±20.1 on 0-100 scale); no differences were observed based on *CDH1* variant type. Those with VUS were less satisfied with healthcare providers' knowledge about their *CDH1* result than were those with PV (p= .02). Those with PV were more likely than those with VUS to have received a recommendation for prophylactic gastrectomy (44% vs 0%, p< .001). Only 2 participants, both with PV, had a prophylactic gastrectomy. Those with VUS had less knowledge about *CDH1* than those with PV (63% vs 93% correct knowledge; p <.001); yet, participants had similar perceptions of cancer risks (ps > .05). Those with PV reported greater testing-related distress (p <.001) and worry about genetic discrimination (p= .05); there were no differences between groups on other emotional outcomes including testing-related uncertainty, positive experiences, or quality of life (ps > .05). **Conclusions:** Many patients reported being well informed and satisfied with their *CDH1* genetic testing decision; yet, patients with VUS and PV each have unique informational and emotional needs warranting additional support.

1584 Poster Session (Board #155), Sat, 1:15 PM-4:45 PM

Impact of germline BRCA identification on subsequent breast cancer stage and therapy: Implications for routine screening. *First Author: Tal Hadar, Shaare Zedek Medical Center, Jerusalem, Israel*

Background: Screening healthy Ashkenazi Jews (AJ) for germline BRCA1/BRCA2 mutations (gBRCA) is not standard policy, despite high (2.5%) carrier rates. Most carriers are identified only after breast cancer diagnosis. We hypothesized that pre-symptomatic knowledge of carrier status would favorably affect breast cancer stage and management. **Methods:** We reviewed records of gBRCA carriers who did not undergo risk-reduction mastectomy and were diagnosed with breast cancer between 4/1996-4/2016. Patient age, parity, family history, genotype, screening compliance, method of breast cancer detection, disease characteristics and treatment (breast and axillary surgery, chemotherapy) were compared between carriers whose gBRCA was identified pre-breast cancer vs. post-breast cancer. **Results:** 165 females with gBRCA and breast cancer were identified, of whom carrier status was determined pre-breast cancer in 45 (27%) and post-breast cancer in 120 (73%); both groups had similar mean age at cancer diagnosis (50.6y vs. 50.5y, range 27-86) and BRCA1:BRCA2 distribution (64%:36% and 65%:35%). Pre-breast cancer carriers were significantly ($p < 0.001$) more likely to have a suggestive family history (90% vs. 62%), prior breast cancer screening (78% vs 60%), and breast cancer diagnosed by imaging (78% vs 25%) rather than clinical symptoms (19% vs 73%). Pre-breast cancer carriers had a higher DCIS: invasive breast cancer presentation (40%:60% vs. 2%:98% in post-breast cancer) and lower stage ($p < 0.005$). No differences in tumor grade, ER or Her2 status were identified. Pre-breast cancer carriers were more likely to undergo sentinel lymph node biopsy (91% vs 45%), less likely to receive chemotherapy, and more likely to elect bilateral mastectomies (62% vs 10%) than post-breast cancer carriers ($p \leq .001$ for all comparisons). Overall, pre-breast cancer gBRCA identification and routine screening predicted for early stage (0-I) breast cancer diagnosis ($p <$ 0.001, OR 16.8). **Conclusions:** Presymptomatic identification of gBRCA status is significantly associated with earlier stage breast cancer diagnosis, requiring less extensive treatment. This supports routine gBRCA testing in all healthy AJ women.

1585 Poster Session (Board #156), Sat, 1:15 PM-4:45 PM

Implementing genetic risk assessment in a community free clinic. *First Author: Leah Marsh, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Assessment of hereditary cancer risk plays an integral role in reproductive healthcare. ACOG and NCCN recommend that OB/GYNs assess hereditary cancer risk annually. The Saban Community Clinic is a Resident-run clinic in Los Angeles, California, serving a predominantly non-white, uninsured patient population of low socioeconomic status (SES) with no access to genetic counseling. Prior to this study, no formal cancer family history was elicited. **Methods:** We adapted a bilingual screening tool developed at the UCSF Cancer Risk Program that is compliant with NCCN and ACOG guidelines. It relies on fact recall that patients can complete independently assuming low health literacy. Clinic providers were briefed on the project and distribution commenced in April of 2017. The questionnaires were scored and entered into a secured database. **Results:** Between April 2017-January 2018, a total of 98 questionnaires were collected. Ages ranged from 19-67. Thirty-two percent (32%) of the patients identified as Hispanic. Of those who identified as non-Hispanic, only 3 of these identified as White, the others identified as Asian or Black. Twenty-one percent (21%) of the forms were completed in Spanish. First degree relative with ovarian cancer and/or multigeneration presence of breast cancer accounted for 11% of the patients who screened "positive" for referral to further genetic counseling. **Conclusions:** This study sought to 1) determine the feasibility of implementing a brief genetic risk screening tool and 2) assess the unmet need for referral to genetic counseling/testing in a community clinic serving predominantly non-white, low SES patients without health insurance. The preliminary data is promising that a patient administered survey can aid clinicians in identifying patients for referral. It also demonstrates the unmet need in this population, with 32% of these patients meeting criteria for referral. This tool identified an important area of health inequity in cancer prevention in this population.

1586 Poster Session (Board #157), Sat, 1:15 PM-4:45 PM

The incidence of germline cancer susceptibility mutations in primary CNS neoplasm patients. *First Author: Katharine Lord, Texas Oncology - Austin Brain Tumor Center, Austin, TX*

Background: Genomic profiling is performed on primary brain (CNS) tumors to identify somatic mutations. Several syndromes, (e.g. Neurofibromatosis) are well known causes of CNS neoplasms but data is limited on other germline cancer susceptibility mutations in CNS tumor patients. After a somatic mutation was unexpectedly found to be germline, we interrogated our database of somatic CNS tumor mutations. **Methods:** This IRB approved study reviewed patients at our center from May 2013 - November 2017. Tumors from 319 patients underwent next generation sequencing. At least 1 somatic mutation on a gene of interest was found in 208 tumors; 108 patients were deceased prior to study start. Of the remaining 100 patients, 28 were offered germline testing. **Results:** 26 patients completed germline testing: 12 had germline mutations (12%), 6 had germline variants of uncertain significance (6%) and 8 had negative germline testing (8%). Germline mutations were identified in the following genes: BRCA2 (3 patients), CHEK2 (4 patients), APC (3 patients), ATM (3 patients), MUTYH (2 patients), PMS2 (2 mutations in 1 patient). Of the 12 patients with germline mutations, five (41.6%) did not meet guidelines for hereditary cancer genetic testing. As a result of the germline findings, medical management was altered and additional family members with pathogenic mutations were identified. **Conclusions:** Based on somatic and germline mutational data from 319 CNS tumor patients, we estimate 5.8% of all CNS tumor patients (without an obvious CNS tumor syndrome) carry a germline cancer susceptibility mutation. Twelve percent of patients whose tumor contains a somatic mutation of possible "germline" interest carry a germline cancer susceptibility mutation. Pathogenic germline variants were identified in the following genes: BRCA2, CHEK2, APC, ATM, MUTYH and PMS2. Five patients (41.6%) did not meet recognized criteria for germline cancer genetic testing, thus without the somatic data, would have been overlooked. Nearly 50% of CNS tumor patients with germline cancer susceptibility mutations are overlooked when using routine testing criteria; tumor genomic profiling is the only means for identifying these undiscovered germline mutations.

1587 Poster Session (Board #158), Sat, 1:15 PM-4:45 PM

Value of germline multi-gene panel next generation sequencing (NGS) in identification of hereditary cancer syndromes (HCS) in colorectal cancer population (CRC). *First Author: Jing Gu, University of Southern California, Los Angeles, CA*

Background: Identification of HCS in probands (PB) provides a mechanism for cancer screening and prevention in 1st degree relatives (FDR). Lynch syndrome (LS) is the most common HCS in CRC. However, other HCS known to increase risk of breast and ovarian cancers (BC/OC) have been reported in CRC. We evaluated the value of NGS vs. tumor immunohistochemistry followed by MMR gene sequencing (T-MMR) in a CRC cohort with $>$ 5% probability of HCS based on a predictive model. **Methods:** In a modeled cohort of CRC patients, those with over 5% probability of HCS by MMRpro are assessed using either T-MMR or NGS. FDR of PB with a HCS are offered target genetic testing for the known mutation. The output of this population is input in a Markov model, which simulates the life history of FDR to calculate their costs and quality adjusted life years (QALYs). This model incorporates the effects & costs of cancer screening strategies, preventive procedures, and treatments. The model has 3 states: cancer free, diagnosed with cancer, and deceased; subjects transition among these states based on their known cancer risk and US life tables. Our model takes a US societal perspective and a 3% annual discount rate for both costs and QALYs. **Results:** For a cohort of newly diagnosed CRC with US epidemiology, 27,775 individuals had a MMRPro score $>$ 5%. T-MMR identified 2,584 (9.3%) PB with LS and subsequently 1,915 FDR with LS and 516 false negative relatives. With NGS, 8,076 (29.1%) PB with a HCS are identified, and 5,984 FDR tested positive for a HCS; including 3,814 with a mutation in a CRC associated gene and 2,170 with BC/OC associated gene mutation. The T-MMR arm failed to identify 2,929 PB and 4,393 FDR with a BC/OC associated gene mutation. Testing for T-MMR arm yields 645,874 QALYs while NGS arm yields 671,507 QALYs for CRC. Total costs are $1,215,670,597 for T-MMR tested group vs. $1,036,167,834 for NGS tested group, defining NGS as the dominant strategy for testing for HCS. One-way sensitivity analysis shows robust results. **Conclusions:** Compared to the T-MMR testing for LS, using a multi-gene NGS panel that included BC/OC cancer risk genes for HCS among CRC patients increases QALYs and saves costs.

1588 Poster Session (Board #159), Sat, 1:15 PM-4:45 PM

Multiplex germline testing in selected melanomas presenting to oncology clinic. *First Author: Pauline Funchain, Cleveland Clinic, Cleveland, OH*

Background: A recent twin study found melanoma to be the most heritable cancer with high twin-twin concordance (Mucci et al., JAMA 2016). Of melanoma patients presenting to oncology, 29% had a family history of $\geq$3 cancers, 59% had cancer in a 1st degree relative, and 17% had a family history of melanoma (Sussman et al., SMR 2017). The clinical utility of multiplex germline testing in the oncologic melanoma population has not yet been established. **Methods:** Consecutive patients who met criteria were offered germline testing with a multiplex panel (Invitae, San Francisco, CA) comprised of 12 genes related to melanoma and 69 additional cancer-related genes not known to be related to melanoma. Eligibility criteria included $\geq$ 2 melanomas in an individual or family; melanoma and other cancer(s) in an individual; melanoma and at least 2 other cancers in 1st- or 2nd-degree relatives, including a 1st-degree relative; age $\leq$35 at diagnosis; and limited family structure. **Results:** Of 81 patients with completed testing, 15 (18.5%) had a pathogenic/likely pathogenic mutation. 8 (53%) mutations were in genes previously associated with melanoma (*CDKN2A, BRCA1/2, BAP1, TP53*), and 7 (47%) were in genes from an extended pan-cancer panel (*CHEK2,PMS2,RAD51C, BLM, MUTYH*). Study eligibility met by mutation-positive individuals included 9 (60%) with a personal history of multiple cancers, 6 (40%) with multiple relatives with cancer, 4 (33%) with family history of $\geq$2 melanomas, 3 (20%) age $\leq$35 years, 2 (13%) with personal history of $\geq$3 melanomas, and 1 (7%) with limited family history. Melanoma subtypes of mutation-positive probands included 12 cutaneous, 1 mucosal, and 2 uveal. Other cancers observed in probands/families: bladder, brain, renal, pancreatic, carcinoid, thyroid, lymphoma, colon, breast, and ovarian cancers. **Conclusions:** Multiplex germline testing in a melanoma cohort selected by family or personal history of multiple cancers resulted in an 18.5% mutation-positive rate, nearly half identified in genes not previously associated with melanoma. Patients with melanoma, particularly with a personal or family history of other cancers, may benefit from germline testing. More data will be required to further refine testing guidelines for melanoma.

1589 Poster Session (Board #160), Sat, 1:15 PM-4:45 PM

Incidence of pathogenic variants in individuals with a personal or family history of pancreatic cancer. *First Author: Pashtoon Murtaza Kasi, Mayo Clinic, Jacksonville, FL*

Background: Genetic testing related to pancreatic cancer is expanding. Many companies offer a multi-gene panel with a focus on pancreatic cancer. The purpose of this study was to evaluate the incidence and types of pathogenic variants detected in individuals with a personal and/or family history of pancreatic cancer. **Methods:** The genetic test results of patients visiting a genetic counselor at Mayo Clinic Florida from January 2012 to February 2018 were examined. Clinical notes and three generation pedigree taken at the time of initial genetics consult were reviewed. **Results:** Of the 2038 patients that completed testing, 223 (10.9%) were diagnosed with a hereditary cancer syndrome. 59 were referred due to personal history of pancreatic cancer, of which 3 (5.1%) were found to carry a germline mutation discovered in *BRCA1/2*. One additional patient was found to carry a mosaic pathogenic variant in *ATM*. Of the 285 that reported any family history of pancreatic cancer, 35 (12.3%) carried a pathogenic variant. These variants were present in *APC* (3), *ATM* (4), *BRCA1* (5), *BRCA2* (13), *CHEK2* (5), *MSH6* (1), *NBN* (1), *PALB2* (3), and *PRSS1* (1). The incidence of pathogenic variants nearly doubled (21.4%) if the individual had at least two relatives with a history of pancreatic cancer. **Conclusions:** It has been difficult to determine who may benefit from pancreatic cancer screening, but identifying a pathogenic variant in an individual with a family history of pancreatic cancer is sometimes enough evidence to suggest surveillance. Gathering family history is an important piece of evaluating value of pancreas screening.

Number of individuals diagnosed with a hereditary cancer syndrome who had a personal and/or family history of pancreas cancer.

Category	Number of positives / Total (%)	Genes
Personal history of pancreas cancer	3-4/59 (5.1-6.8%)	*ATM*[1], *BRCA1 (2)*, *BRCA2*
Family history of pancreas cancer	36/285 (12.6%)	*APC*[2] *(3)*, *ATM (4)*, *BRCA1 (5)*, *BRCA2 (13)*, *CHEK2 (5)*, *MSH6*, *NBN*, *PALB2 (3)*, *PRSS1*
Family history of 2+ relatives with pancreas cancer ca	12/56 (21.4%)	*APC*[2] *(2)*, *ATM (2)*, *BRCA1 (2)*, *BRCA2 (4)*, *CHEK2 (2)*

[1]Apparently mosaic pathogenic variant in ATM. [2]The *APC* Ashkenazi Jewish Founder mutation, I1307K.

1590 Poster Session (Board #161), Sat, 1:15 PM-4:45 PM

Implementation of strategies to increase genetic counseling referral rates for ovarian cancer patients. *First Author: Kara J. Milliron, University of Michigan, Ann Arbor, MI*

Background: Genetic counseling is recommended for all women diagnosed with epithelial ovarian cancer, independent of family history. Despite the potential benefits to the patient and her family, referral rates remain low. We sought to assess referral rates at our institution and implement two strategies to improve both the rate of referral and the completion of counseling and testing – (1) discussion of referral for all patients reviewed at multidisciplinary treatment planning conference and (2) option of telephone counseling. **Methods:** Patients with a diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer since 10/1/14 were identified through pathology reports and chart review was performed to obtain demographic data and cancer details including histology, grade and stage. Personal and family history of cancer, date of genetic counseling referral, method of genetic counseling (in-person vs. telephone), date of genetic testing and the result of genetic testing were also abstracted. **Results:** The rate of genetic counseling referral was 63.5% (214/337 patients). Of those referred, 61% (131/214) underwent counseling, with 77% (165/214) in person and the 23% (49/214) via telephone after initiation of the telephone counseling program in September 2017. Overall, 90% of patients who received genetic counseling underwent testing, including 92.7% of the in-person counseling cohort and 67.9% of the telephone counseling cohort to date. In total, 24.1% of patients harbored a pathogenic gene mutation, with *BRCA1* mutations most common (16.5% of patients). Variants of undetermined significance were identified in 11.3% of patients. **Conclusions:** Telephone genetic counseling and mandatory discussion of referral at the time of treatment planning conference both appear to facilitate genetic counseling and ascertainment of actionable germline mutations. Overall, referral rates are high at our institution. The implementation of telephone-based genetic counseling programs has the potential to improve both counseling and testing rates, particularly when in-person counseling is not available or is delayed.

1591 Poster Session (Board #162), Sat, 1:15 PM-4:45 PM

Referral patterns and attrition rate for germline testing in pancreatic cancer (PC) patients. *First Author: Evan Justin Walker, University of California San Francisco, San Francisco, CA*

Background: Hereditary predisposition is estimated to account for 10% of all PC cases. Identification of pathogenic germline mutations can inform not only screening recommendations for family members but also, increasingly, treatment selection for pts. However, referral patterns and clinical workflow for germline testing in this disease differ significantly by institution, and many pts may not undergo recommended testing for a variety of reasons. **Methods:** We performed a retrospective review of all pts diagnosed w/ PC referred to our University of California, San Francisco Clinical Genetics program over a 3-yr period (1/2015 – 10/2017). Medical records were reviewed for demographic, medical/family history, and disease-specific data as well as genetic testing results. If testing did not occur, the reason was documented. Results were categorized as negative, variants of unknown significance (VUS), or established pathogenic mutations. Descriptive statistics included means with standard deviations (SD); associations were analyzed with t-test and Fisher's Exact Test. **Results:** ~29% (n = 137) of pts seen at UCSF w/PC dx were referred to Clinical Genetics during this time period. Of these, only 64% attended the appt and 60% ultimately underwent germline testing. Reasons for attrition inc. lack of pt f/u (n = 20), worsening disease severity (n = 11), insurance concerns (n = 7), and logistic/travel difficulties (n = 6). Pathogenic germline mutations were detected in 20% (n = 16) of pts tested [CFTR (n = 4), BRCA2 (n = 3), CHEK2 (n = 2), ATM (n = 2), MLH (n = 1), MUTYH (n = 1), other (n = 3)]; while 48% (n = 39) of pts had $\geq$1 VUS. Confirmed pathogenic mutations in our cohort were distributed across races/ethnicities, and assoc w/ younger age (mean age 53.3 vs 60.5 y. o.; p = 0.02) and FHx of breast cancer (p = 0.05). **Conclusions:** PC pts frequently do not undergo genetic counseling/germline testing despite appropriate referrals, highlighting the need to develop streamlined processes to engage more pts in testing, esp those w/ high-risk features such as young age and (+) FHx of cancer. Based on these data, our Center plans to pilot a genetic testing station for all new PC pt visits, incorporating both same-day testing and f/u remote counseling.

1592 Poster Session (Board #163), Sat, 1:15 PM-4:45 PM

The impact of genetic counseling on patients' knowledge about tumor genomic profiling. *First Author: Rebecca D. Pentz, Emory University School of Medicine, Atlanta, GA*

Background: Molecular testing is increasingly being integrated into cancer management. However, despite rapid advancements in this area, little work has been done to explore strategies for communicating genomic information to patients undergoing tumor profiling. This study evaluated the impact of an educational tool combined with genetic counseling on patients' understanding of key terms related to tumor genomic profiling. **Methods:** A genetic counseling intern designed a picture book to explain six words found in prior research to be difficult for patients to understand: mutation, germline mutation, somatic mutation, biomarker, molecular testing, and targeted therapy. The picture book was cognitively tested with oncology patients and revised. After consent, patients who had previously discussed molecular testing with their oncologist were asked to define the six words in their own terms. The same patients then received an explanation of each word from the intern using the picture book, and were asked to redefine each word directly afterwards. All definitions were scored for correctness by two independent coders. The proportion of patients who defined each term correctly and total knowledge scores were compared before and after genetic counseling. **Results:** Twenty-eight patients with melanoma, colon, lung, or breast cancer were recruited. Correct understanding rates improved for all six terms, with significant improvement for germline mutation ($p < 0.001$), somatic mutation ($p < 0.001$), biomarker ($p < 0.001$) and molecular testing ($p < 0.001$). Mean total knowledge score significantly improved from 30% to 83.3% ($p < 0.001$). **Conclusions:** Our data suggest that the use of a simple educational tool combined with genetic counseling in the setting of genomic tumor testing increases patient knowledge and may improve the process of informed consent. Future studies are warranted to determine the feasibility of providing in person genetic counseling in this setting and whether the picture book can be effectively used by other advanced practice providers with knowledge of genomics.

1593 Poster Session (Board #164), Sat, 1:15 PM-4:45 PM

Incidence and risk of second primary malignancy after an index potentially-human papillomavirus-associated cancer. *First Author: Eric Adjei Boakye, Saint Louis University Center for Health Outcomes Research, St. Louis, MO*

Background: Approximately 39,000 HPV-associated cancers are diagnosed annually in the US. Oncogenic HPV-infections are associated with virtually all cases of cervical, 95% of anal, 73% of oropharyngeal, 65% of vaginal, 50% of vulvar, and 35% of penile cancers. Cancer survivors are at increased risk of a second primary malignancy (SPM). We assessed the risk of developing a SPM after an index potentially-HPV-associated cancer (P-HPV-AC). **Methods:** This was population-based cohort study of patients with P-HPV-AC in the Surveillance, Epidemiology, and End Results registry (2000-2014). Only patients with invasive P-HPV-AC [cervical, vagina, vulva, penile, anal canal, and oropharynx] per International Classification of Diseases for Oncology, 3rd edition, were included. SPM was defined as the first subsequent primary cancer occurring at least 2 months after first cancer diagnosis. Excess SPM risk was quantified using standardized incidence ratios (SIRs) stratify by gender. **Results:** A total of 100,960 patients with an index P-HPV-AC were identified, and 7.37% developed a SPM overall. In all P-HPV-AC patients, the overall SIR was 1.72 (95% CI: 1.68–1.76). All index P-HPV-AC sites presented with a statistically significant increase in the risk of SPM. Among males, the greatest increase in risk of SPM was observed among patients diagnosed with an index P-HPV-AC oropharynx (SIR = 1.83; 95% CI, 1.76–1.90). Among females, the greatest increase in risk of SPM was observed among patients diagnosed with an index P-HPV-AC oropharynx (SIR = 2.47; 95% CI, 2.29–2.65, Table). **Conclusions:** HPV cancer survivors experience significantly excess risk of SPM; thereby calling for a more effective program for surveillance of patients with HPV-associated cancers.

			SIR	
	Cancers	Observed	Rate	95% CI
Overall	All potentially-HPV-associated cancers	7,447	1.72	1.68 – 1.76
Male and female	Oropharynx (head and neck)	3,240	1.91	1.84 – 1.98
	Anal	1,131	1.52	1.43 – 1.61
Male	Oropharynx (head and neck)	2,672	1.83	1.76 – 1.90
	Anal	453	1.48	1.35 – 1.62
	Penile	251	1.41	1.24 – 1.59
Female	Oropharynx (head and neck)	568	2.42	2.22 – 2.62
	Anal	678	1.55	1.44 – 1.67
	Cervical	2,017	1.51	1.44 – 1.58
	Vulvar	618	2.33	2.15 – 2.52
	Vaginal	190	1.78	1.54 – 2.06

TPS1594 Poster Session (Board #165a), Sat, 1:15 PM-4:45 PM

Evaluating intermittent dosing of aspirin for colorectal cancer prevention. *First Author: Katrina M. Alber, Northwestern University, Chicago, IL*

Background: Colorectal cancer (CRC) remains the 4th most common cancer in the United States. Thus the identification of effective and safe prevention methods remains important. While long-term use of COX-2 inhibitors, NSAIDs, and aspirin are associated with a reduced risk of CRC, the cardiovascular (CV) toxicity of COX-2 inhibitors and NSAIDs inhibits use in the prevention setting. Aspirin (ASA) does not confer risk of CV side effects and is a promising chemopreventive agent for CRC, but risks include gastrointestinal side effects and bleeding. Preclinical data suggest that intermittent dosing of aspirin would retain efficacy, with reduced toxicity [Mohammed, AACR 2018, NCI-N01-CN-250026]. **Methods:** This ongoing double-blind placebo-controlled randomized trial will enroll 90 subjects (men and women) to three arms: daily oral ASA 325 mg for 12 weeks (N = 40); intermittent aspirin 325 mg daily (4 cycles, alternating 3 weeks aspirin/placebo for a total of 12 weeks, N = 40); or daily placebo for 12 weeks (N = 10). The primary objective is to test for the equivalence of the two aspirin schedules, as demonstrated by similar changes in the ratio of cell proliferation to apoptosis in rectal biopsy samples (Ki67: Bax). Secondary endpoints include spectral markers of colon cancer risk and DNA methylation changes. Eligibility requirements include a history of colorectal adenoma (any grade), and no history of the following: invasive malignancy in the past 2 years; chronic renal or liver disease; unstable angina, hemorrhagic stroke or uncontrolled hypertension; anemia, peptic ulcer, gastrointestinal bleeding, active colitis, or inflammatory bowel disease. Participants must not have taken aspirin, other NSAIDs, or COX-2 inhibitors 3 weeks prior to the intervention; alcohol use $<$ 2 drinks/day. They will undergo blood draws and rectal biopsies at entry, at 9 weeks, and at end of intervention. A 3-month follow-up visit is planned. Statistical analyses will be based on 32 evaluable subjects in each of the two aspirin arms (allowing for drop-outs); we will have 81% power to detect a change in the Ki67:Bax ratio of -3.0 to +3.0, based on the standard deviation of similar data from an ongoing trial. Enrollment began in January 2018. Funding: NCI #HHSN2612201200035I. Clinical trial information: NCT02965703.

TPS1595 Poster Session (Board #165b), Sat, 1:15 PM-4:45 PM

A phase IIB pre-surgical trial of oral tamoxifen (TAM) versus transdermal 4-hydroxytamoxifen (4-OHT) in women with DCIS of the breast. *First Author: Kelly A. Benante, Northwestern University, Chicago, IL*

Background: Ductal carcinoma in situ (DCIS) is diagnosed in 60,000 women annually in the US. TAM is proven to reduce risk of local recurrence and new primary breast cancer in women with estrogen receptor (ER) positive DCIS. However, acceptance of TAM has been low, primarily because of toxicity related to systemic exposure. Local delivery to the breast is an attractive alternative as low systemic levels could minimize toxicity. 4-OHT is an active metabolite of TAM. When formulated as a gel and applied to the breast, it is well tolerated, and results in 4-OHT breast tissue drug levels comparable to oral TAM. In small pilot studies, its anti-proliferative effects on invasive breast tumors and DCIS are also similar to oral TAM [Lee O, et al. PMID 25028506]. The goal of our study is to validate these results in preparation for a Phase III trial of 4-OHT gel compared to oral TAM. **Methods:** We are conducting a randomized, double-blinded, placebo-controlled, Phase IIB pre-surgical trial to demonstrate that daily application of 4-OHT gel will result in a reduction in the Ki-67 labeling index of DCIS lesions that is not inferior to that seen in women receiving daily oral TAM. Ki-67 of the base-line diagnostic core needle biopsy will be compared to that of the therapeutic surgical excision sample after oral TAM or 4-OHT gel for 8 $\pm$ 2 weeks. Secondary endpoints include changes in Oncotype DCIS-Score, IHC markers, hormone levels, coagulation markers, drug concentration in the plasma and breast, and experienced symptoms. 100 women (assuming 20% non-evaluable samples or non-compliance) with DCIS (10% ER-positive) will be enrolled across 6 institutions into two intervention arms: oral TAM 20mg daily, placebo gel and 4-OHT gel 4mg daily (2mg/breast), placebo capsule. All participants will be evaluable for toxicity from first dose. To date 8 of 100 participants have been enrolled. Since study open, 39 potential participants have been contacted, 28 did not consent for screening, 9 consented, 2 are pending consent, and 9 have started study intervention. The most common reason potential participants chose not to consent is wanting to schedule surgery as soon as possible. Funding Source: NCI Contract # HHSN26122012000035I. Clinical trial information: NCT02993159.

2000 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

GAPVAC-101: First-in-human trial of a highly personalized peptide vaccination approach for patients with newly diagnosed glioblastoma. *First Author: Wolfgang Wick, Neurology Clinic, DKFZ, DKTK, Heidelberg, Germany*

Background: The need for treatment personalization is obvious as every cancer is molecularly unique. In addition glioblastoma (GB) are immunologically regarded as resistant, "cold" tumor with few targetable antigens available from mutations, thus demanding new personalized immunotherapies. **Methods:** The GAPVAC consortium realized an immunotherapy, for which personalized selection of 2 peptide-based actively personalized vaccines (APVAC) per patient for treatment of newly diagnosed GB was based not only on whole-exome sequencing but also on human leukocyte antigen (HLA)-ligandome analyses providing insight into the actual presentation of relevant epitopes in the tumor. GAPVAC-101 (NCT02149225) enrolled 16 patients in a European phase I feasibility, safety and immunogenicity trial integrated into standard of care. For APVAC1, up to 7 peptides were selected from a trial specific warehouse based on individual biomarker data. Vaccination (i.d.) with GM-CSF and poly-ICLC in 15 patients started with the 1st adjuvant cycle of temozolomide (TMZ). For APVAC2, analyses revealed a median of 36 somatic, non-synonymous mutations in the patients' tumors. From the 4th TMZ cycle, 11 patients received APVAC2 with usually 2 *de novo* antigens per patient selected according to mutation, actual or putative HLA presentation and immunogenicity. Overall 20 APVAC2 antigens incl. 14 mutated were vaccinated. **Results:** Adverse events were largely reversible injection site reactions but also 2 anaphylactic reactions and one increase in cerebral edema. Short, non-mutated APVAC1 antigens induced sustained CD8 responses with memory phenotype, being with regard to CD8 immunogenicity rate (51%, *ex vivo* readout) numerically at least not inferior to long mutated antigens (45%, readout after *in vitro* culture). Mutated APVAC2 antigens induced predominantly CD4 responses of favorable TH1 type. Median PFS and OS were 14.2 and 29 months from diagnosis, respectively, in patients that received $\geq$1 APVAC vaccination (N = 15). **Conclusions:** Overall, the GAPVAC approach displayed expected safety profiles and high biological activity warranting further development. Clinical trial information: NCT02149225.

2001 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A mutation-specific peptide vaccine targeting IDH1R132H in patients with newly diagnosed malignant astrocytomas: A first-in-man multicenter phase I clinical trial of the German Neurooncology Working Group (NOA-16). *First Author: Michael Platten, Mannheim University Hospital, German Cancer Research Center (DKFZ), Mannheim, Germany*

Background: Hot-spot point mutations in the gene for isocitrate dehydrogenase type 1 (IDH1R132H) are a frequent founder event in gliomas and other tumors. Preclinical studies have defined IDH1R132H as a clonal neoantigen presented on MHC class II to induce tumor-specific therapeutic T helper cell responses. **Methods:** NOA-16 (NCT02454634) is a first-in-man, multicenter, phase I trial, which enrolled 33 patients with newly diagnosed WHO °III and °IV astrocytomas with IDH1R132H mutations. After completion of radiochemotherapy a total of eight vaccinations with an IDH1R132H peptide in incomplete Freund's adjuvant produced at a central GMP site was to be administered subcutaneously with topical imiquimod over a period of 32 weeks together with maintenance temozolomide. The primary end points were safety and immunogenicity. **Results:** The safety dataset comprised 249 vaccines administered to 32 patients. One patient withdrew after screening. 29 patients received all eight vaccines. Vaccine-related adverse events (AE) were restricted to grade 1 reactions, according to common toxicity criteria for AE(CTCAE v4.0). Two serious AE were observed in two patients; one probably related to the peptide vaccine. 28/30 patients (93.3%) evaluable for immunogenicity displayed IDH1R132H-specific T cellular (detected by ELISPOT assays in 24/30 (80%)) or humoral (detected by ELISA in 26/30 patients (87%)) immune responses not detectable before vaccination. Until end of study (EOS, week 32), 4/32 (12.5 %) patients had progressive disease (PD) according to RANO criteria, all other patients (N = 28, 87.5%) had stable disease (SD). 12/32 (37.5%) patients displayed pseudoprogressions. Single-cell T cell receptor (TCR) sequencing allowed for the identification of IDH1R132H-specific TCRs. **Conclusions:** NOA-16 met its primary endpoints by demonstrating safety and immunogenicity of a mutation-specific IDH1R132H peptide vaccine. Pseudoprogressions observed after the initiation of the vaccine may indicate intratumoral immune reactions warranting further development, including TCR cell therapy. Clinical trial information: NCT02454634.

2002 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Phase 1 study of AG-881, an inhibitor of mutant IDH1/IDH2, in patients with advanced IDH-mutant solid tumors, including glioma. *First Author: Ingo K. Mellinghoff, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Isocitrate dehydrogenase 1 and 2 mutations (mIDH1/2) occur in solid tumors including glioma, and result in production of the oncometabolite 2-hydroxyglutarate (2-HG), promoting tumorigenesis. AG-881 is an oral, potent, brain-penetrant inhibitor of mIDH1/2 that reduces 2-HG by up to 98% in glioma models. **Methods:** Patients (pts) with recurrent/progressive mIDH1/2 glioma (G) and non-glioma (NG) solid tumors were eligible to receive AG-881 daily in continuous 28-day cycles. Dose escalation cohorts for G and NG solid tumors enrolled using a Bayesian logistic regression model (BLRM) escalation guided by the overdose control (EWOC). Blood and tumor samples were evaluated for pharmacokinetics (PK)/pharmacodynamics (PD). Dose-limiting toxicity (DLT) was defined as a Grade (Gr) $\geq$3 AG-881-related event in Cycle 1 or by sponsor designation. **Results:** As of 1Dec2017, 93 pts had received AG-881 (G: 52; NG: 41) and 20 remain on AG-881 (G: 19, NG: 1). Demographics: M/F = 40/53; median age = 51; median no. prior systemic therapies = 3 (range 1–7). Seven initial dose levels were tested: 25mg QD (n = 10); 50mg QD (n = 12); 100mg QD (n = 21); 200mg QD (n = 22); 200mg BID (n = 5); 300mg QD (n = 5) and 400mg QD (n = 6). To further assess safety and PK in the G cohort, a 10mg dose level was tested (n = 6) and 6 additional pts enrolled in the 50mg cohort. PK showed less than dose-proportional plasma exposure with a mean effective half-life of 71$\pm$54 hrs. Common adverse events (AEs) across all pts regardless of attribution: fatigue (38.7%), nausea (35.5%), ALT/AST increase (34.4% each). Elevated ALT/AST AEs were dose-dependent (n = 0 at 10mg, n = 7 at $\leq$50mg, n = 10 at 100mg, n = 20 at $>$ 100mg). Five G pts experienced DLTs at 100mg and above: Gr $\geq$2 ALT/AST which resolved to Gr $\leq$1 with dose modification (n = 4) or discontinuation (n = 1). The MTD or RP2D were not reached by BLRM with EWOC. **Conclusions:** AG-881 was associated with a favorable safety profile at doses $<$ 100mg in pts with glioma and non-glioma solid tumors. No ALT/AST AEs Gr $>$ 2 were observed at 10mg and 50mg. These doses are being explored in an ongoing perioperative glioma study. Updated safety, PK/PD, and efficacy data will be presented. Clinical trial information: NCT02481154.

2003 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

ALLELE: A consortium for prospective genomics and functional diagnostics to guide patient care and trial analysis in newly-diagnosed glioblastoma. *First Author: Mehdi Touat, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: Multi-dimensional genomic analyses may improve outcome in glioblastoma (GB) but are not widely available as routine clinical care. ALLELE is an ABC^2-funded consortium to generate prospective clinical genomics and develop novel biomarkers for use in GB patients. **Methods:** Multicenter prospective study of tumor genotyping in newly diagnosed GB. Clinical (CLIA) genome-wide tumor whole exome sequencing (WES) and chromosomal microarray (CMA) were performed following surgery. Primary objective: to evaluate the feasibility of genotyping tumors in a time-frame to support real-time use in clinical trials. Comparisons with orthogonal genomic and functional methods were incorporated to inform best practices. **Results:** As of 1/30/18, 46 patients with GB enrolled among 5 sites. Median age was 60. WES and CMA were completed in 39 patients, with a median time between surgery and biomarker analysis completion of 51 days. Actionable findings, including activating BRAF and FGFR1 mutations were identified in 2 patients, and two tumors were reclassified as non-GB based on genomics. 26 patients with MGMT unmethylated GB were enrolled in INSIGhT, a companion randomized multi-arm trial comparing standard of care versus adjuvant CC-115, neratinib or abemaciclib in newly diagnosed GB (NCT02977780). Pre-defined biomarker groups (EGFR-, PI3K- and CDK-positive) will be evaluated for their ability to predict outcome in each arm. 10 patients received standard of care, and 3 patients enrolled in other clinical trials. In a subset of patients, exploratory functional biomarker assays were generated on live cells from freshly resected tumors and patient-derived GB cell line models were derived. Updated outcomes and results of exploratory biomarker analyses will be presented at the conference. Prospectively generated genomic data will be made publicly available. **Conclusions:** Molecular profiling with WES and CMA is feasible within a clinically acceptable time frame following surgery for patients with newly diagnosed GB. Genomic analyses conducted in a prospective manner can inform subsequent clinical trial analysis aiming at matching outcome with tumor genotyping.

2004 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Feasibility and benefit of molecularly-informed enrollment into early phase trials for patients with recurrent gliomas. *First Author: Capucine Baldini, Gustave Roussy, Villejuif, France*

Background: Recent reports showed that patients (pts) with recurrent glioma may be good candidates for early phase clinical trials (eaCTs), however clinical benefit is often limited to a small subset of pts in all-comers design trials. We aimed to evaluate whether selecting pts through tumor genotyping is associated with better outcome in this population. **Methods:** From 2008 to 2017, individual records of pts enrolled in eaCTs of cytotoxic therapies, small molecule inhibitors or immune checkpoint blockers were analyzed for clinical and histomolecular characteristics, toxicity, tumor response, and progression-free survival (PFS). The primary objective was to evaluate the feasibility and potential benefit of using tumor genotyping for guiding enrollment in eaCTs. Molecular screening methods included immunohistochemistry and PCR-based assays, array CGH, next-generation sequencing, and RNA sequencing. **Results:** Seventy pts were enrolled, of whom 41/70 (58.6%) patients were molecularly oriented. Therapeutic targets included FGFR mutations/fusions (n = 11), BRAF (7) and IDH (15) mutations, MDM2 amplification (1) and mismatch repair deficiency (7). In addition, 34 pts participated in the MOSCATO 01 and 02 precision medicine study (NCT01566019), which allowed the identification of potentially actionable targets in 12/34 (35%) pts, of whom 4/12 (33.3%) received a molecularly-informed therapy. Grade 3/4 adverse events were reported in 6/70 (8.6%) pts. In the subgroup of IDH1/2-wild type high-grade tumors, response rate and disease control rate were 16.7% (3/18) and 55.6% (10/18) respectively in pts who were molecularly oriented, versus 0% (0/14) and 31.5% (5/14) in molecularly-unselected pts. There was no statistically significant difference in median PFS between molecularly-oriented and -unselected pts (2.83 months [95% CI 1.3-4.6] vs. 1.54 months [1.05-2.85], *P*= 0.29). **Conclusions:** A subset of pts with recurrent glioma may benefit from incorporating tumor genotyping to guide their enrollment in eaCTs. Accelerating the use of prospective genomics could increase the percentage of pts who may benefit from this strategy.

2005 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Actionable targets involving FGF receptors in gliomas: Molecular specificities, spatial distribution, clinical outcome and radiological phenotype. *First Author: Anna Luisa Di Stefano, Foch Hospital, Suresnes, France*

Background: to characterize clinical, molecular and radiological features of diffuse gliomas with *FGFR3-TACC3* fusions or *FGFR1* mutations, which are both actionable with new oral anti-FGFR inhibitors. **Methods:** We screened for *FGFR3-TACC3* fusions 1112 gliomas (861 grade IV, 140 grade III and 111 grade II) by RT-PCR. We performed sequencing for hotspot *FGFR1* mutations (N546 and K656) in 73 midline gliomas (8 grade II, 10 grade III, 54 grade IV, affecting cerebellum, spinal cord, brainstem, thalamus and diencephalon) and 479 hemispheric gliomas (170 grade IV, 151 grade III, 157 grade II). **Results:** We identified 50 gliomas (all *IDH* wild-type) with *FGFR3-TACC3* fusion (45 grade IV, 2 grade III and 3 grade II). *FGFR3-TACC3* fusion was mutually exclusive with *EGFR* amplification (p = 0.000) and co-occured with *CDK4* and *MDM2* amplifications (p = 0.011 and p = 0.005). *FGFR3-TACC3* positive glioblastoma patients had a longer median overall survival (OS) (40.1 months versus 19.0; p = 0.006). Multivariate analysis showed that *FGFR3-TACC3* fusion is an independent predictor of better outcome for glioblastoma patients. Paired case-control analysis on pre-operative Magnetic Resonance Imaging MRI (24 *FGFR3-TACC3* positive cases and 48 controls) by the VASARI vocabulary and sparse canonical correlation showed that *FGFR3-TACC3* gene fusions have specific radiological features, are constantly unifocal and involve specifically cortico-subcortical regions. We identified recurrent *FGFR1* mutations in 13 out of 73 midline gliomas with diverse locations and in only one hemispheric glioma with corpus callosum involvement. *FGFR1* mutations occurred in both *K27M* mutated and *K27*wild-type and were constantly *IDH* wild-type. *FGFR1* mutations tended to be associated with younger age (p = 0.06) and ATRX loss (p = 0.05) and was an independent predictor of better outcome (median OS 45.0 months versus 13.8 months, p = 0.01). **Conclusions:** gliomas with *FGFR3-TACC3* gene fusions and *FGFR1* mutations represent two specific entities with distinct anatomical, clinical and molecular features . They should be recognized because both alterations are eligible for currently ongoing anti-FGFR clinical trials.

2006 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase II study of pembrolizumab or pembrolizumab plus bevacizumab for recurrent glioblastoma (rGBM) patients. *First Author: David A. Reardon, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: Blockade of programmed-death 1 (PD-1) mediated immunosuppression has achieved meaningful benefit across many cancers. Vascular endothelial growth factor (VEGF), a highly upregulated proangiogenic growth factor in GBM tumors, can contribute to tumor-associated immunosuppression. We evaluated the safety and efficacy of pembrolizumab (P), a fully human IgG4 PD-1 blocking antibody, with and without bevacizumab (Bev) in rGBM patients. **Methods:** Bev-naïve patients at $1^{st}/2^{nd}$ recurrence requiring $\leq$ 4 mg dexamethasone/day were randomized to receive P (200 mg IV Q3W) with (Cohort A; n = 50) or without (Cohort B; n = 30) Bev (10 mg/kg IV Q2W). The primary endpoint, PFS-6 per RANO, was assessed independently per cohort relative to historical benchmarks. Archival tumor PD-L1 expression and inflammatory gene expression signature were explored as potential biomarkers. **Results:** Grade 2 or 3 treatment related adverse events (TRAEs) occurring in $\geq$10% patients included: Cohort A- hypertension (50%), fatigue (18%), headache (16%), infection (14%) and proteinuria (14%); Cohort B – headache (30%), and fatigue (17%). There were no grade 4 or 5 TRAEs. With a median follow-up of 25.3 months, PFS-6 was: Cohort A-26.0% (95% CI: 16.3, 41.5); Cohort B-6.7% (95% CI: 1.8, 25.4). Median OS was: Cohort A-8.8 mths (95% CI: 7.7,14.2); Cohort B- 10.3 mths (95% CI: 8.5, 12.5). As of 14Jan18, 10 patients remain alive (cohort A – 7; cohort B – 3) including 2 receiving study therapy (both cohort A). **Conclusions:** P is well tolerated +/- Bev but has limited monotherapy activity for rGBM. The anti-tumor activity of P+standard-dosed Bev was comparable to historical Bev monotherapy data. Clinical trial information: NCT02337491.

2007 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase II study of pembrolizumab in leptomeningeal carcinomatosis. *First Author: Priscilla Kaliopi Brastianos, Massachusetts General Hospital, Boston, MA*

Background: Approximately 5-8% of patients with cancer develop leptomeningeal carcinomatosis (LMD). Median survival of patients with LMD is approximately 4-6 weeks and there are no effective treatment options. We performed a phase II study of pembrolizumab in LMD from any solid tumor malignancy (NCT02886585). **Methods:** The primary endpoint is the rate of overall survival at 3 months (OS3). A Simon two-stage design was used to compare a null hypothesis OS3 of 18% against an alternative of 43%. Ten patients were to be enrolled in the first stage. If 2 or more patients were alive at 3 months, an additional 8 patients would be enrolled. If at least 6 patients among the total of 18 patients were alive at three months, then the treatment would be deemed promising in the cohort. Serial CSF, blood samples and tumor samples were collected to elucidate the genomic and transcriptional determinants of immunotherapy response in central nervous system (CNS) lesions. **Results:** A total of 18 patients were accrued (15 with breast cancer, 2 with lung cancer and 1 with gastric cancer). The median follow-up of patients still alive was 2.9 months (range: 2.2 to 6.3 months). The percentage of patients with one or more grade-3 or higher adverse events that were at least possibly related to treatment is 33.3%. At the time of the data retrieval, eight (8) patients (44%) were alive at three months after enrollment (OS3). Therefore, the study met its primary endpoint. Whole exome sequencing of tissue samples and cell-free DNA from CSF and blood, as well as single-cell RNA sequencing of CSF, were carried out to track the evolution of the tumor and the immune system in the CNS and identify biomarkers of response. Genetic and transcriptomic differences within the CSF were detected between the pre- and post-treatment samples and in patients that reached OS3 compared with those that did not. **Conclusions:** Pembrolizumab is well-tolerated and has activity in LMD. CSF provides an opportunity to monitor the clonal evolution of tumor and the immune microenvironment in LMD. Clinical trial information: NCT02886585.

2008 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Window-of-opportunity clinical trial of a PD-1 inhibitor in patients with recurrent glioblastoma. *First Author: John Frederick De Groot, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX*

Background: A Phase III study failed to demonstrate a therapeutic benefit of anti-PD-1 therapy in recurrent GBM. This study was initiated to ascertain tumor immune modulatory properties of pembrolizumab in these patients requiring surgery. The primary objectives were to evaluate immune effector function in resected GBM tissue after pembrolizumab treatment and to determine progression-free survival at 6 months (PFS6). **Methods:** In an open label, single-center, single-arm biomarker-driven Phase 2 trial, 15 patients with GBM, at first or second recurrence who required reoperation for tumor progression were enrolled (NCT02337686). Patients were treated with up to two doses of pembrolizumab prior to surgery and afterwards received pembrolizumab until disease progression or the development of unacceptable toxicities. Recurrent GBM patients receiving standard of care (SOC) were immunologically analyzed (n = 10) as a comparator. **Results:** 21 patients were screened. 15 were enrolled and received at least one dose of pembrolizumab. The most common adverse event was grade 1 or 2 fatigue in 40% of patients. There were no treatment-related deaths. The median follow-up time for all patients was 12 months (95% CI: 3-31). The longest ongoing duration of response exceeded 34 months in two patients (one IDH1 mutant, one wild-type). Median PFS was 7 months (95% CI: 4-16) and PFS6 was 53% (95% CI: 33%-86%). Median overall survival has not been reached (95% CI: 15 to not reached), with an estimated 1-year overall survival of 72% (95% CI: 52%–99.6%). Analysis with 35 immune markers by mass cytometry revealed that GBM tumors are poorly infiltrated with T cells but are enriched with distinct CD68+ populations. These CD68+ cells are less frequent in pembrolizumab-treated patients (n = 6) relative to those treated with SOC (n = 10; $P = 0.01$); however, GBM-infiltrating Tregs are more frequent in patients treated with pembrolizumab ($P = 0.02$). **Conclusions:** Although pembrolizumab was well tolerated, PFS6 data and immune analysis indicates that anti-PD-1 monotherapy is insufficient for a response in the majority of GBM patients, likely secondary to a marked scarcity of T cells within the tumor microenvironment and a preponderance of CD68+ cells. Clinical trial information: NCT02337686.

2009 Poster Discussion Session; Displayed in Poster Session (Board #167), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. *First Author: Sarah B. Goldberg, Yale School of Medicine, New Haven, CT*

Background: Pembrolizumab can have significant and durable activity in patients (pts) with advanced NSCLC, however the activity in the central nervous system (CNS) and the long-term benefit in pts with active brain metastases (BrM) have not been well-described. **Methods:** This is a Phase II trial for pts with NSCLC or melanoma with at least 1 BrM between 5 and 20 mm that is asymptomatic and either untreated or progressing after prior local therapy. For NSCLC pts, cohort 1 is for PD-L1 positive and cohort 2 for PD-L1 negative or unevaluable pts. Pembrolizumab 10mg/kg is administered every 2 weeks. The primary endpoint of this trial is BrM response rate (RR), as determined by modified RECIST (mRECIST) in which brain lesions $\geq$ 5mm are considered measurable and up to 5 target lesions are allowed. **Results:** By this interim analysis, 67 pts with advanced NSCLC were screened, and 39 were eligible and treated with pembrolizumab: 34 in cohort 1 and 5 in cohort 2. 12 pts (30.8%) were treated as initial therapy for metastatic disease, 14 (35.9%) had 1 prior systemic therapy, and 13 (33.3%) had 2 or more prior lines of therapy. 10 of 34 pts in cohort 1 had a response in CNS, for a BrM RR of 29.4% (95% CI 15.1-47.5). 7 pts had discordance between CNS and systemic responses (4 with PD in brain and PR in body, and 3 with PR in brain and PD in body). Progression-free survival in the CNS among pts with a BrM response or stable disease was 10.7 months (95% CI 6.6-not reached). Median OS among all pts was 8.9 months (95% CI 6.6-29.7), with 31% of pts living at least 2 years (95% CI 19-51%). No pts in cohort 2 had a BrM response, but 2 of the 5 lived $>$ 1 year. Treatment was well-tolerated, with no neurologic adverse events (AEs) $>$ grade 1 considered related to treatment; the only grade $\geq$ 3 AE related to treatment in more than 5% of pts was grade 3 pneumonitis in 2 pts. **Conclusions:** Pembrolizumab can result in durable benefit and long-term survival in patients with untreated BrM from NSCLC, with almost a third of patients living more than 2 years after initiation of therapy. We have demonstrated that a PD-L1 inhibitor can have activity in the CNS and may be a safe and active treatment option for patients with small, asymptomatic BrM. Clinical trial information: NCT02085070.

2010 Poster Discussion Session; Displayed in Poster Session (Board #168), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Risk of CNS adverse events (CNS-AEs) for patients with non-small cell lung cancer (NSCLC) and melanoma brain metastases (BM) treated with CNS radiation (CNS-RT) and immune checkpoint inhibitors (CPIs). *First Author: Michael Edward Devitt, University of Virginia, Charlottesville, VA*

Background: CPIs are widely used in the treatment of both metastatic melanoma and NSCLC. BM frequently occur and are treated with CNS-RT. Since both CNS-RT and CPIs can cause neuro-inflammation, we tested the hypothesis that concomitant treatment with CPIs and CNS-RT results in an increased risk of CNS-AEs. **Methods:** We identified patients with melanoma and NSCLC with BM treated with CNS-RT and seen at our institution between 2014 and 2016. Concomitant treatment with CPIs and CNS-RT was defined as administration of CPIs within 3 months before or after CNS-RT. CNS-AEs were defined as new or worsening edema on brain MRI without disease progression, new or worsening neurological deficit, or need to start or increase corticosteroids. A generalized linear model incorporated significant variables from a univariate analysis to model the incidence of CNS-AEs. Variables considered included the use of CPIs within 3 months of CNS-RT, cancer type, type of CNS-RT (gamma knife [GKRS] versus whole brain radiation therapy [WBRT]), number of metastases, and maximum metastasis size. **Results:** We identified 213 cases of CNS-RT (NSCLC 167 [78%], GKRS 147 [69%], WBRT 63 [30%], median 2 BM [1 to $>$ 20], median 17 mm max diameter [2 mm-74 mm]). Patients were 52% female with median age 61 (range 21-87), and ECOG 0-2 in 93% at time of CNS-RT. CNS-AEs occurred in 40 (19%) cases. Receipt of CPIs within 3 months of CNS-RT was the only factor associated with an increased risk of CNS-AEs (odds ratio 3.9, 95% CI 1.6-9.2, p-value 0.002). The rates of CNS-AEs were 11 of 28 (39%) in cases which received CPIs within 3 months of CNS-RT and 29 of 184 (16%) in cases which did not. The characteristics of the 11 cases with CPI exposure and CNS-AEs were: 73% underwent GKRS, 45% were NSCLC, 18% received CTLA4 alone, 55% PD-(L)1 alone, 27% combined CTLA4/PD-1, and 55% had a neuro deficit as part of their CNS-AE. **Conclusions:** This retrospective analysis demonstrates that the use of CPIs within 3 months of CNS-RT is associated with an increased risk of CNS-AEs. CNS-RT modality, cancer type, and metastasis size or number were not associated with an increased risk of CNS-AEs.

2011 Poster Discussion Session; Displayed in Poster Session (Board #169), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Risk-adjusted survival for melanoma brain metastases in the era of checkpoint blockade immunotherapies: Results from a national cohort. *First Author: Bryan Iorgulescu, Brigham and Women's Hospital, Boston, MA*

Background: The recent successes of checkpoint blockade immunotherapy (CBI) and $BRAF^{V600}$-targeted therapy trials have generated exciting promise for revolutionizing the management of patients with advanced melanoma. However, because early clinical trials of CBIs and $BRAF^{V600}$-targeted therapy either excluded or included disproportionately fewer cases of melanoma brain metastases (MBM), the survival benefit of these novel therapies for MBM remains unknown. **Methods:** The characteristics, management, and overall survival (OS) outcomes of patients who presented with cutaneous MBMs during 2010-2015 were evaluated using the National Cancer Database, which comprises approximately 70% of all newly diagnosed cancers in the U.S. OS was analyzed with risk-adjusted Cox proportional hazards and compared by Kaplan-Meier techniques. **Results:** 2,753 (36%) of patients presenting with stage 4 melanoma had MBMs. MBM patients who presented after the 2011 FDA approvals for CBI and $BRAF^{V600}$-targeted therapy demonstrated a 91% relative increase in 4-yr OS to 14.1% (95CI: 12.2-16.1) from 7.4% pre-approval (95CI: 5.3-10.0, $p < 0.001$). In the post-approval era, the proportion of MBM patients that received CBI rose from 10.5% in 2011 to 34.0% in 2015 ($p < 0.001$). Initial CBI in MBM patients displayed a 2.4x improved median and 4-yr OS of 12.4 mos (95CI: 10.4-15.8; vs. 5.2 mos, 95CI: 4.7-5.9, $p < 0.001$) and 28.1% (95CI: 22.1-34.4; vs. 11.1%, 95CI: 9.3-13.1). These benefits were particularly pronounced in MBM patients without extracranial metastases, in which CBI demonstrated improved median and 4-yr OS of 56.4 mos (95CI: 25.0-not reached; vs. 7.7 mos, 95CI: 6.7-8.7, $p < 0.001$) and 51.5% (95CI: 38.9-62.8; vs. 16.9%, 95CI: 13.5-20.6) that persisted in MBMs that underwent resection or SRS. **Conclusions:** Using a large national cohort comprised of a "real-life" treatment population of MBMs, we demonstrate the dramatic improvements in OS associated with novel checkpoint blockade immunotherapies.

2012 Poster Discussion Session; Displayed in Poster Session (Board #170), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A large, multicenter, retrospective study to identify a cutoff of MGMT methylation status by quantitative pyrosequencing approach in patients (PTS) with glioblastoma (GBM). *First Author: Giuseppe Lombardi, Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy*

Background: MGMT promoter methylation status representsan important prognostic factor for GBM PTS in terms of progression free survival (PFS) and overall survival (OS). Quantitative pyrosequencing approach is a valid alternative to methylation-specific PCR but a cut-off value in still unclear. We performed a large, multicenter, retrospective study to identify a real cut-off value to discriminate its impact on clinical outcome in terms of PFS and OS. **Methods:** Retrospectively, from italian neuro-oncology centers, we collected GBM PTS from 2005 to 2016 with assessment of MGMT promoter methylation by pyrosequencing approach evaluating CpG islands from 74 to 83. Other inclusion criteria were: confirmed histological diagnoses of GBM, ECOG PS $\geq$2, treatment with concomitant radiation therapy and temozolomide. Kaplan-Maier method was used to estimate the survival curves and ROC curve for defining cut-off value for PFS and OS. **Results:** 376 GBM PTS were enrolled;median age was 62 ys (25-86); ECOG PS was 0 in 129 PTS, 1 in 160 PTS, 2 in 87 PTS; 212 PTS (58%) had a complete resection. 67 PTS (18%) received a second surgery. Median PFS and OS was 8.6 and 14.3 months. The optimal cut-off value to identify a strong prognostic value of MGMT methylation status in terms of PFS and OS, was 26% (sensitivity 72%, specificity 61%, accuracy 71%) and 24% of methylation (sensitivity 72%, specificity 61%, accuracy 71%), respectively. On multivariate analyses, corrected for age, KPS, type of surgery and second surgery, the MGMT cut-off values remained significantly correlated to longer PFS (HR = 0.5, 95%CI 0.4-0.7) and OS (HR = 0.47, 95% CI 0.3-0.6). **Conclusions:** From this large, multicenter study, we identify, by pyrosequencing approach, a strong prognostic value of MGMT methylation, in terms of PFS and OS. This value could be used as stratification factor in prospective clinical trials.

2013 Poster Discussion Session; Displayed in Poster Session (Board #171), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Differential elevation of TERT activity and sensitivity to temozolomide by type of TERT mutation in MGMT promoter-methylated glioblastoma. *First Author: Michael Weller, Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

Background: Benefit from temozolomide chemotherapy in glioblastoma is essentially limited to patients with tumors with O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation. The impact of the MGMT status on chemosensitivity may be modulated by telomerase reverse transcriptase (TERT) promoter mutations which affect two regions of the TERT promoter, designated as C228T and C250T. **Methods:** TERT promoter mutation status and TERT activity were determined in a panel of glioma cell lines and correlated with sensitivity to irradiation or temozolomide. TERT status alterations were induced using sh-mediated gene TERT silencing or wildtype TERT overexpression. TERT mutation and MGMT promoter methylation status were also determined in a clinical patient cohort from the German Glioma Network. **Results:** C228T-mutant glioma cell lines (n = 8) express higher levels of TERT mRNA (mean 0.046 ± 0.012 vs 0.012 ± 0.004 arbitrary units, p = 0.049) and exhibit higher TERT catalytic activity (mean 122 ± 16 vs 53 ± 11 arbitrary units, p = 0.022) than C250T-mutant glioma cell lines (n = 5). C228T-mutant glioma cell lines are also more sensitive to irradiation (mean ED90 4.6 ± 0.7 versus 7.1 ± 0.8 Gy, p = 0.039) or temozolomide (mean EC50 101.6 ± 58.5 versus 295.2 ± 53.8 μM, p = 0.045) *in vitro*. Targeted alterations of TERT status result in profound changes in radiosensitivity and chemosensitivity: TERT gene silencing is protective whereas TERT overexpression sensitizes to either genotoxic treatment. Consistent with these preclinical observations, patients with C228T TERT mutation and MGMT promoter methylation appeared to derive more benefit from temozolomide chemoradiotherapy (median overall survival 26.5 months, 95% CI 20.3-32.7) than patients with the C250T mutation (median overall survival 16.2 months, 95% CI 8.5-23.8) or patients without TERT mutation (median overall survival 23.7 months, 95% CI 18.7-28.8). **Conclusions:** These data refine current models on how TERT and MGMT interact to determine outcome in human glioblastoma and illustrate how future targeted interventions focusing on TERT and MGMT may help to tailor pharmacotherapy of glioblastoma.

2014 Poster Discussion Session; Displayed in Poster Session (Board #172), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The natural course of hypermutator gliomas. *First Author: Carlos Kamiya-Matsuoka, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX*

Background: Hypermutator genotype (HMGen) is seen in glioblastoma (GB) and lower-grade gliomas. It may be induced by temozolomide (TMZ) and leads to TMZ resistance. We describe demographics, mutational features, treatments and outcomes of HMGen gliomas. **Methods:** Retrospective review at MD Anderson between 02/2006-02/2017 identified 309 gliomas with tissue analyzed by next-generation sequencing (T200-1, Oncomine, FoundationOne). HMGen was defined as tumor mutation burden (TMB-30) of 30 or more mutations (mut) per Mb, or displaying mut in mismatch repair (MMR) or DNA polymerase (Pol) genes. **Results:** 38 (12.3%) patients had HMGen. 25 (66%) were men. 19 (50%) had TMB-30, 10 (26%) had mut in Pol gene, 6 (16%) in MMR (1 had mut in both MLH and MSH6 genes), 1 had mut in both MMR and Pol genes and only 2 met all three criteria. GB (N = 26, 68%) was the most common tumor (N = 6, 23.1% IDH1-mut), followed by WHO grade III oligodendroglioma (N = 8, 21%), grade II astrocytoma (N = 3, 8%) and grade II oligodendroglioma (N = 1, 3%). HMGen was found as initial genotype in 17 (45%) cases, the rest after treatment with alkylating agents. Of those patients with de novo HMGen, Pol gene mut was most common (N = 9, 53%), followed by MMR mut (N = 4, 23.5%) and TMB-30 (N = 4, 23.5%). Of those 17, 15 (88%) were GB followed by WHO grade II gliomas: 1 oligodendroglioma with MMR mut (MSH6) and 1 astrocytoma with TMB-30. For post-treatment HMGen, the most common alterations was TMB-30. The mean cumulative TMZ dose at HMGen diagnosis for GB, WHO grade II/III astrocytoma and grade II/III oligodendroglioma was 16g, 24.6g/28g, and 41g/29.6g, respectively with a mean monthly dose of 1.5-1.8g. Only 1 patient received CCNU (0.4g). For de novo and post-treatment HMGen GB IDH1-wild-type, the OS and PFS from HMGen diagnosis was 19.6/15 and 23.7/3.9 months (m) respectively. The latency interval from histopathologic GB to HMGen was 17.5 m and the total OS was 43.6 m. Most of this subgroup (65%) are still alive with a time from initial diagnosis to last follow-up of 35.7 m. **Conclusions:** HMGen gliomas may occur spontaneously at initial diagnosis before treatment and may be associated with longer survival than historical controls. Further investigation is needed to determine whether HMGen can be predicted due to potential clinical implications.

2015 Poster Discussion Session; Displayed in Poster Session (Board #173), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase 1b/2 study of pexidartinib (PEX) in combination with radiation therapy (XRT) and temozolomide (TMZ) in newly diagnosed glioblastoma. *First Author: Howard Colman, Hunstman Cancer Institute, Salt Lake City, UT*

Background: PEX is an oral small molecule inhibitor of KIT and CSF1 receptor expressed on microglia, blood vessels, and glioblastoma (GBM) tumor cells. PEX achieved good tissue exposure in a prior recurrent GBM study, and preclinical studies indicate PEX may sensitize GBM to standard of care (SOC) therapy through effects on both tumor and microenvironment. **Methods:** Phase Ib determined the recommended Phase II dose (RP2D) with SOC XRT/TMZ. Phase II primary endpoint was progression free survival (PFS); secondary endpoints included overall survival (OS) and safety. Patient entry criteria were designed to replicate the RTOG 0525 control arm, which was used as a historical control. **Results:** The identified RP2D was PEX 400mg BID 5 days/week during and 7 days/week after SOC XRT/TMZ. Of the total RP2D population, 42 were evaluable for comparison and demonstrated similar characteristics to the RTOG 0525 control arm. As of November 2017, mPFS from registration is 6.7 months in PEX patients (95% CI 4.2, 10.2) vs. 7.5 months in historical controls. Estimated mOS for PEX is 15.4 months (95% CI 12.3, 20.7) vs. 18.9 months in controls. PEX was well tolerated, with most common drug-related toxicities including neutropenia and increased ALT/AST. MGMT unmethylated patients comprised 60% of the patients, with estimated mOS of 13.8 months (95% CI 12.3, 20.7) vs. 68% and estimated mOS of 16.6 months in historical controls. MGMT methylated patients comprised 40%, and mOS not yet reached vs. 32% and estimated mOS of 23.5 months in historical controls. Tumors with high expression of monocyte/macrophage marker CD163 and macrophage stimulating factor CSF1 trended to worse overall survival. mOS was 13.8 months for tumors with high expression of CD163 vs. 19.2 in tumors with low expression (p = .323). mOS was 12.3 months in tumors with high CSF1 expression vs. 19.2 in tumors with low (p = .328). **Conclusions:** PEX can be safely combined with SOC XRT/TMZ in newly diagnosed GBM. Results suggest minimal PEX activity when added to XRT/TMZ in an unselected GBM population for improving PFS and OS compared to robust, well-matched historical controls. Further investigation in relevant biomarker subgroups is ongoing. Clinical trial information: NCT01790503.

2016 Poster Discussion Session; Displayed in Poster Session (Board #174), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Safety and preliminary efficacy data from a phase I study of an implantable low intensity pulsed ultrasound (LIPU) device for disrupting the blood-brain barrier (BBB) in patients treated by chemotherapy for recurrent glioblastoma (GBM). *First Author: Ahmed Idbaih, Inserm U 1127, CNRS UMR 7225, Sorbonne Universités, UPMC Univ Paris 06 UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France*

Background: The BBB limits the efficacy of many chemotherapies in GBM patients by blocking the passage of drugs to the brain. Two to four minutes of LIPU in combination with injection of micron-sized microbubbles can transiently disrupt the BBB to increase the passage of drugs such as carboplatin. **Methods:** This first-in-man, single arm, monocentric trial was performed at Hôpital Universitaire Pitié-Salpêtrière, Paris, France from 2014-2018. Recurrent GBM patients were implanted with (1) or (3) 1 MHz, 10-mm diameter cranial devices in burr holes during debulking surgery or during a dedicated procedure under local anesthesia. Ultrasound dose was escalated using a Simon titration design. The device was activated monthly to transiently disrupt the BBB before IV administration of carboplatin (AUC4-6). BBB disruption was visualized using MRI and patients were monitored clinically. **Results:** Twenty-seven patients were implanted with LIPU devices and 25 per-protocol were sonicated: 19 patients with (1) US emitter and six patients with (3) US emitters. In 85 ultrasound sessions, BBB disruption was visible on post-sonication T1w MRI for 72 sonications and was ultrasound dose dependent. Few transient and manageable severe related adverse events were observed: a partial seizure, two cases of transient edema (H1 and D15) and one transient facial palsy. No carboplatin-related neurotoxicity was observed. All patients treated with (1) emitter had tumor progression and 3/19 patients were alive. In this cohort, patients with no or poor BBB disruption (n = 8) had a median PFS of 13 weeks, and a median OS of 8.9 months. Patients with clear BBB disruption (n = 11) had a median PFS of 15 weeks, and a median OS of 13 months. **Conclusions:** LIPU was well tolerated and may increase the effectiveness of drug therapies in the brain. The sonication of larger volumes of brain in recurrent GBM will be investigated in a future trial and may further enhance the observed effectiveness of this treatment modality. Clinical trial information: NCT02253212. Clinical trial information: NCT02253212.

2017 Poster Discussion Session; Displayed in Poster Session (Board #175), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

VXM01 phase I study in patients with progressive glioblastoma: Final results. *First Author: Wolfgang Wick, Neurology Clinic, DKFZ, DKTK, Heidelberg, Germany*

Background: VXM01 consists of an attenuated *Salmonella typhi* Ty21a carrying a plasmid encoding for vascular endothelial growth factor receptor (VEGFR)-2. The bacterium is a vector *via* the oral route of administration carrying the plasmid into the Peyer's plaques. The vaccine elicits a systemic T-cell response targeting VEGFR-2. This trial examined safety and tolerability, clinical and immunogenic response to VXM01 after at least four vaccinations [10^6 or 10^7 colony-forming units (CFU)] in patients with progressive glioblastoma who have failed at least radiochemotherapy with temozolomide. **Methods:** Patients with progressive operable glioblastoma were subjected to VXM01 in one oral administration each on day 1, 3, 5, and 7. In addition, VXM01 was allowed to be administered in 4-weekly single doses every 4 weeks during the tumor follow-up period after surgery. Follow-up was done by weekly safety laboratories and physical examinations in the treatment period and 12-weekly thereafter T-cell immunomonitoring in the peripheral blood, and brain tumor immunohistochemistry. **Results:** Fourteen patients have been treated with VXM01. Three out of them with additional nivolumab. Surgery has been performed in eight patients. Under VXM01 treatment 119 adverse events, mostly unrelated to VXM01, were observed after a median of 8 doses per patient. ELISpot analysis showed a detectable VEGFR-2 specific T cell response in 7 out 12 (58%) patients measured. In the observation period of up to 20 months 7 patients are alive, 5 out of them survived for more than one year, 2 patients are ongoing at month 10. In one patient there was an objective and durable T1 response. Survival seemed to be correlated with a higher CD8/Treg ratio in progressive and primary tumor, which further increased after VXM01 treatment. In patients with prolonged survival a decrease in intratumoral PD-L1 was observed arguing for combination of VXM01 with an anti-PD-L1 checkpoint inhibitor. **Conclusions:** VXM01 was safe and produces detectable specific peripheral immune responses as well as CD8/Treg ratio increase in post-vaccine tumor tissue. There was one patient with an objective response. As a next step, a combination study of VXM01 and anti-PD-L1 checkpoint inhibitor has been launched. Clinical trial information: NCT02718443.

2018 Poster Discussion Session; Displayed in Poster Session (Board #176), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase I clinical trials evaluating olaparib in combination with radiotherapy (RT) and/or temozolomide (TMZ) in glioblastoma patients: Results of OPARATIC and PARADIGM phase I and early results of PARADIGM-2. *First Author: Anthony J. Chalmers, University of Glasgow, Glasgow, United Kingdom*

Background: The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (O) has radio and chemosensitizing properties in GBM models. Clinical development of PARP inhibitor combinations has been restricted by exacerbation of hematological toxicity and acute radiation toxicity. We studied pharmacokinetics (PK), safety and toxicity of O with RT and/or TMZ in three phase I studies. **Methods:** OPARATIC determined PK of O (AZ tablet formulation) in core and margins of recurrent GBM and maximum tolerated dose (MTD) of O with 42 day cycles of daily TMZ. PARADIGM determined recommended phase II dose (RP2D) of O with 40 Gy 15 fractions of radiotherapy in newly diagnosed patients aged $>$ 70. PARADIGM-2 comprises two phase I studies of O+RT (60 Gy 30#, MGMT unmethylated) or O+RT+TMZ (MGMT methylated) in newly diagnosed patients aged $<$ 70. **Results:** OPARATIC: 48 patients recruited; 27 underwent surgery, 36 receiving O/TMZ were evaluable. O detected in 71/75 tumor core specimens (27 patients); mean conc. 588nM (97-1374nM), and 27/28 tumor margin specimens (10 patients); mean conc. 500nM (97-1237 nM). Myelosuppression necessitated intermittent O dosing. MTD defined as O 150 mg (OD) days 1-3 weekly plus TMZ 75 mg/m2 daily. For 36 evaluable patients receiving 0/TMZ, progression-free survival at 6 months was 39%. PARADIGM: 16 patients (median age 72) treated in four O dose cohorts. One DLT (agitation grade 3) recorded (cohort 3, 100 mg BID). RP2D of O +40Gy 5# in elderly GBM was 200 mg BID daily. Median overall survival 10.3 months (80% CI: 6.3 – 11.7 months) at 12.9 months median follow up. PARADIGM-2: 29 patients screened, 14 commenced study treatment. Three MGMT unmethylated patients completed cohort 1 (50 mg QID) with no DLTs and 4 recruited to cohort 2 (100 mg QID) with no DLTs to date. Seven MGMT methylated patients recruited to cohort 1 (100 mg x1 per week); 1 DLT reported to date (low platelets). **Conclusions:** O penetrates core and margins of recurrent GBM. Combination with TMZ requires intermittent dosing but is safe and well tolerated. Combination with radiotherapy is extremely well tolerated and randomized phase II evaluation is underway. Clinical trial information: NCT01390571.

2019 Poster Discussion Session; Displayed in Poster Session (Board #177), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

CXCR4 blockade at the end of irradiation to improve local control of glioblastoma (GBM). *First Author: Reena Parada Thomas, Stanford University, Palo Alto, CA*

Background: Based on preclinical work identifying an important role for the CXCL12 (SDF1)/CXCR4 chemokine axis in reestablishing vascularity after irradiation of GBM, we launched a Phase I/II study assessing the impact of CXCR4 blockade with a continuous infusion of Plerixafor (AMD3100, Mozobil), an established CXCR4 small molecule antagonist, already in clinical use for bone marrow stem cell mobilization. **Methods:** Open label Phase I/II study for newly diagnosed adult GBM patients, ages 75 or younger, with KPS of at least 60 were administered a 4-week continuous intravenous infusion starting one week prior to the completion of standard irradiation. **Results:** 29 patients (median age: 60 years) were enrolled and completed the infusion course. The Phase I study established that 16.6 μg/kg/hr was well tolerated (no Gr III drug associated toxicity) with achievable Plerixafor serum values above the threshold level for CXCR4 blockade. A total of 19 patients underwent DSC-MRI for quantification of relative cerebral blood volume (rCBV) at their 1-month and 6-month follow up scans. Compared to a group of 11 contemporaneous patients treated with standard chemo-radiation, there was a significant reduction of mean rCBV within the 95% isodose radiation field at 1-month (0.76 vs 0.88, $p = 0.04$) and 6-months (0.67 vs 0.87, $p = 0.001$), as observed in our preclinical studies. In association with this, was an out of field (i.e., beyond the 95% isodose field or within leptomeninges) first recurrence rate of 58.8% compared to 10% in the control group ($p = 0.018$, Fisher exact test). The Kaplan-Meier estimated median overall survival in months was 20.7, 95% CI (17.3, NA) and was not correlated with surgical extent, age, or MGMT status. **Conclusions:** GBM recurrences using standard treatment are generally local in 80% of patients. The high out of field first recurrence rate in this series, in conjunction with a marked decrease in rCBV, is therefore extremely notable. When viewed with the favorable survival data, it suggests improved local control and enhancement of the therapeutic response to radiation. We therefore conclude that blockade of the SDF1/CXCR4 axis represents a novel, clinically impactful strategy worthy of further investigation in GBM.

2020 Poster Discussion Session; Displayed in Poster Session (Board #178), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Effect of dexamethasone in glioblastoma (GBM) patients on systemic and intratumoral T-cell responses induced by personalized neoantigen-targeting vaccine. *First Author: David A. Reardon, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA*

Background: The impact of individualized neoepitope vaccination targeting neoantigens arising from tumor-specific mutations for GBM, a low mutation burden tumor with an immunologically cold tumor microenvironment, as well as that of concurrently administered dexamethasone (dex), are unknown. **Methods:** Individualized vaccination of up to 20 synthetic, long neoepitope peptides with high predicted HLA binding affinity admixed with poly-ICLC, were administered subcutaneously using a prime-boost schedule after RT to newly diagnosed, MGMT unmethylated, at least partially resected, GBM patients without progression after radiation (RT) in our phase 1b study. **Results:** 9 of 10 screened patients had sufficient ($\geq$ 10) identified neoepitope peptides. 8 patients without progression after RT received vaccine consisting of a median of 12 peptides (range, 7-20) beginning a median of 18.6 wks (range 16.0-23.2) after surgery. Adverse events were limited to infrequent grade 1/2 local reactions and fatigue. Median PFS and OS were 7.5 mths (90% CI: 6.2, 9.7) and 16.8 mths (90% CI: 9.6, 21.3). Evaluation of neoepitope-specific immune responses and tumor immune infiltrate analyses were performed on five patients with pre- and post-vaccination samples. Three patients on dex for post-RT edema during vaccine had no immune responses and no change in tumor infiltrating effector cells. In contrast 2 patients not on dex had robust, de novo immune responses against multiple predicted personal neoantigens including polyfunctional neoantigen-specific CD4+ and CD8+ T cell responses that were enriched for memory and activated phenotypes as well as increased numbers of tumor-infiltrating CD4+ and CD8+ T cells. T cell receptor analysis from one patient identified identical clonotypes isolated from post-vaccination tumor tissue and peripheral blood including a clonotype specific for ARHGAP35, a neoantigen targeted by vaccination. **Conclusions:** Individualized, multi-neoepitope vaccines are feasible, safe and capable of generating systemic and intra-tumoral immune responses in GBM patients that appear to be abrogated by dex. Clinical trial information: NCT02287428.

2021 Poster Session (Board #179), Sat, 1:15 PM-4:45 PM

Long-term stroke risk of single-fraction photon-based stereotactic radiosurgery for meningioma. *First Author: Shearwood McClelland, Oregon Health and Science University, Portland, OR*

Background: A recent randomized study of fractionated radiation therapy (RT) examining 44 subtotally resected/recurrent benign meningioma patients revealed that at median follow-up of 17.1 years, the risk of stroke following proton-photon RT was 20.5%; the average stroke developed 5.6 years following RT completion (Sanford et al., 2017). This stroke risk is up to 10 times higher than the 2-6% rate expected for the general population of ages 40-79 (Mozaffarian et al., 2015). The stroke rate following single-fraction stereotactic radiosurgery (SRS) has not been previously studied in meningioma patients. **Methods:** A PubMed database search for relevant articles examining SRS for meningioma with minimum mean/median follow-up of six years was undertaken. Stroke rate was assessed either from direct description in manuscripts, or from extrapolating post-SRS complications from reported clinical examinations (i.e. hemiparesis/weakness, pituitary dysfunction following treatment of cavernous sinus lesions). Results were then culled to determine an overall stroke rate. **Results:** Fourteen studies met inclusion criteria; 1,431 patients received photon-based SRS for meningioma with a sufficient long-term follow-up. Median/mean follow-up ranged from 75-144 months. Operative resection prior to SRS occurred in 769/1377 patients (55.8%) for whom surgical history was reported. Twenty-four patients suffered a stroke following SRS, yielding a rate of 1.7%. **Conclusions:** The long-term stroke rate following single-fraction photon-based SRS for benign meningioma was 1.7%, more than twelve times lower than for fractionated proton-photon RT and comparable to that expected for the general population. The majority of patients underwent resection prior to SRS. These findings indicate that for patients with benign meningioma desiring to avoid the high stroke risk of fractionated proton-photon RT, SRS has a comparable stroke risk profile to observation. Such findings are pertinent for radiation oncology, neuro-oncology, and neurosurgery management of these patients.

2022 Poster Session (Board #180), Sat, 1:15 PM-4:45 PM

A unique MRI-based radiomic signature predicts hypermutated glioma genotype. *First Author: Islam Hassan, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hypermutation is defined as the excessive accumulation of DNA mutation in cancer cells and is reported in several forms of cancer including low and high grade gliomas. Incidence of hypermutated genotype was associated with failure of DNA repair machinery such as mismatch repair (MMR) or disruption of DNA fidelity due to mutations in DNA polymerase genes (POLE and POLD).Hypermutated gliomas (mainly glioblastoma (GB)) are largely seen at recurrence with associated resistance to temozolomide therapy. Herein, we sought to identify an imaging-based signature for hypermutated gliomas using a radiomics-based approach. **Methods:** In this IRB-approved retrospective study, we analyzed a total of 101 patients with primary gliomas from the University of Texas MD Anderson Cancer Center. Next generation sequencing (NGS) platforms (T200 and Foundation 1) were used to determine the Mutation burden status in post-biopsy (stereotactic/excisional). Patients were dichotomized based on their mutation burden; 77 hypomutated ($<$ 30 mutations) and 24 hypermutated ($>$ = 30 mutations or $<$ 30 with MMR gene or POLE/POLD gene mutations). Radiomic analysis was performed on the conventional MR images (FLAIR and T1 post-contrast) obtained prior to tumor tissue surgical sampling; and a total of 2480 rotation-invariant radiomic features were extracted using: (i) the first-order histogram and (ii) grey level co-occurrence matrix. The Maximum Relevance Minimum Redundancy technique was used to select the most relevant radiomic features. ROC analysis and leave-one-out cross-validation (LOOCV) were used to assess the performance of the Support Vector Machine (SVM) classifier as and AUC, Sensitivity, Specificity, and p-value were obtained. **Results:** We found 100 radiomic features that can discriminate between hypermutated versus hypomutated gliomas, AUC 96.3% (CI: 90.2%-98.9%), Sensitivity 100%, Specificity 95%, p-value = 3.769e-6. **Conclusions:** Hypermutated gliomas has a unique radiomic quantitative signature that can be used to predict mutation burden regardless of tumor grade or histopathology.

2023 Poster Session (Board #181), Sat, 1:15 PM-4:45 PM

Updated results of the INTELLANCE 2/EORTC trial 1410 randomized phase II study on Depatux –M alone, Depatux-M in combination with temozolomide (TMZ) and either TMZ or lomustine (LOM) in recurrent EGFR amplified glioblastoma (NCT02343406). *First Author: Martin J. Van Den Bent, Erasmus MC Cancer Center, Rotterdam, Netherlands*

Background: Depatux-M is a tumor-specific antibody-drug-conjugate consisting of an antibody (ABT-806) bound to the toxin monomethylauristatin-F. In the primary analysis on EORTC 1410 we reported a trend (p = 0.06) towards improved overall survival (OS) in patients with EGFR-amplified (amp) recurrent glioblastoma treated with Depatux-M in combination with TMZ. **Methods:** Eligible were patients with centrally confirmed EGFRamp glioblastoma at 1st recurrence after TMZ chemo-irradiation, occurring $\geq$3 months after radiotherapy. Patients were randomized to either a) Depatux-M 1.0 mg/kg every 2 weeks intravenously, or b) the same treatment combined with TMZ 150-200 mg/m^2 day 1-5 every 4 weeks, or c) either LOM or TMZ (TMZ/LOM) depending on the time of relapse. Primary endpoint was OS. Pharmacokinetic (PK) sampling was done on day (d) 1 before and after dosing, d 4-7, d 1 course 2 before and after dosing, d 5-7 course 4, d 1 course 3, and then every 2 cycles. All available PK samples were used to calculate the Depatux-M average concentration during course 1 (CavgC1). The level of EGFRamp was determined using both qPCR, next generation sequencing and FISH. **Results:** An updated OS comparison of Depatux-M in combination with TMZ versus TMZ/LOM with longer follow-up, performed after 220 observed deaths using log-rank test and cox models stratified by stratification factors at randomization showed a HR of 0.68 (95%CI [0.48, 0.95]; p = 0.024) and 1-year OS rates of 40% versus 28%. In multivariate analysis including performance status, MGMT, surgery for the recurrence, time from last TMZ to relapse and lesion diameter, CavgC1 was a significant predictor for OS (HR 0.96, 95% CI [0.93, 0.98], p = 0.0013). In Depatux-M treated patients, EGFR status (high vs low level amplification) did not correlate with OS. **Conclusions:** This updated OS analysis of Depatux-M in combination with TMZ confirmed the OS improvement in EGFRamp recurrent glioblastoma. In Depatux-M treated patients, higher drug levels during course 1 were associated with improved OS but high levels of EGFR amplification at first diagnosis were not. Clinical trial information: NCT02343406.

2025 Poster Session (Board #183), Sat, 1:15 PM-4:45 PM

Depression and survival of glioma patients: A systematic review and meta-analysis. *First Author: Nayan Lamba, Harvard Medical School, Boston, MA*

Background: There is currently a lack of well-established meta-analyses examining the association between depression and patient survival in glioma patients. The aim of this meta-analysis was to study the effect of depression on glioma patients' survival. **Methods:** A meta-analysis was conducted according to the PRISMA guidelines. PubMed, Embase, and Cochrane databases were searched for studies that reported depression and survival among glioma patients through 11/06/2016. Both random-effects (RE) and fixed-effect (FE) models were used to compare survival outcomes in glioma patients with and without depression. **Results:** Out of 619 identified articles, six were selected for the meta-analysis. Using RE model, the various measures of survival outcomes displayed worsened outcomes for both high and low grade glioma patients with depression compared to those without depression, with an overall pooled risk ratio for survival of 0.67 (95%CI: 0.46, 0.99; I2 = 51.4%, P-heterogeneity = 0.06); an overall pooled standard mean difference for the overall survival time (in months) of -0.88 (95%CI: -1.89, 0.13; I2 = 87.1%, P-heterogeneity $<$ 0.01); and a pooled hazard ratio of death of 1.42 (95% CI: 1.00, 2.01; I2 = 0%, P-heterogeneity = 0.85). Using the FE model, results were similar except for overall survival time, where the shorter survival time in glioma patients with versus without depression reached statistical significance (-0.70; 95%CI: -0.86, -0.53). Among high-grade glioma patients, pre-operative depression diagnosis was associated with fewer months of survival compared to postoperative diagnosis, as shown under the FE model (P-interaction $<$ 0.01), but not under the RE model (P-interaction = 0.14). **Conclusions:** Among patients with either low or high-grade glioma, depression was associated with significantly worsened survival regardless of time of diagnosis.

2026 Poster Session (Board #184), Sat, 1:15 PM-4:45 PM

Association between treatment facility volume and mortality in patients with glioblastoma (GBM): A large national analysis. *First Author: Sonikpreet Aulakh, Mayo Clinic, Jacksonville, FL*

Background: Glioblastoma (GBM) is an aggressive primary malignancy of the brain, treated with surgical resection and chemo-radiotherapy, yet it has a dismal prognosis of 12-14 month overall survival (OS). Optimal outcomes require an experienced team providing multidisciplinary management. We explored the association of treatment facility volume and mortality in patients with GBM. **Methods:** We identified incident GBM (ICD-O-3 code: 9440/3) cases from the National Cancer Database (NCDB) (2004-2013) and utilized Cox-regression to determine the facility volume-outcome (volume = quartiles; Q) relationship, adjusting for year of diagnosis, demographic (sex, age, race, ethnicity), socio-economic (income, education, insurance type), geographic (area of residence, treatment facility location, travel distance) and co-morbidity factors (Charlson-Deyo score). **Results:** There were 114,467 patients (median age 60 years, range: 18-90) with GBM treated at 1207 facilities of which, 54.8% were men. Median annual facility volume was 5 patients/year (range: 0.1-136.4). The top 14 (1.2%) facilities treated $>$ 60 patients/year (10%). Median overall survival (OS) was 15 months There were significant differences (all $p < 0.001$) in patient characteristics by facility volume (Table). Unadjusted median OS by facility volume (months) was Q1: 29.1, Q2: 32.9, Q3: 36.4, Q4: 48.2 ($p < 0.0001$). Multivariate analysis showed facility volume to be independently associated with all-cause mortality (Reference Q4; Q3 HR: 1.30, 95% CI 1.28-1.33; Q2 HR: 1.36, 95% CI 1.36-1.43; Q1 HR: 1.58 95% CI 1.50-1.67). OS disparity by facility volume is persistent but not worsening in recent years (2010-2013 vs 2004-2005). **Conclusions:** In GBM, facility-volume independently affects OS of the patients. Attempts should be made to address modifiable factors and get patients access to high-volume centers earlier in the disease course.

Characteristic	Lower Quartile (Q1, Q2, Q3)	Higher Quartile (Q4)
Patients seen/year	$<$ 1-12.2	12.2-136.4
Academic centers	7.3%	48.9%
Median age (years)	63	58
Median travel distance to facility (miles)	7.2	14.7
Private Insurance	41.2%	50.4%
Medicare/Medicaid	51%	40.7%
Income > $46000	38.7%	43.6%

2027 Poster Session (Board #185), Sat, 1:15 PM-4:45 PM

Angiotensinogen gene silencing to predict bevacizumab response in recurrent glioblastoma patients. *First Author: Thomas Urup, Rigshospitalet, Copenhagen, DK*

Background: Bevacizumab in combination with chemotherapy has shown activity in recurrent glioblastoma patients. Patients who achieve response to bevacizumab have improved survival as well as quality of life. Recently, we found that low gene expression of angiotensinogen (*AGT*) was a predictive factor for bevacizumab response in recurrent glioblastoma patients. Because promoter methylation of *AGT* has been associated with *AGT* gene silencing, we investigated if *AGT* promoter methylation in tumor tissue predicts response to bevacizumab combination therapy in recurrent glioblastoma patients. **Methods:** The study includes 82 recurrent glioblastoma patients treated with bevacizumab combination therapy whom were both RANO response and biomarker evaluable. DNA methylation of 7 CpG sites in the CEBPA binding site (~200 bp from TSS) of the *AGT* promoter was measured using pyrosequencing. *AGT* gene expression in tumor tissue was measured by NanoString analysis. For each CpG site, methylation levels were associated with angiotensinogen gene expression using Spearman correlations and to treatment response using Mann-Whitney U test and logistic regression analysis. **Results:** *Preliminary results on 58 of 82 patients analyzed: AGT* gene expression was inversely associated with *AGT* promoter methylation on CpG site 1 (P = 0.049) and borderline significant on CpG site 2 (P = 0.074). Compared to non-responding patients, responders expressed significantly higher methylation levels of CpG site 1 (P = 0.015), 2 (P = 0.013) and 3 (P = 0.045). DNA methylation levels at CpG site 4-7 were not associated with *AGT* gene expression or response. By univariate analysis, increased methylation of the *AGT* promoter region were predictive for bevacizumab response on CpG site 1 (2-fold increase: OR = 1.81; 95%CI: 1.02-3.23; P = 0.043) and on CpG site 2 (2-fold increase: OR = 2.08; 95%CI: 1.04-4.17; P = 0.040). **Conclusions:** Increased methylation of the *AGT* promoter regions is associated with *AGT* gene silencing and is predictive for bevacizumab response in recurrent glioblastoma patients. Updated results will be presented.

2028 Poster Session (Board #186), Sat, 1:15 PM-4:45 PM

Genomic landscape of pineoblastoma. *First Author: Bryan Kincheon Li, Hospital for Sick Children, Toronto, ON, Canada*

Background: Pineoblastoma (PB) is a rare but aggressive pediatric brain tumour arising from the pineal gland. Overall survival rates are estimated at 50-60%, with younger patients ($<$ 5 years old) faring much worse (15-40%) despite intensive treatment regimens. Although germline RB1 and DICER1 alterations have been reported in a small proportion of PB, the clinical significance of such alterations and the biology of sporadic cases remains unknown. **Methods:** We collected tumor tissue from 75 cases of PB diagnosed at their local centres from across five continents. We undertook global DNA methylation profiling and performed multiple orthogonal consensus clustering analyses to elucidate PB subgroups. Chromosomal copy number alterations were determined using Conumee then GISTIC 2.0. Mutational analysis was conducted by whole exome and RNA sequencing. Clinical data was analyzed with correlative statistical methods and outcomes were measured by Kaplan-Meier survival estimates. **Results:** We discovered that PBs comprise four molecular sub-types, designated groups 1 to 4, with characteristic copy number alterations and mutational patterns. These molecular sub-groups exhibit distinct clinical features and survival outcomes. While PB groups 1-3 arose in older children (median ages 5.2-12.6 years), group 4 PB was restricted to much younger children (median age 1.4 years). Group 4 PB exhibited the highest incidence of metastases (53%) and had the worst 5-year event-free survival (EFS) and overall survival (OS) at 7.7% and 16.7%, respectively. In contrast, group 2 patients had a 5-year EFS and OS of 100%, while groups 1 and 3 had intermediate outcomes (5-year EFS 36.1% and 53.3%, 5-year OS 68.1% and 53.3%, respectively). **Conclusions:** PBs divide into four groups, each with a distinct genetic and clinical profile. These findings will have important implications for precise patient stratification and form the foundation for preclinical studies of biology-informed therapies.

2029 Poster Session (Board #187), Sat, 1:15 PM-4:45 PM

Contrast enhancement as a prognostic factor in IDH1/2 mutant glioma. *First Author: Bogdana Suchorska, Department of Neurosurgery LMU, Munich, Germany*

Background: Mutational status of the *IDH1/2* gene and co-deletion of on chromosome 1p/19q (co-del 1p/19q) is gaining further relevance for the evaluation of clinical outcome in lower grade glioma. Out of the established clinical and imaging parameters known to influence survival in these tumors, contrast enhancement (CE) has been reported to indicate poor outcome in the past. The present study aimed at re-assessing the value of clinical and imaging parameters in lower grade glioma within the framework of molecular markers using a machine learning approach (random survival forests, RSF) as well as conventional Cox regression modeling. **Methods:** 301 patients with grade II (n = 181) or grade III diffuse glioma (n = 120) were stratified according to their molecular profile (presence of *IDH1/2* mutation and/or co-deletion 1p/19q.) Preoperative magnetic resonance (MR) imaging was reviewed and volumetrical analyses of CE and T_2 volumes were performed. Multivariate cox models and RSF were trained on this data set using five-fold cross validation to assess the predictive value of pre-therapeutic molecular and imaging factors as well as age, Karnofsky performance status, surgical procedure and adjuvant therapy to predict the individual risk for each patient. As a measure of prediction accuracy, the concordance indices for Cox and RSF models were determined. **Results:** RSF modeling revealed presence of *IDH1/2* mutation, co-deletion 1p/19q and WHO II to be the most relevant factors for favorable outcome in lower grade glioma. In *IDH1/2* mutant tumors, both conventional Cox regression modeling and RSF analyses show that CE on initial MR imaging is a prognostic factor for survival independently of its magnitude in both co-deleted and non-co-deleted tumors ($p < 0.05$). In contrast, presence of CE on initial MRI is not associated with outcome in *IDH1/2* wildtype tumors. Likewise, the RSF model identified predictive influence of CE in the *IDH1/2* mutant tumors only. **Conclusions:** In patients with diffuse *IDH1/2* wildtype gliomas WHO grade II/III, CE is not associated with survival. In tumors with an *IDH1/2* mutation, presence of CE on initial MRI is linked to inferior survival.

2030 Poster Session (Board #188), Sat, 1:15 PM-4:45 PM

Meningioma: Association of mean and "hot spot" MIB1 with grade. *First Author: Christopher Dardis, Barrow Neurological Institute, Phoenix, AZ*

Background: The MIB1 labeling index is typically measured by counting cells in the region ('hot spot') with the highest proliferative activity. MIB1 is not currently one of the criteria used to classify meningioma as WHO Grade 1 or 2. Here we compare this 'hot spot' MIB1 ($MIB1_{hs}$) with the mean MIB1 ($MIB1_m$) of the whole sample. **Methods:** Both methods used computer-assisted quantitative analysis on images/optical fields at 400x magnification. $MIB1_{hs}$ was taken by counting a minimum of 1,000 cells in the most proliferative field of the tumor. $MIB1_m$ was estimated by taking the mean of 14x fields, from randomly selected regions of the tumor. This was done for meningiomas which underwent resection at our institution in 2009: 108x Grade 1, 32x Grade 2. **Results:** $MIB1_{hs}$ was more than double that of $MIB1_m$ (5.9% vs. 2.7%; two-sided t-test $p = 6\times10^{-9}$). The log of both measures was found to increase in a linear fashion, irrespective of grade. Using recursive partitioning, an optimal 'cutpoint' for MIB1 (in terms of Grade) was found to be 1.5% for both methods. As shown in the classification table, the methods were concordant in 100/140 (70%) cases. With these cutpoints, Fisher's exact test showed a stronger association with Grade for $MIB1_m$ vs. $MIB1_{hs}$ ($p = 0.04$ vs. $p = 0.0008$). **Conclusions:** For meningioma, $MIB1_m$ shows a significantly greater association with Grade than $MIB1_{hs}$. The method can be implemented with minimal additional burden to the practicing pathologist. The result appears to be of greater importance clinically. As MIB1 also increases in an exponential manner in breast cancer, schwannoma and low-grade glioma, we propose that this is a general property of the test.

$MIB1_{hs}$	$MIB1_m$	WHO Grade	
		1	2
< 1.5%	< 1.5%	59	28
	≥ 1.5 %	35	4
≥ 1.5%	≥ 1.5 %	13	0
	< 1.5 %	1	0

2031 Poster Session (Board #189), Sat, 1:15 PM-4:45 PM

Interrogating machine learning classifiers and dimensionality reduction techniques for radiomic prediction of glioma tumor grade. *First Author: Kareem Wahid, McGovern Medical School, Houston, TX*

Background: Radiomics derives quantitative features from medical images to reveal novel information about imaging phenotypes. Although significant research has been conducted on the application of machine learning algorithms to radiomic features for clinical prediction, much remains unknown about which models are best. Further, for models to be reproducible in the clinical setting, machine learning models should be explored using open-source tools and data. Herein, we assess the performance of various machine-learning classifier methods and dimensionality reduction techniques in predicting brain tumor grade with open-source tools and data. **Methods:** We utilized the publicly available 2017 BraTS Challenge magnetic resonance imaging dataset for lower-grade gliomas (n = 44) and glioblastomas (n = 191). Radiomic features were extracted using PyRadiomics, an open-source radiomics toolbox. A bootstrap approach was used to assess model predictive performance. **Results:** Logistic regression (area under curve [AUC] = 0.91) and factor analysis (AUC = 0.90) demonstrated the highest average performance among dimensionality reduction techniques and classifier methods, respectively. The highest overall performance was achieved by a support vector machine classifier coupled with factor analysis (AUC = 0.94). Variance analysis revealed that classifier method is the major contributor to performance variation (42%), followed by number of dimensions (15%) and dimensionality reduction technique (4%). **Conclusions:** This study demonstrated that the appropriate choice of classifier methods and dimensionality reduction techniques plays a significant role in machine learning model performance for prediction of glioma grade.

2032 Poster Session (Board #190), Sat, 1:15 PM-4:45 PM

Phase II trial of ponatinib in patients with bevacizumab-refractory glioblastoma. *First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

Background: Responses to bevacizumab in recurrent glioblastoma (GBM) are not durable. Plasma levels of basic fibroblast growth factor (bFGF) increase at the time of tumor progression. By concomitantly targeting vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and FGF receptor (FGFR) pathways, the multikinase inhibitor ponatinib may potentially help overcome some of the putative mechanisms of resistance and demonstrate antitumor effects. **Methods:** We performed a phase II trial of ponatinib in patients with bevacizumab-refractory GBM. Adult patients with KPS ≥ 60, measurable disease, normal organ and marrow function received ponatinib at 45 mg daily. No limit on the number of prior therapies but only one prior bevacizumab-containing regimen was allowed. Primary endpoint was 3-month progression free survival (PFS3). Based on a Simon optimal two-stage design, the trial was powered to discriminate between a 15% and 35% PFS3 rate, with an alpha error 0.10 and beta error 0.2. Plasma biomarkers of angiogenesis and inflammation were evaluated before and after treatment. **Results:** The study closed after the first stage. Fifteen patients enrolled, median age 62 [28-75], median KPS 80 [70-90], median number of prior relapses 2 [2-4]. PFS3 rate was 0, median OS was 98 days [95% CI 56, 257] and median PFS was 28 days [95% CI 27, 30]. No responses were seen, and 2 patients had SD (13%). Grade 3 adverse events possibly related to ponatinib included fatigue (n = 3), hypertension (2), lipase elevation (2), ALT elevation (1), AST elevation (1), GGT elevation (1), and lymphopenia (1). There were no grade 4 or 5 events attributable to treatment. Ponatinib treatment significantly increased plasma soluble (s)VEGFR1, sVEGFR2, sTIE2, VEGF, IFNγ, TNF-a, IL-6, IL-8, and IL-10 rapidly (at day 1) and persistently (until the end of treatment). **Conclusions:** Ponatinib was tolerated but associated with minimal activity in bevacizumab-refractory GBM patients. Circulating biomarker data indicate potent anti-VEGFR activity, and suggested that resistance to ponatinib may be related to inflammation. Clinical trial information: NCT02478164.

2033 Poster Session (Board #191), Sat, 1:15 PM-4:45 PM

Effect of therapeutic pressure on stability of EGFR amplification in glioblastoma. *First Author: Manmeet Singh Ahluwalia, Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH*

Background: Depatuxizumab mafodotin (depatux-m, formerly ABT-414) is an EGFR-directed antibody-drug conjugate being developed for treatment of *EGFR*-amplified glioblastoma (GBM). As therapeutic pressure engenders tumor adaptations, it is important to understand the stability of biomarkers targeted by precision medicine approaches such as depatux-m. Therefore, we assessed *EGFR* amplification (amp) and expression in longitudinally-sampled GBMs from patients (pts) treated +/- depatux-m to explore biomarker stability. **Methods:** Formalin-fixed, paraffin embedded GBM tumor tissue was analyzed from 68 patients who underwent at least 2 surgeries; *EGFR* amp was detected by *in situ* hybridization (*e.g.*, FISH) or next-generation sequencing in all samples. Fifty-six pts did not receive depatux-m; among 12 pts who did, *EGFR* expression was also evaluated by RNA sequencing. **Results:** Of 56 pts who did not receive depatux-m, 31 (55%) had tumors harboring *EGFR* amp at 1st surgery (initial diagnosis); among those, *EGFR* amp was maintained at re-operation in 27 (87%), and not maintained in 4 (13%). None of the 25 cases without baseline *EGFR* amp acquired it at the 2nd surgery. Of 12 pts treated with depatux-m between surgeries, 9 cases harbored *EGFR* amp at baseline which was maintained in 4 (44%) at the 2nd surgery, all 4 of which had the highest levels of *EGFR* expression at baseline. Of the 3 cases without *EGFR* amp at baseline, none acquired amplification at the 2nd surgery, and all 3 had the lowest levels of *EGFR* expression at study start. **Conclusions:** The presence of *EGFR* amp in GBM tissue at baseline was maintained at 2nd surgery in 87% of pts who received treatment other than depatux-m, and in 44% following depatux-m exposure. Therefore, depatux-m exposure appears to reduce *EGFR* amp maintenance ($p = 0.0159$ by Fisher's exact test); accordingly, the therapeutic approach may influence EGFR status. In no case was *EGFR* amp acquired at recurrence, regardless of depatux-m therapy. Ongoing analyses of additional tumor samples will increase power and further examine concordance among *EGFR* amp assays.

2034 Poster Session (Board #192), Sat, 1:15 PM-4:45 PM

NKG2D chimeric antigen receptor-T cells to target GBM. *First Author: Hong-jiu Dai, Nanjing Kaedi Biotech Inc, Nanjing, China*

Background: GBM is the most common and the most lethal brain tumors with the 5-year survival rate of ~4% for patients over age 55. Recently people are exploring the potential of chimeric antigen receptor T (CAR-T) cell therapy in glioblastoma, yet the clinical outcome is limited. It's reported that NKG2DLs are wildly expressed in glioma stem-like cells, which supports NKG2D system might play an important role in GBM therapy. Here we used NKG2D as antigen binding domain to construct a second generation of CAR (KD-025) for GBM treatment. **Methods:** U251 cell line as well as GBM cancer patient samples were evaluated for NKG2DLs expression. The KD-025 CAR T cells showed antigen-specific stimulation by cytokine secretion and target cell lysis. U251 were used to establish in vivo subcutaneous and xenograft models in NSG mice. Mice received a single treatment of 10 million KD-025 CAR-T cells intravenously. The main organs of mice were examined by hematoxylin and eosin (HE) staining after different doses of KD-025 administration. **Results:** NKG2DLs were detected on U251 cells and most of screened glioma patient samples. The KD-025 expression was $>$ 50% on the surface of T cells confirmed by flow cytometry. Co-incubation of KD-025 CAR with U251 cell specifically upregulates TNFa, IFN-γ, IL-10 and IL-2 cytokines and strongly lysis tumor cells even at low E:T ratio (50-60% at 1:1, 70% at 10:1). Strikingly, KD-025 CAR demonstrate very potent anti-tumor activity in vivo. All the tumor cells are gone 14 days after single treatment of KD-025 CAR T cells. Regarding to T cell persistence, the CAR-T cells are barely detectable 24 days after injection, which is comparable with CD19 CAR in our experiments as well as published data. No obvious pathological changes were found in the tested organs. **Conclusions:** Our work with the KD-025 CAR contributes to the growing body of research committed to discovering a novel therapy for GBM. NKG2D ligands are highly expressed on human GBM samples. NKG2D based CAR T cells KD-025 potently respond to GBM and eliminate tumor in a xenograft mouse model with no obvious safety issue. The results support future clinical trial of KD-025 CAR in patients with GBM, where the need for effective treatment is great.

2035 Poster Session (Board #193), Sat, 1:15 PM-4:45 PM

A phase I/II clinical trial of autologous CMV-specific cytotoxic T cells (CMV-TC) for glioblastoma: Dose escalation results. *First Author: Marta Penas-Prado, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX*

Background: Cytomegalovirus (CMV) antigens are present in $>$ 90% of GBMs but not in normal brain, and can be targeted as a tumor-specific antigen. CMV-TC present in GBM tumor tissue have their effector function suppressed. Highly functional CMV pp65 specific T cells can be expanded *in vitro* from peripheral blood (PB) of GBM patients. We have established GMP-compliant conditions for *ex vivo* expansion of polyclonal CD8+ and CD4+ CMV-TC from GBM patients. **Methods:** We explored 4 dose levels of autologous CMV-TC (from 5×10^6 cells to 1×10^8 cells) with a 3+3 design. CMV-TC were given after 3 weeks of lymphodepleting dose-dense temozolomide (ddTMZ, 100 mg/m2 for 3 weeks). Treatment was repeated q 6 weeks for a total of 4 cycles. Patients ≥18 years of age with KPS ≥60, CMV seropositivity, receiving ≤ 2 mg of dexamethasone daily, and any number of relapses were eligible. Imaging response was evaluated by MRI q 6 weeks. *In vivo* persistence and expansion of adoptively-infused CMV-TC was determined by dextramer staining and multiparameter flow cytometry in serially-sampled PB. **Results:** 27 patients were screened, of whom 15 underwent leukapheresis. Twelve patients (3 at each level) completed cycle 1. Median age 51 (27-65), median KPS 90; 9 were at 1st and 3 at 2nd relapse. MGMT was methylated in 5, unmethylated in 3, indeterminate or unknown in 4. IDH status was wildtype in 7, mutated in 3, unknown in 2. Number of cycles received was 4 in 4 patients, 2 in 3, and 1 in 5. No dose limiting toxicities (DLTs) were observed at any level. Complete radiographic response was observed in 1 patient, partial response in 1 patient, stable disease in 5 patients, and progressive disease in 5. Repeated infusions of CMV-TC were associated with a significant increase in circulating CMV+ CD8+ T-cells. **Conclusions:** Adoptive infusion of CMV-TC after lymphodepleting therapy with ddTMZ was well tolerated with no DLTs or serious CMV-TC related adverse events. The final dose level is currently being enrolled. Thereafter efficacy will be evaluated in expansion cohorts in newly diagnosed and recurrent GBM. The expansion in recurrent GBM will include correlative studies in tumor tissue after administration of CMV-TC. Clinical trial information: NCT02661282.

2036 Poster Session (Board #194), Sat, 1:15 PM-4:45 PM

Phase I study of afatinib and radiotherapy (RT) with or without temozolomide (TMZ) in newly diagnosed glioblastoma (GB). *First Author: Frank Saran, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: GB is a malignant primary incurable CNS tumor with poor prognosis. RT + TMZ is standard treatment for newly diagnosed GB suitable for radical treatment. ErbB pathway dysregulation has a role in the pathogenesis of GB and EGFR activation contributes to RT resistance. The irreversible ErbB family blocker afatinib has a manageable safety profile and modest activity in recurrent GB. This Phase I study assessed the feasibility of first-line afatinib + RT ± TMZ in GB. **Methods:** This 3+3 dose-escalation study enrolled 36 pts with newly diagnosed GB. Treatment was stratified by *MGMT* promoter methylation status. Pts with promoter methylation received RT + TMZ + afatinib (20, 30, 40 mg/day) for 6 wks (RT period), then afatinib 40 mg/day + TMZ for up to 6 months before afatinib 40 mg/day until progression/undue AEs (maintenance period; Regimen M). As TMZ has limited benefit in pts with unmethylated *MGMT*, these pts received RT + afatinib then afatinib (Regimen U). Primary endpoint: MTD of afatinib + RT ± TMZ. Secondary endpoints: AEs, ORR, PK. **Results:** In regimen M, 20 pts (median [range] age: 52.5 [2566] yrs) were treated for median [range] 151 [62340] days (20 mg n = 7; 30 mg n = 6; 40 mg n = 7); of those evaluable for MTD, 1/6, 0/6 and 2/5 had dose-limiting toxicities (DLTs) in the RT period (2 grade [G] 4 thrombocytopenia and 1 G3 vomiting). MTD of afatinib + RT + TMZ was 30 mg/day. In regimen U, 16 pts (53.5 [3468] yrs) were treated for median [range] 168 [1397] days (20 mg n = 3; 40 mg n = 13); of those evaluable for MTD, 0/3 and 1/6 had DLTs (1 G3 diarrhea) in the RT period. MTD of afatinib + RT was 40 mg/day. Common treatment-related AEs (TRAEs) are shown in the Table. ORRs were 25% and 6% in regimens M and U, respectively. PK evaluation indicated that combination of afatinib with RT + TMZ had no influence on afatinib exposure. **Conclusions:** The MTD of afatinib + RT was 30 mg/day with TMZ and 40 mg/day without TMZ. The safety profile of afatinib + RT ± TMZ was as expected, based on the known profiles of the individual agents. *Common TRAEs* Clinical trial information: NCT00977431.

	Regimen M (n = 20); n (%)		Regimen U (n = 16); n (%)	
	Grade		Grade	
	All	≥3	All	≥3
Diarrhea	16 (80)	1 (5)	13 (81)	1 (6)
Rash	13 (65)	1 (5)	12 (75)	2 (13)
Fatigue	9 (45)	1 (5)	6 (38)	0
Nausea	9 (45)	0	2 (13)	0
Thrombocytopenia	3 (15)	3 (15)	1 (6)	0

2037 Poster Session (Board #195), Sat, 1:15 PM-4:45 PM

Neurologic assessment in neuro-oncology (NANO) scale in a prospective phase II trial of anti-PD1 antibody, pembrolizumab with or without bevacizumab in patients with recurrent glioblastoma. *First Author: Lakshmi Nayak, Dana-Farber Cancer Institute, Boston, MA*

Background: The neurologic assessment in neuro-oncology (NANO) scale was developed as a standardized metric to objectively measure neurologic function in patients (pts) with brain tumors to complement radiographic assessment in defining overall outcome. The scale has been incorporated in various prospective studies to assess pts and to determine its utility. **Methods:** A multicenter, open label, phase II trial of pembrolizumab with and without bevacizumab in pts with recurrent glioblastoma (GBM) incorporated NANO scale as an exploratory endpoint. Neurologic examination by NANO was documented at baseline and each cycle until pts came off study. Statistical analyses including descriptive data analysis and generalized linear models were performed using R (version 3.4.3). **Results:** Eighty pts received treatment on study and underwent NANO evaluations. NANO compliance rate was 94%; of a total 388 expected NANO evaluations, 24 were missing. Of 80 pts, 7 missing NANO at baseline visit were excluded from analysis. Fifteen pts did not have end of treatment NANO evaluation. Of 73 pts, 35 (48%) had a normal neurologic examination at baseline by NANO. Two NANO domains (strength and language) accounted for the majority of variability in neurologic function over the course of study treatment. There was a significant correlation between NANO at each cycle and Karnofsky performance status score ($p = 0.02$). Nineteen pts were on dexamethasone at baseline; 42 required it during study. Corticosteroid requirement (OR = 1.9, $p < 0.001$) and an increase in corticosteroid dose (OR = 2.6, $p < 0.001$) were associated with higher risk of NANO progression (PD). Eighteen pts (25%) met NANO criteria for PD, including 2 without PD on MRI. Three pts (4%) had a neurologic response per NANO criteria associated with stability on MRI. **Conclusions:** Evaluation of neurologic function by NANO was feasible in a multicenter prospective study in GBM pts with a high compliance rate. NANO was able to objectively track neurologic function throughout the trial including preservation of baseline status in non-progressors. Clinical trial information: NCT02337491.

2038 Poster Session (Board #196), Sat, 1:15 PM-4:45 PM

How far have we really come? Trends in survival and mortality for gliomas between 1973 to 2014 from SEER. *First Author: Shehryar Rahim Sheikh, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH*

Background: Historical controls are often used as benchmarks for early stage, single arm trials of novel agents. We have investigated whether general or specific changes in the treatment of patients with gliomas drive meaningful changes in outcome and affect the validity of the use of historical control arms. Furthermore, we evaluated factors that impact on selection bias. **Methods:** We used data from the NCI SEER database and included 92,182 gliomas in our analysis. We identified 4 distinct epochs from 1973 to 2014 and compared survival curves between epochs using 2-year survival, median survival, and Cox-proportional hazards ratio (PHR) analysis. We also compared relative risk of mortality after diagnosis (RRM i.e. risk of death compared to age/sex matched controls) profiles between these periods. Gliomas were stratified by histological grade and age of diagnosis. **Results:** For low grade tumors, the most significant improvements occurred between the first (1973-1992) and second (1992-2000) epochs (PHR 0.4 and 0.6 for Grades I and II, $p < 0.001$), while for higher grade tumors it was in between the third (2000-2007) and fourth (2007-2014) epochs (PHR 0.8 for both Grades III and IV, $p < 0.001$) Since 2005, 2-year survival probability and median GBM survival have increased consistently (slope: 0.3 months/yr, R^2: 0.8, $p < 0.001$); no such trend was discernable in earlier data. RRM profiles for high grade gliomas demonstrate a characteristic pattern that varies with time from diagnosis. RRM rises sharply for the first 1.5 years after diagnosis, and then approaches baseline. **Conclusions:** The most meaningful improvements in survival measures coincide with the emergence of phase III evidence supporting combined treatment with temozolomide (TMZ) and radiation around 2005. Since at least 2005, there has been a trend of increasing baseline survival in GBM patients; commonly used survival estimates for historical controls may thus be inaccurate and future clinical trials should acknowledge this trend when setting expectations of the control arm. RRM varies as a function of time from glioma diagnosis which may provide a basis for selection bias; patients recruited for clinical trials should be comparable in respect to RRM.

2039 Poster Session (Board #197), Sat, 1:15 PM-4:45 PM

Comprehensive genomic profiling of brain tumors to provide targeted therapy options and diagnostic certainty for oligodendrogliomas. *First Author: Lee A. Albacker, Foundation Medicine, Cambridge, MA*

Background: Genomic profiling of gliomas is vital to ensure diagnostic accuracy, inform prognosis, and identify therapeutic options for primary and recurrent tumors. The integration of genomic biomarkers into brain tumor classification has advanced the development of molecularly stratified clinical trials and the need to characterize tumors by genomic signature. **Methods:** Comprehensive genomic profiling (CGP) was performed on FFPE material from 6304 consecutive cases of pediatric and adult brain tumors initially diagnosed by submitting institutions based on histology. We analyzed tumors via CGP in 395 cancer-associated genes (including *IDH1/2*) and for 1p/19q codeletion using a validated algorithm. **Results:** Of 6304 brain tumor samples, known *IDH* point mutations included 1182 *IDH1* R132, 50 *IDH2* R172, and 1 *IDH2* R140 variants. In the *IDH*-mutant cohort, 1p/19q codeletion was detected in 72% (260/363) of histologically defined oligodendrogliomas (ODGs), 21% (17/82) of oligoastrocytomas (OAs), 6% (22/360) of glioma (NOS, not otherwise specified), 4% (2/50) of gliosarcomas, 3% (26/859) of astrocytomas (NOS), and 1% (32/3200) of glioblastomas. ODG with 1p/19q loss were enriched for *TERT, CIC,* and *FUBP1* alterations, whereas 1p/19q intact tumors were enriched for *TP53* and *ATRX* alterations. Actionable alterations in ODG included 8% (29/363) with high tumor mutational burden (potential immunotherapy responsiveness) and 15% (56/363) with *PIK3CA* mutation. Analysis of OA (mixed glioma) revealed genomic subtypes similar to well-defined gliomas including ODGs (*IDH*-mutant, 1p/19q loss, *TERT*, *CIC*, *FUBP1*), diffuse astrocytomas (*IDH*-mutant, *TP53*, *ATRX*), and high-grade gliomas (*IDH*-wild-type, *EGFR*, *NF1*). **Conclusions:** Using co-occurring *IDH* mutation and 1p/19q codeletion as the diagnostic signature of ODG, we show that as many as 25% may be misclassified on morphologic criteria alone. OAs exhibit genomic features of defined glioma subtypes, suggesting CGP may provide diagnostic clarity in this setting. This study highlights how CGP can improve diagnostic accuracy and provide additional treatment options for patients.

2040 Poster Session (Board #198), Sat, 1:15 PM-4:45 PM

Concordance between RTOG and EORTC risk factors in low grade gliomas: Who will remain standing in the ring at bell's sound? *First Author: Enrico Franceschi, Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy*

Background: Low grade gliomas (LGG) are a heterogeneous group of brain primary tumors. The EORTC and the RTOG criteria are the most valuable scores to evaluate risk factors and for treatment decision. However, there is no data about concordance between criteria. **Methods:** We conducted an analysis on LGG patients treated in our Institution from 1998 to 2015. The population was stratified by RTOG criteria and whenever feasible we assessed the risk using both RTOG and EORTC criteria. **Results:** Median follow up (mFU) was 78.6 months. We evaluated 204 patients with histologically diagnosed LGG. All the patients were stratified by RTOG criteria and a subgroup of 51 patients by both RTOG and EORTC criteria. The univariate analysis showed a statistically significant difference according to RTOG criteria (p = 0.01) for both OS and PFS. Low risk patients had a better OS compared to high risk group (211.0 vs 145.5 months, p = 0.01) and a longer PFS (60.0 vs 39.8 months, p = 0.005). The multivariate analysis confirmed that RTOG risk was an independent prognostic factor (p = 0,024). In the subgroup of 51 patients stratified by both RTOG and EORTC risk-factor criteria, the concordance was 54.9% (K = 0.113, p = 0.08). All the EORTC high risk patients (n = 25) were high risk also with RTOG criteria. Among the 26 EORTC low risk patients, only 3 (11.5%) were low risk with RTOG criteria, while 23 (88.5%) would have been deemed as high risk. In this population, after a FU or 91 months, no statistical difference regarding OS and PFS was documented applying either RTOG or EORTC criteria, probably due to the limited population. **Conclusions:** The concordance between RTOG and EORTC criteria is low, especially in the evaluation of low risk patients. So far, we cannot compare clinical trials adopting different risk criteria.

2041 Poster Session (Board #199), Sat, 1:15 PM-4:45 PM

Phase II trial of SurVaxM combined with standard therapy in patients with newly diagnosed glioblastoma. *First Author: Manmeet Singh Ahluwalia, Cleveland Clinic, Cleveland, OH*

Background: To determine 6-month progression-free survival (PFS-6), 12-month overall survival (OS-12) and immunologic response in newly diagnosed glioblastoma (nGBM) treated with concurrent temozolomide (TMZ) and radiation, followed by adjuvant TMZ and survivin-targeted immunization with SurVaxM (SVN53-67/M57-KLH). **Methods:** A single-arm, multi-center phase II trial was conducted in 63 evaluable patients with nGBM with HLA-A*02, -A*03, -A*11 and -A*24 haplotypes and Karnofsky performance status $\geq$70. Patients (Pts) underwent craniotomy with near-total resection (< 1 cm^3 residual contrast enhancement), followed by chemoradiation (Stupp) were eligible. Pts received 4 priming doses of SurVaxM (500 mcg) with Montanide and sargramostim (100 mcg) every 2 weeks, followed by adjuvant TMZ and maintenance SurVaxM every 12 weeks until progression. Immunogenicity of SurVaxM was assessed using expansion of survivin-specific CD8+ T-cells (dextramers) and survivin antibody (IgG) levels. **Results:** Interim analysis of the first 55 pts. Pts ranged in age from 20-82 yrs (median = 60), male:female = 32:23 with survivin tumor expression of 1-40% (median = 12%) by immunohistochemistry. PFS-6 was 96.3% (+2.8, -10.3)(n = 55) measured from diagnosis and 62.8% (+12.5, -16.2) (n = 43) from first immunization. OS-12 was 90.9% (+6.1, -16.5)(n = 33) from diagnosis and 70.8% (+14.1, -22.4)(n = 24) from first immunization. Median time to first immunization was 3.0 mo (1.9-4.0 mo). The regimen was generally well tolerated and immunization-related adverse events were mild with no serious adverse events attributable to SurVaxM. The drug was highly immunogenic and produced survivin-specific antibody (IgG) titers and CD8+ T-cells detectable by survivin dextramers. IDH-1, MGMT methylation status, HLA class I haplotype, survivin expression levels, and the relationship of these variables to survival will be presented. Outcomes will be compared to historical patients receiving Stupp regimen, and Stupp plus Optune. **Conclusions:** Standard therapy plus SurVaxM appears promising in nGBM compared to standard therapy alone. The use of SurVaxM is safe in nGBM. A randomized, prospective trial of SurVaxM in glioblastoma is planned. Clinical trial information: NCT02455557.

2042 Poster Session (Board #200), Sat, 1:15 PM-4:45 PM

Secondary prophylaxis with romiplostim for temozolomide-induced thrombocytopenia in newly diagnosed glioblastoma. *First Author: Emilie Le Rhun, University of Lille, U-1192, F-59000 Lille, France; Inserm, U-1192, F-59000 Lille, France; CHU Lille, General and Stereotaxic Neurosurgery service, F-59000 Lille, France; Oscar Lambret Center, Medical Oncology Department, F-59000 Lille, Lille, France*

Background: Thrombocytopenia is a major adverse event of temozolomide (TMZ) chemotherapy. It may lead to dose reduction/interruption or bleeding. Platum (NCT 02227576) was a phase II open label, multicenter single arm trial evaluating the thrombopoetin receptor agonist, romiplostim, for secondary prevention of TMZ-induced thrombocytopenia in patients with newly diagnosed glioblastoma. **Methods:** Patients diagnosed with CTCAE grade 3/4 thrombocytopenia during standard treatment of glioblastoma received weekly subcutaneous injections of romiplostim at a starting dose of 750 μg. Dose adjustments were based on weekly platelets counts. The study aimed at demonstrating that the percentage of thrombopenic patients treated with romiplostim able to complete 6 cycles of maintenance TMZ chemotherapy exceeded 10% (p0 = 0.10; pA = 0.35) (Gerber et al., 2007). Using type I error equal to 0.05 and 95% power, 31 patients had to be recruited. According to a Fleming's two step design, an interim analysis was planned after recruitment of 20 evaluable patients. Three scenarios were pre-defined: (1) $\leq$2 patients meeting the endpoint: termination for futility ($p < P0$), (2) $\geq$6 patients meeting the endpoint: termination for success ($p > P0$), (3) 3 to 5 patients meeting the endpoint: enrollment of 11 more evaluable patients. **Results:** 20 patients were enrolled in step 1 between July 2014 and December 2016. Median age was 61 (range: 33-73 years). Surgery included biopsy (n = 8), partial (n = 5), subtotal (n = 1) or gross total resection (n = 6). Isocitrate dehydrogenase 1^{R132H} mutations were noted in 2 cases. 12 patients enrolled in step 1 received the 6 planned maintenance TMZ cycles, corresponding to a success rate of 60% (95% confidence interval 36-81). Three of 8 patients discontinued TMZ because they did not respond to romiplostim, 3 for progression and 1 for clinical deterioration prior to completion of six cycles, 1 due to an adverse event. Romipostim was well tolerated. The trial was terminated early for success. **Conclusions:** Thrombopoetin receptor agonists such as romiplostin allow to assure adequate exposure to chemotherapy in glioblastoma patients experiencing early, severe chemotherapy-induced thrombocytopenia. Clinical trial information: NCT 02227576.

2043 Poster Session (Board #201), Sat, 1:15 PM-4:45 PM

Association of anticonvulsant prophylaxis in patients with primary and metastatic brain tumors and 1-year overall survival: A systematic review and meta-analysis. *First Author: Timothy J Brown, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Despite high-quality evidence suggesting anticonvulsant prophylaxis in primary and metastatic brain tumors does not improve seizure outcomes, debate persists on the use of anticonvulsants in these patients. Valproic acid use has attracted particular interest due to its histone deacetylase and CYP2C9 inhibitory action. We sought to determine if the body of the world's literature supports the use of anticonvulsant prophylaxis to improve survival in patients with primary or metastatic brain tumors. **Methods:** A systematic review of PubMed and EMBase was performed with MeSH headings to identify all studies of anticonvulsant prophylaxis in adult patients with primary or metastatic brain tumors. Data was extracted from the text of included studies or from survival curves. Statistics were performed using Cochrane ReviewManager software. Endpoints of interest were one-year overall survival. **Results:** Two-hundred seventy-six studies were reviewed. Eleven studies of 3767 patients with primary and metastatic brain tumors were included in the analysis of survival with any anticonvulsant, while ten studies of 3576 patients provided survival data with valproic acid. Compared to control, any anticonvulsant prophylaxis was associated with a relative risk (RR) of death of 0.88 [95% confidence interval 0.81-0.94, p = 0.0006]. Valproic acid compared to control was associated with RR of death at one year of 0.86 [95% CI 0.78-0.95, p = 0.003]. Eight studies of 3194 patients with glioblastoma associated a RR of death at one year of 0.86 [95%CI 0.75-0.99, p = 0.04] with any valproic acid prophylaxis compared to none. Two studies of 344 patients examined the effects of non-valproic acid anticonvulsant prophylaxis demonstrated no significant effect on the RR of death at one year, 0.90 [95%CI 0.79-1.03, p = 0.13], compared to control. **Conclusions:** In this meta-analysis of anticonvulsant prophylaxis in patients with primary and metastatic brain tumors, anticonvulsant prophylaxis was associated with a significant survival benefit at one year. This association appears to be driven primarily by valproic acid prophylaxis.

2044 Poster Session (Board #202), Sat, 1:15 PM-4:45 PM

Phase I factorial study of temozolomide plus memantine, mefloquine, and metformin as post-radiation adjuvant therapy for newly diagnosed glioblastoma. *First Author: Stefania Maraka, Neuro-Oncology Department, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Repurposing non-cancer drugs may represent a new source of novel therapies for glioblastoma (GBM). Memantine, mefloquine, and metformin have putative anticancer activity potentially relevant to gliomas. The aim of this phase I factorial study was to determine the maximum tolerated doses (MTD) of combinations of these agents with temozolomide (TMZ) for newly diagnosed GBM. **Methods:** Adults ($\geq$18 years of age) with newly diagnosed GBM who received chemoradiation with TMZ, with no progressive disease on post-treatment imaging, were eligible. The patients were sequentially enrolled to one of seven treatment arms (doublet, triplet, or quadruplet therapy with TMZ combined with mefloquine, memantine, and/or metformin). Dose-limiting toxicities (DLTs) were determined over the first 28 days of treatment, using a 3+3 study design. **Results:** Of 85 enrolled patients, 81 patients completed the MTD period. The final MTDs for doublet therapy arms (TMZ plus 1 drug) were memantine 20 mg twice a day (BID), mefloquine 250 mg 3 times/week, and metformin 850 mg BID. For triplet therapy arms, the MTDs were memantine 10 mg BID, mefloquine 250 mg 3 times/week, and metformin 850 mg BID. For quadruplet therapy, the MTDs were memantine 10 mg BID, mefloquine 250 mg 3 times/week, and metformin 500 mg BID. DLTs included dizziness related to memantine and gastrointestinal effects related to metformin. Lymphopenia was the most common adverse event (66%); fatigue was the second most common (65%). From study entry, median survival was 21 months; the 2-year survival rate was 43%. **Conclusions:** Memantine, mefloquine, and metformin can be safely combined with TMZ as treatment for newly diagnosed GBM. The MTDs determined by this study can be used for subsequent clinical trials.

2045 Poster Session (Board #203), Sat, 1:15 PM-4:45 PM

A randomized phase 2 trial of veliparib (V), radiotherapy (RT) and temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) glioblastoma (GBM): Feasibility and safety outcomes (the VERTU study). *First Author: Mustafa Khasraw, Royal North Shore Hospital/ University of Sydney, St Leonards, Australia*

Background: TMZ offers minimal benefit in uMGMT GBM pts. V is synergistic with both RT and TMZ in preclinical models, safe when combined with either RT or TMZ clinically but the triplet (V+RT+TMZ) is poorly tolerated. This study examines a novel approach to patients with uMGMT GBM. **Methods:** VERTU is a randomized Phase 2 trial comparing Arm A (experimental arm) = RT (60gy/30 fractions) + V (200mg BID) followed by TMZ (150-200mg/m^{2}D 1-5) + V (40mg bid, D 1-7) every 28 days for 6 cycles vs Arm B (Standard of care) = RT (60gy/30 fractions) + TMZ (75mg/m^2 daily) followed by TMZ (150-200mg/m^{2}D 1-5) every 28 days for 6 cycles in pts with newly diagnosed uMGMT GBM. The study aims to randomize 120 pts (2:1 to the experimental arm). The primary endpoint is 6 months Progression Free Survival (6PFS) with multiple secondary and tertiary endpoints. Evaluation of feasibility and safety was planned after completion of RT in the first 60 pts (Stage 1). Acceptable feasibility and safety criteria for study continuation was defined as ≥70% of pts on the experimental arm completing ≥70% of the planned treatment with ≤30% of pts having any ≥ Grade (G) 3 Adverse Events (AEs). (ANZCTR #ACTRN12615000407594) **Results:** 60 pts have been randomized in Stage 1 (Arm A = 39, Arm B = 21). Patient characteristics (age, gender, performance status, and extent of resection) were well matched. All 39 pts in the experimental arm completed at least 80% of the planned V treatment, receiving at least 70% of the full V dose and 80% of the planned RT dose. Eleven pts (28%) in the experimental arm experienced ≥ G3 AEs during concurrent treatment. The commonest severe AEs were seizures observed in 3pt in each arm, 7% in the experimental arm and 15% in the standard treatment arm followed by thrombocytopenia seen in 2 pts in each arm, 5% in the experimental arm and 10% in the standard arm. **Conclusions:** Stage 1 of VERTU satisfied the predefined feasibility and safety criteria and the study will continue until the accrual target (120pts) is reached (anticipated mid-2018). Efficacy endpoints will be analyzed and reported after completion of accrual. Clinical trial information: 12615000407594.

2046 Poster Session (Board #204), Sat, 1:15 PM-4:45 PM

Hypofractionnated stereotactic radiotherapy and anti-PDL1 durvalumab combination in recurrent glioblastoma: Results of the phase I part of the phase I/II STERIMGLI trial. *First Author: Damien Pouessel, Saint Louis Hospital, Paris, France*

Background: Glioblastoma (GBM) is the most aggressive primary brain tumor with inevitable local relapse and no standard treatment. Hypofractionated stereotactic radiotherapy (hFSRT) has shown signs of efficacy with tolerable safety with PFS ranging from 3.4 to 5 months, but needs improvement. Radiotherapy (RT) causes immunogenic tumor cell death but also induces PDL1 and PD1 expression on tumors and immune cells, potentially evoking resistance to RT. Pre-clinical studies combining hFSRT with an anti-PD-1 antibody in GBM have shown increased efficacy of the combination. Clinical studies also show encouraging results when checkpoint inhibitors have been combined with high dose RT. We hypothesized that combining the anti PD-L1 Durvalumab (Durva) with hFSRT will be an effective regimen for patients with recurrent GBM. We designed a phase I and a phase II clinical trials studying the combination of hFSRT with Durva for recurrent GBM≤35 mm diameter. Results of the phase I are presented. **Methods:** A standard 3+3 dose escalation design was used. Patients were treated by hFSRT 24 Gy, 8 Gy/fraction at 80% isodose, every other day, combined with Durva infusion 1500mg first dose (Level 1) or 750 mg (Level -1) delivered on the last hFSRT, day followed by 1500 mg Durva infusion every four weeks until relapse and for a maximum of 12 months. The schema was defined as safe if one patient or less among 6 presents a dose limiting toxicity (DLT). DLT period started on the first Durva infusion with radiotherapy until 4 weeks. Brain MRI were performed before RT and then every 8 weeks until relapse. **Results:** Among the 6 patients (3 methylated MGMT, 3 unmethylated MGMT) included at the level 1, all completed the hFSRT course, only one had a DLT which was an immune related grade 3 vestibular neuritis. No DLT related to hFSRT or the Durva combination was reported. No other serious adverse event (SAE), immune-related AE or AE of special interest was reported. **Conclusions:** Combining three 8 Gy fractions of hFSRT with 1500 mg Durvalumab on the 3rd fraction hFSRT and every 4 weeks for recurrent GBM is well tolerated justifying exploration of its efficacy in the phase II component of the study. Clinical trial information: NCT02866747.

2047 Poster Session (Board #205), Sat, 1:15 PM-4:45 PM

Updated results of REGOMA: A randomized, multicenter, controlled open-label phase II clinical trial evaluating regorafenib in relapsed glioblastoma (GBM) patients (PTS). *First Author: Giuseppe Lombardi, Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy*

Background: There is no established treatment regimen for recurrent GBM. GBMs have activation of multiple signaling pathways in the tumor microenvironment, including the receptor tyrosine kinases, VEGFR, FGFR, and PDGFR. REG, an oral multikinase inhibitor, inhibits these angiogenic kinases and the mutant oncogenic kinases KIT, RET, and B-RAF. **Methods:** We present, after the first analysis, the updated results of REGOMA trial. The primary aim of this trial was to assess REG activity in prolonging overall survival (OS) in PTS with relapsed GBM after surgery and Stupp regimen (α = 0.2, 1-sided; β = 0.2). Secondary objectives were PFS, disease control rate (DCR), safety, quality of life (QoL); exploratory objectives included analysis of metabolic tissue biomarkers as possible predictors of response. PTS with histologically confirmed GBM, ECOG PS 0-1, documented disease progression were randomized 1:1 to receive REG 160 mg/day (3 weeks on, 1 week off) or lomustine (LOM) 110 mg/m2 (every 6 weeks) until disease progression or unacceptable toxicity. Tumor response was evaluated by brain MRI every 8 weeks according to the RANO criteria. **Results:** 119 PTS were randomized (n = 59 REG; n = 60 LOM) and stratified for surgery at recurrence; baseline characteristics, including MGMT methylation status, were balanced. Median age was 57.3 yrs; 27 PTS (22.7%) had surgery at recurrence, 22% and 23.3% in REG and LOM arm. At the time of analysis (cut-off date: Dec 31, 2017), median follow up was 15.4 months(m), 99 PTS had died. Median OS was 7.4m (95% CI 5.8-12.0) for REG and 5.6m (95% CI 4.7-7.3) for LOM (HR = 0.50, 80%CI 0.38-0.65; p = 0.0007; 1-sided Log-rank test); 12m-OS rates were 38.9% and 15.0% for REG and LOM. 6m-PFS rates were 16.9% and 8.3% (HR = 0.65; 95% CI 0.45-0.95; p = 0.0223) for REG and LOM , DCR was 44.8% and 21.1% (p = 0.009) for REG and LOM. Grade ≥3 adverse events were reported in 56% and 40% for REG and LOM, no treatment-related deaths were reported. **Conclusions:** In this multicenter, randomized study, REG significantly improved OS, PFS and DCR in recurrent GBM PTS. REG treatment was feasible and well tolerated. QoL and biomarker analyses are ongoing. A phase 3 study will be planned. Clinical trial information: NCT02926222.

2048 Poster Session (Board #206), Sat, 1:15 PM-4:45 PM

Plasma cell-free DNA (cfDNA) concentration and radiographic tumor burden in patents with glioblastoma (GBM). *First Author: Stephen Joseph Bagley, Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: Distinguishing between radiographic pseudoprogression and true tumor progression is a significant challenge in patients with GBM. A non-invasive means of assessing GBM disease activity is needed. Recent data has suggested that plasma cfDNA concentration may serve as a viable surrogate for tumor burden and disease activity in other solid tumors. We performed a pilot study to determine the feasibility of using plasma cfDNA concentration as a surrogate of radiographic tumor burden in patients with GBM. **Methods:** We collected blood in Streck cfDNA tubes from patients with radiographically suspected high grade glioma prior to planned surgical resection. Plasma was isolated using a 3 step centrifugation protocol. cfDNA was extracted from using a QIAamp Circulating Nucleic Acid Kit. cfDNA was stored at -20 degrees C and quantified the following day using an Invitrogen Qubit dsDNA kit. Tumor burden was defined as the sum of products of diameters (SPD) of the target enhancing lesions plus the SPD of the T2 FLAIR signal abnormality on preoperative magnetic resonance imaging (MRI). Correlation between cfDNA concentration and tumor burden was assessed using Spearman's correlation coefficient. **Results:** 10 preoperative patients were enrolled. Following surgery, 9 patients were diagnosed with GBM and 1 with diffuse midline glioma, H3K27M mutant. The median cfDNA concentration was 12.4 ng/mL (IQR 5.5-19.7, range 4.3 - 34.5). Median SPD of target enhancing lesions was 15.7 cm^2 (IQR 10.8-24, range 1.2 – 29.8), and median SPD of T2 FLAIR lesions was 35.7 cm^2 (IQR 21.6-43.5, range 12.7 – 81.8). There was a significant correlation between cfDNA concentration and the sum of the SPDs of the target enhancing lesions and T2 FLAIR lesions (Spearman's rho = 0.70, p = 0.025). **Conclusions:** In this small pilot study, we demonstrated a correlation between the preoperative plasma cfDNA concentration and radiographic tumor burden by MRI in patients with newly diagnosed high grade glioma. This preliminary finding suggests that cfDNA yield may serve as a viable surrogate for tumor burden in patients with GBM. A larger, longitudinal study of cfDNA quantification and its relationship to GBM disease status is ongoing at our institution.

2049 Poster Session (Board #207), Sat, 1:15 PM-4:45 PM

Preoperative and non-invasive prediction of chromosome arm 1p/19q codeletion in oligodendroglial tumors using MRI-based radiomics. *First Author: Jingwei Wei, Chinese Academy of Sciences, Beijing, China*

Background: Oligodendroglial tumor (OT) is a main subtype of gliomas, carrying poor prognosis. Fortunately, part of OT patients with chromosome 1p/19q codeletion show favorable response to chemo/radiotherapy and improved survival. Preoperative knowledge of 1p/19q codeletion could beyond doubt provide seasonable evidence for personalized treatment decision making. However, the 1p/19q co-deletion genotype is currently examined via invasive biopsy-based methods, which are highly risky causing neurologic deficit. Thus, it arouses an urgent need to develop a non-invasive approach for early prediction of 1p/19q codeletion. Hence, we used a new technique termed radiomics to perform the prediction on 1p/19q status using magnetic resonance imaging in this study. **Methods:** A cohort of 262 OT patients was collected from Beijing Tiantan Hospital and divided into training (n = 175) and validation (n = 87) datasets. We extracted 647 three-dimensional imaging features on T2-weithed images to describe the archetypal cancer phenotypes. Qualified features were selected by reproducibility and stability analysis. Random forest algorithm was finally adopted to perform the classification between 1p/19q codeletion and non-codeletion groups. Moreover, comparisons were explored between relevant clinical predictors and the proposed radiomics model. **Results:** The radiomics model demonstrated satisfactory performance on both the training and validation cohorts with areas under curve (AUCs) of 0.889 and 0.743, respectively. Among the top three most significant features, there were two first-order intensity features (Coif1_fos_kurtosis, ori_fos_skewness), and one textural feature (ori_glcm_cluster_shade). The radiomics model outperformed the clinical factor: heterogeneous intensity, the AUCs of which were 0.580 and 0.616. When combining the radiomics features and the clinical factor together, it turned out to be the best predictive result with AUCs of 0.891 and 0.739. **Conclusions:** Our study highlights that radiomics model can effectively identify the 1p/19q codeletion in OTs by a non-invasive manner, thereby offering preoperative evidence for the treatment regime planning.

2050 Poster Session (Board #208), Sat, 1:15 PM-4:45 PM

IDH-wild type low grade gliomas: An AINO (Italian Association of Neuro-Oncology) retrospective study. *First Author: Roberta Ruda, Department of Neuro-Oncology, University of Turin and City of Health and Science, Turin, Italy*

Background: Information regarding clinical characteristics and response to treatments of IDH-wild type grade II gliomas are still lacking. This national retrospective study aimed to investigate natural history, management, factors affecting response to treatments and outcome of a cohort of WHO grade II IDH-wild type glioma patients. **Methods:** We collected all clinical data of patients diagnosed with WHO grade II IDH-wild type glioma from 1999 to 2017 in six major Italian Institutions. IDH mutation was assessed by either immunohistochemistry or sequencing (in cases with negative immunohistochemistry). Exclusion criteria were the presence of minimal anaplastic foci or radiological features of HGGs. Kaplan-Meier curves and Cox-regression models were used for univariate and multivariate analysis. **Results:** Overall, 194 patients were collected and ultimately 122 met the inclusion criteria. Median age was 45 years. Non-enhancing tumors on MRI accounted for 74% while 26% had minimal/mild contrast enhancement. Surgery consisted in gross total resection in 29%, partial/subtotal in 45%, biopsy in 24%, and unknown in 2%. According to WHO 2007 astrocytomas were 44%, oligodendrogliomas 35%, and mixed gliomas 21%. MGMT methylation was available in 68% of patients and in 40% of them was methylated. Post-surgical management consisted in watch and wait in 42%, chemoradiation in 21%, chemotherapy alone in 21%, radiotherapy alone in 5%, radiotherapy followed by chemotherapy in 5%, and 6% unknown. Median time of follow-up was 31 months. Progressive disease was observed in 64% of patients. Median PFS was 24.0 months (1.2 – 147.0), and median OS was 45.3 months (1.0 – 225.6). Factors positively associated with PFS and OS in univariate analysis were younger age, absence of contrast enhancement, and gross total resection. Age and extent of surgery retained a statistically significant importance in multivariate analysis. **Conclusions:** WHO grade II IDH-wild type gliomas have worse outcome compared with IDH-mutant tumors. This is the first study that details clinical and radiological presentation of this rare subgroup of tumors and suggests that gross total resection is critical in improving survival.

2051 Poster Session (Board #209), Sat, 1:15 PM-4:45 PM

Non-invasive determination of the O^6-methylguanine-DNA-methyltransferase (*MGMT*) promoter methylation status in glioblastoma (GBM) using magnetic resonance imaging (MRI). *First Author: Saima Rathore, Center for Biomedical Image Computing and Analytics, Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: *MGMT* promoter methylation is associated with better prognosis and increased benefit from temozolomide in patients with GBM. The methylation status of the *MGMT* promoter is typically determined by tissue-based polymerase chain reaction assays, which can be limited by inadequate specimen or assay failures. We hypothesized that multivariate analysis of quantitative imaging (QI) features, extracted from multi-parametric MRI (mpMRI), could enable the non-invasive determination of *MGMT* promoter methylation status. **Methods:** We performed a retrospective cohort study of 111 GBM patients at the University of Pennsylvania whose tumors underwent *MGMT* methylation testing (pyrosequencing across 4 CpG sites in the *MGMT* promoter) and for whom pre-operative structural mpMRI data (T1, T1-Gd, T2, and T2 FLAIR) were available. For each enhancing and non-enhancing tumor sub-region and its peritumoral edema/invasion, we extracted a diverse set of QI features comprising volumetric, morphologic, and texture characteristics, histogram-based signal profiling, and spatial distribution patterns. These features were multivariately integrated via a support vector machine to construct a non-invasive marker of *MGMT* promoter methylation that was quantitatively evaluated using a 10-fold cross-validation (CV). **Results:** 40 patients (36%) were positive for *MGMT* promoter methylation and 71 (64%) were negative. The accuracy of the non-invasive *MGMT* methylation marker was 88.28% [Specificity = 97.0%, Sensitivity = 75.0%, Area under the curve (AUC) = 0.80]. The most predictive features were consistently selected across the 10-fold CV. **Conclusions:** Multivariate integrative analysis of QI features extracted from mpMRI yields an accurate, non-invasive marker of *MGMT* promoter methylation status in GBM. If validated in larger datasets, this marker may allow for early stratification of newly diagnosed GBM trial candidates by *MGMT* methylation status, non-invasive *MGMT* methylation testing in patients for whom tissue is inadequate, and potential monitoring of *MGMT* methylation status during treatment.

2052 Poster Session (Board #210), Sat, 1:15 PM-4:45 PM

Improved prognostic accuracy of alternative MGMT methylation status cutpoint: A single institution experience. *First Author: Jacob Easaw, Cross Cancer Institute, Edmonton, AB, Canada*

Background: We evaluated the clinical relevance of the current cutpoint used to define methylation status in patients (pts) with glioblastoma (GB) in comparison to a proposed alternative cutpoint (PAC) that was derived based on clinical outcomes of pts from Calgary, AB, Canada. **Methods:** We identified and reviewed all pts diagnosed with GB treated in our institution between2015 and 2016. We analyzed prognostic value, sensitivity and specificity of the current cutpoint (9%) and PAC (12.2%) for MGMT promoter methylation status. **Results:** We included 153 pts with a median age of 61.7 years (range; 29 – 86); 53% male. Maximal safe tumor resection was subtotal in 61 (39.0%) and gross-total in 75 (49%) of pts. A biopsy was performed in 17 cases (11.1%). Thirteen pts (8.5%) did not receive any postoperative treatment, 105 (68.8%) of pts received standard concurrent temozolomide (TMZ) with radiotherapy (RT) followed by monthly TMZ; and the rest received mostly RT alone +/- sequential TMZ. MGMT methylation status, extent of resection, age and KPS ($<$ vs $\geq$ 70) were included in multivariate analysis and only MGMT status and age were independently associated with median overall survival ($p < 0.001$ and $p < 0.003$, respectively) using either cutpoints. However, there was an improvement in accuracy using the PAC. **Conclusions:** In this cohort we found an alternative cutpoint with improved correlation with overall survival in patients with newly diagnosed GB. This finding warrant further evaluation as deeming a tumor as unmethylated implies not only a worse prognosis but may impact therapeutic options; i.e. clinical trial participation.

	Current MGMT cutpoint (9%)	Proposed alternative cutpoint (12.2 %)
Sensitivity	59	60
Specificity	63.2	67.6
Positive Predictive Value	35.4	38.2
Negative Predictive Value	81.8	83.5
Accuracy	62.1	65.7

2053 Poster Session (Board #211), Sat, 1:15 PM-4:45 PM

NRG BN002: Phase I study of checkpoint inhibitors anti-CTLA-4, anti-PD-1, the combination in patients with newly diagnosed glioblastoma. *First Author: Andrew E. Sloan, University Hospital Case Medical Center, Cleveland, OH*

Background: Glioblastoma (GBM) remains an incurable disease that is associated with impaired immunity. Recently, immune checkpoint inhibitors (ICIs) have demonstrated efficacy in several solid tumors including brain metastases. This study evaluated the safety of anti-CTLA-4 (Ipilimumab; IPI) and anti-PD-1 (Nivolumab; NIVO) ICIs alone or in combination in newly diagnosed GBM during adjuvant temozolomide (TMZ) treatment. **Methods:** This is a phase I study of IPI (3mg/kg), NIVO (3mg/kg), and the combination (1 mg/kg & 3 mg/kg respectively) followed by an expansion cohort for the combined treatment of adults with confirmed unifocal, supratentorial newly diagnosed GBM after gross or near total resection. Treatment with ICIs started after standard chemo-radiotherapy along with adjuvant TMZ; starting dosing of ICIs were at target with dose reduction planned for toxicity. The primary endpoint was the dose limiting toxicity (DLT) from the start of ICIs to 8 weeks after in each arm. A standard up-and-down design was used, with 6 evaluable patients enrolled at a given dose level. The dose level would be declared safe if no more than 1 of 6 had an DLT. **Results:** Thirty-two patients were enrolled at 9 institutions, 6 to each arm and 14 to the expansion cohort. One patient was not treated, yielding 31 analyzable. Median age was 54 years (range: 23-74), 68% were male and 84% were white. Overall, treatment was well tolerated with a 16% rate of Grade 4 events; the combination did not have an increased toxicity rate and there was no reported Grade 5 event. One DLT was seen in each single-agent arm; none in the combination arm. Median follow-up time was 7.1 months (range: 0.5-21.3) for all analyzable patients, at which time 10 had progressed (32%) and 8 had died (26%), 7 due to disease progression and 1 due to pulmonary embolism. For the 18 patients who had at least 1-year follow-up, 6 on each arm, 3 died within 1 year, 1 on each arm. **Conclusions:** IPI and NIVO are safe and tolerable with similar toxicity profiles noted with other cancers when given with adjuavant TMZ for newly diagnosed GBM. These results provide necessary safety data justifying the performance of a subsequent trial to test the efficacy of ICIs in this disease. Clinical trial information: NCT02311920.

2054 Poster Session (Board #212), Sat, 1:15 PM-4:45 PM

GEINO 1402: A phase Ib dose-escalation study followed by an extension phase to evaluate safety and efficacy of crizotonib in combination with temozolomide (TMZ) and radiotherapy (RT) in patients with newly diagnosed glioblastoma (GB): Results of the dose-escalation phase. *First Author: Maria Martinez Garcia, Hospital del Mar, Barcelona, Spain*

Background: Crizotinib is an ALK, ROS-1 and c-MET inhibitor with an interesting rationale to be tested in NDGB due to the role of MET signaling in gliomagenesis and stem cell maintenance and capability of midkine, a recently discovered ALK ligand, to promote resistance of glioma cells to anticancer therapies such as RT and TMZ. Primary objective of this trial was to determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of crizotinib in combination with RT and TMZ. **Methods:** Eligible patients received crizotinib with standard RT and TMZ and afterwards continued crizotinib daily with sequential adjuvant TMZ. Additional treatment with crizotinib beyond 6 TMZ cycles was allowed at the discretion of physician. Crizotinib MTD was determined using a standard "3+3" dose escalation design. Dose-limiting toxicities were observed during the first 12 weeks of therapy. **Results:** 12 patients (median age: 53,5 (33-60 y)) were enrolled in 3 crizotinib cohorts (200 mg/QD, 250 mg/QD and 200 mg/BID). Most common related adverse events (all grades) were: nausea (66.7%), asthenia (58.3%), transaminitis (50%), neutropenia (50%), constipation (41.7%) and diarrhea (41.7%). Thirteen drug-related AEs $\geq$ G3 were reported, 5 neutropenia, 2 thrombopenia, 2 transaminitis, 1 asthenia, 1 lymphopenia, 1 constipation and 1 hypophosphatemia. 3 DLTs were observed (transaminitis G3, neutropenia G4 and constipation G3): 0/3 in cohort 1 (200 mg/QD); 1/6 in cohort 2 (250 mg/QD) and 2/3 in cohort 3 (200 mg/BID). Median follow-up of 18.3 m (months) (5.4-34.5) and 8 events, median PFS was 16.8 m (95% IC: 8,2-25,3). Three patients died and median OS has not been reached. OS at 6m was 92%, at 12m 80% and 60% at 24m. **Conclusions:** On the basis of observed DLTs, the safety profile and MTDs, a dose regimen of crizotinib 250 mg/QD in association to standard RT and TMZ has been selected for further investigation in the expansion phase. At this point, efficacy results, especially PFS, seem very encouraging. Funding for this study was provided by Pfizer, Inc, New York, USA Clinical trial information: NCT02270034.

2055 Poster Session (Board #213), Sat, 1:15 PM-4:45 PM

Correlation of immune infiltration of cytotoxic T cells and activated microglia in glioblastoma (GBM) post anti-PD1 therapy with response. *First Author: Andrew Silverman, Columbia University Medical Center, New York, NY*

Background: Glioblastoma (GBM) is an aggressive malignancy of the central nervous system with an abysmal prognosis. Recent advances in immunotherapy, including anti-programmed cell death-1 (anti-PD1), has shown potential to improve outcomes for some GBM patients. In this study, we evaluate the immune cell densities in post-treatment biopsies from patients treated with anti-PD1 for refractory GBM. We hypothesized that density of both cytotoxic T lymphocytes (CTLs) and activated microglia is higher within the tumor mircro-environment (TME) in patients who respond to anti-PD1. **Methods:** Formalin-Fixed, Paraffin-Embedded (FFPE) tumor samples from a preliminary cohort of five patients with GBM, 2 non-responders and 3 responders, were stained using quantitative multiplex Immunofluorescence (qmIF). Response was classified as decrease in tumor volume by $>$ 50% and/or survival for 6 months without growth of tumor by $>$ 25%. Stains were sequentially applied, using Opal multiplexing/qmIF for CD3 (T cells), CD8 (cytotoxic T lymphocytes (CTLs)), FOXP3 (regulatory T cells – Tregs), CD68 (microglia), HLA-DR (immune activation/tumor presentation), and SOX2 (tumor marker). Multispectral images (MSIs) were acquired using Vectra and analyzed using inForm software and R studio to evaluate density of immune phenotypes within the TME. **Results:** We find that post-treatment, the patents who responded to anti-PD1 have a significantly increased CTL/total cell density ($p = 0.0393$) and higher activated microglia CD68+HLA-DR+/total CD68 density ($p = 0.0208$), when compared to non-responders. Tregs were rarely seen in either subset of patients and had no significant correlation with response. **Conclusions:** Preliminary analysis demonstrates higher CTLs and activated microglia in the TME after treatment in patients with GBM who responded to anti-PD1 therapy. Analysis of a larger cohort of 17 patients with specimens at baseline, recurrence and post anti-PD1 is underway and will be presented at the meeting. This data would confirm that anti-PD1 can induce increased inflammation within the TME in GBM despite the blood brain barrier and suggest that further alteration of the immune TME may improve outcomes in GBM.

2056 Poster Session (Board #214), Sat, 1:15 PM-4:45 PM

Preliminary report of a multicenter, phase 2 study of bevacizumab in children and adults with neurofibromatosis 2 and progressive vestibular schwannomas: An NF Clinical Trials Consortium study. *First Author: Scott Randall Plotkin, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Profound hearing loss is common in patients with neurofibromatosis 2 (NF2) and vestibular schwannomas (VS). Bevacizumab treatment at 7.5 mg/kg every 3 weeks has been associated with hearing improvement and tumor shrinkage in 36% and 43% of patients, respectively. However, the optimal treatment dose and schedule are unknown. **Methods:** This multicenter, phase II, open-label study evaluated subjects ($\geq$6 years old) with NF2 and progressive VS. Subjects received bevacizumab 10 mg/kg every 2 weeks during induction therapy (6 months), and 5 mg/kg every 3 weeks during maintenance therapy (18 months). Hearing response was defined as a significant increase in word recognition score above baseline. Radiographic response was defined as $\geq$20% decrease in tumor volume from baseline. The primary endpoint was hearing response rate in the target ear at 6 months. **Results:** We enrolled 22 subjects (median age = 23 years). The overall hearing and radiographic response rates were 41% (9/22) and 23% (5/22), respectively. In an unplanned post-hoc analysis, the hearing and radiographic response rates were 14% (1/7) and 0% in pediatric subjects $\leq$21 years, as compared with 53% (8/15) and 33% (5/15) in adult subjects. Bevacizumab was well tolerated. Adverse events included hypertension, proteinuria, arthralgias, AST/bilirubin elevation, delayed wound healing, fatigue, and irregular menstruation. 11/13 women with elevated FSH underwent evaluation for premature ovarian insufficiency. All continued treatment with bevacizumab. **Conclusions:** Bevacizumab treatment at 10 mg/kg every 2 weeks is associated with hearing and radiographic response rates comparable to previous studies using lower doses. Pediatric subjects appear to benefit less than adults during bevacizumab treatment. Clinical trial information: NCT01767792.

2057 Poster Session (Board #215), Sat, 1:15 PM-4:45 PM

Prospective analysis of cancer stem cell drug response assay for glioblastoma patients. *First Author: Tulika Ranjan, Duke University Medical Center, Durham, NC*

Background: Over the past 20 years even with the aggressive standard of care (SoC) Stupp treatment protocol the prognosis of glioblastoma (GBM) has only minimally improved from 12 to 14 months. This is due in large part to the presence of chemo- and radiation-resistant GBM cancer stem cells (CSCs) that contribute to tumor propagation, maintenance, and treatment resistance. We are using ChemoID, a CLIA certified and CAP accredited drug response assay that identifies the most effective chemotherapy against CSCs and bulk of tumor cells from of a panel of potential treatments, offering great promise for individualized cancer management. A prospective study was conducted evaluating the use of the ChemoID drug response assay in glioblastoma patients. **Methods:** Fresh tissue samples were collected for drug sensitivity testing from 61 glioblastoma patients enrolled in IRB approved protocol. Patients were prospectively monitored for tumor response, time to recurrence, progression-free survival (PFS), and overall survival (OS). Odds Ratio (OR) associations of 12-month recurrence, PFS, and OS outcomes were estimated for CSCs, bulk tumor and combined assay responses to treatment; sensitivities/specificities, areas under the curve (AUC) were examined. **Results:** The data suggests that ChemoID guided treatment significantly enhanced tumor response. For every 5% increase in ex-vivo cell kill of CSCs by assay-guided chemotherapy, 12-month patient response (non-recurrence $_{of}$ cancer) increased 2-fold, OR = 2.2 (p = 0.01). Bulk of tumor assay was found not statistically significant. Median recurrence time was 20 months for patients with a positive ($>$ 40% cell kill) CSCs test versus only 3 months with a negative CSCs test, whereas median recurrence time was 13 months versus 4 months for patients with a positive ($>$ 55% cell kill) bulk test versus negative. Similar favorable results for the CSC test were observed for PFS and OS outcomes. **Conclusions:** The ChemoID CSCs drug response assay has the potential to increase the accuracy of bulk tumor assays to help guide individualized chemotherapy choices. Glioblastoma cancer recurrence may occur quickly if the CSC test has a low ex-vivo cell kill rate, even if the bulk tumor test cell kill rate is high.

2058 Poster Session (Board #216), Sat, 1:15 PM-4:45 PM

Phase 2 trial of SL-701 in relapsed/refractory (r/r) glioblastoma (GBM): Correlation of immune response with longer-term survival. *First Author: David M. Peereboom, Cleveland Clinic, Cleveland, OH*

Background: SL-701 is a novel immunotherapy comprised of synthetic peptides designed to elicit an anti-tumor immune response against GBM targets: interleukin-13 receptor alpha-2, EphrinA2 and Survivin. Updated Phase 2 data are reported. **Methods:** Patients with r/r GBM HLA-A2+, bevacizumab (bev)-naive and KPS $>$ 60, enrolled. Stage 1: SL-701 with adjuvants GM-CSF and imiquimod dosed biweekly for 6 months, then q28 days. Stage 2: SL-701 with adjuvant poly-ICLC dosed biweekly with bev (10 mg/kg) for 6 months, then q28 days. Primary objectives: safety, tolerability, investigator assessed objective response rate (ORR, RANO criteria) and 12-month OS rate (OS-12). SL-701-specific CD8+ T-cell frequency was assessed by flow cytometry. PBMCs were isolated by density gradient and stimulated for 4h with SL-701 peptides (1mg/ml/peptide) before intracellular staining with live/dead, CD3, CD4, CD8, IFNγ, TNFα, IL-2, and PD-1. **Results:** As of 2/7/18, 74 bev-naive patients received median of 8.5 SL-701 doses. Most frequent treatment-related adverse events (TRAEs) were fatigue (22%) and injection site reaction (18%). Grade 3 TRAE was fatigue (3%); no other grade 3 TRAEs. In Stage 1, 1 partial response (PR) (duration: 78 wks) and 15 stable disease (SD) (median 16 wks; range: 1.3–99) seen in 46 patients. In Stage 2, 2 complete responses (CR) (duration: 30, 46 wks), 4 PRs (median 31 wks; range 12–47) and 19 SDs (median 14 wks; range 0.1-41) seen in 28 patients. OS-12: 43% (median 11.7 mos) in Stage 2 and 37% (median 11 mos) in Stage 1. 5 patients receive SL-701 on compassionate use basis. Preliminary flow cytometry analysis of subset of Stage 2 patients: 5/6 responders (CR, PR or SD of $\geq$6 mos) had SL-701-specific T cell responses, with 1 CR patient at wk 16 generating $>$ 6% SL-701-specific CD8+ T cells by wk 58. **Conclusions:** SL-701 with immunostimulants, alone and in combination with bev, was well-tolerated and demonstrated anti-tumor activity including multiple major responses. There is also a preliminarily promising survival tail in r/r GBM patients who received SL-701 with bev Further analyses ongoing; updated data to be presented. Clinical trial information: NCT02078648.

2059 Poster Session (Board #217), Sat, 1:15 PM-4:45 PM

Integrated clinical experience with ONC201 in H3 K27M glioma. *First Author: Andrew S. Chi, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: ONC201 is a DRD2 antagonist in Phase II trials for cancers that exhibit dysregulation of the dopamine pathway. We previously reported an objective response in the first recurrent H3 K27M midline glioma patient who received ONC201 and that H3 K27M gliomas exhibit enhanced sensitivity to the compound *in vitro*. Here, we report the clinical experience with ONC201 to date in adult and pediatric H3 K27M glioma. **Methods:** As of February 1, 2018, 14 patients with H3 K27M glioma have received single agent ONC201 and had at least one post-treatment MRI. This includes 9 adult patients (8 glioblastoma, 1 diffuse midline glioma) and 5 pediatric patients (3 DIPG, 2 other diffuse midline gliomas). All patients had recurrent disease, except for 2 DIPG patients who had completed radiotherapy. Seven patients were enrolled on a clinical trial and seven were enrolled on compassionate use protocols. ONC201 was orally administered at 625 mg to adult patients and scaled based on body weight for pediatric patients. All but one patient were dosed once a week. **Results:** Six out of the 14 patients remain on therapy with a median follow up of 5.4 months (range: 2.9-22.6) with durable radiographic and/or clinical stability or improvement. This includes the first responder who has now been on treatment for 22 months with a 96% overall regression. All 6 patients who experienced benefit had 1-2 prior lines of therapy, whereas 5 patients who had at least 3 prior lines of therapy did not experience benefit. Among the five patients with thalamic glioma, two experienced complete regressions of their thalamic lesions while another underwent a 30% regression. One patient with previously-irradiated DIPG that exhibited a 300nM IC50 ex vivo has experienced improvements in hemiparesis and other disease-related symptoms. Another previously-irradiated DIPG patient has experienced improvements in her facial palsy and other disease-related symptoms, along with a 40% regression. **Conclusions:** Preliminary clinical data indicates ONC201 induces durable radiographic regressions and clinical benefit in a subset of patients with H3 K27M glioma. The clinical activity of ONC201 in pediatric and adult H3 K27M gliomas is being evaluated in ongoing clinical trials. Clinical trial information: NCT03295396, NCT02525692, NCT03416530.

2060 Poster Session (Board #218), Sat, 1:15 PM-4:45 PM

Community socioeconomic status to identify higher-risk patients with malignant glioma. *First Author: Aaron Stephen Bower, Wake Forest School of Medicine, Winston-Salem, NC*

Background: Patients living in rural areas face barriers to accessing optimal, guideline driven care including proximity to tertiary centers and lower socioeconomic status. We sought to examine the impact of geographic and economic variables on clinical outcomes in a cohort of primary malignant glioma patients. **Methods:** A retrospective cohort study of patients newly diagnosed with WHO grade 3-4 glioma between 1999 – 2017 was performed. Relevant clinical and demographic data including marital status, employment, insurance, race, ethnicity, primary physician, and treatment factors were collected. Median household income was obtained from the US Census Bureau, linked to each patient by home zip code, and used to estimate patients residing in advantaged (above median state income, MSI) and disadvantaged (below MSI) communities. Median overall survival (OS) was assessed by Kaplan-Meier method. **Results:** Of the 310 patients identified, 27% resided in high MSI communities (n = 85). Age, sex, WHO grade, radiation and chemotherapy received did not differ by MSI status (all p $>$ 0.19). Patients from high MSI communities were more likely to have undergone any resection compared to biopsy (80% vs 68%, p = 0.04). Median OS was 3.1 months longer for patients from high MSI (22.1 months vs 19.0, Hazard Ratio [HR] 0.81, 95% CI 0.61-1.09, p = 0.16). This survival difference was observed for grade 4 (HR 0.75, 0.54-1.04, p = 0.09) and not grade 3 gliomas (HR 0.97, 0.52-0.82, p = 0.92). When stratified by MSI status, men from high MSI communities showed a trend towards survival advantage (HR 0.71, 0.46-1.08, p = 0.10); this was not observed for women (HR 0.86, 0.51-1.45, p = 0.57). **Conclusions:** Male patients with glioblastoma residing in economically disadvantaged communities in NC experience worse outcomes than similar patients from advantaged areas. Further efforts to understand the patient-specific, community, and socioeconomic barriers are warranted.

Characteristic	Hazard Ratio (95% CI)	P-Value
High vs Low MSI	0.77 (0.57 – 1.03)	0.08
WHO Grade 4 vs 3	2.85 (2.01 – 4.03)	$<$ 0.001
Age (by decade)	1.41 (1.26 – 1.57)	$<$ 0.001
Era of Treatment (Pre- vs Post-Temozolomide)	1.28 (0.96 – 1.70)	0.09

2061 Poster Session (Board #219), Sat, 1:15 PM-4:45 PM

Dianhydrogalactitol in bevacizumab-refractory GBM: Further analysis of a phase 1-2 trial. *First Author: Kent C. Shih, Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, TN*

Background: Dianhydrogalactitol (VAL-083) is a first-in-class DNA-targeting agent with anticancer activity established in prior NCI-sponsored trials. We have previously reported results of DLM-10-001 (NCT01478178), a multicenter Phase 1-2 trial of VAL-083 in bevacizumab refractory GBM (BEV-rGBM), with median overall survival (mOS) of 8.35mo from BEV failure and an observed dose response. Here, we report further analysis of OS in DLM-10-001 from the start of treatment for patients (pts) receiving a clinically active dose of VAL-083 compared to pts receiving an inactive dose of the agent and two derived controls of historical and recent electronic medical records (EMR) data. **Methods:** 45 BEV-rGBM pts were enrolled across 10 cohorts at doses ranging from 1.5mg/m^2 to 50mg/m^2. Pts received VAL-083 IV on days 1, 2, 3 of a 21-day cycle. MTD was established at 40mg/m^2/day. A clinically active dose of VAL-083 was determined at or below MTD based on PK data and *in vitro* studies against GBM cell-lines included pts from 20, 30 & 40 mg/m^2 dose cohorts. OS in DLM-10-001 was calculated from the 1st dose of VAL-083. DLM-10-001 trial data are also compared to historical publications of BEV-rGBM, and recent EMR for BEV-rGBM pts receiving salvage therapy with TMZ, CCNU or carboplatin. mOS and hazard ratios (HR) were estimated by Kaplan-Meier and nominal p-values to compare survival curves by log-rank test (MedCalc Software v18). **Results:** OS for BEV-rGBM pts treated with a clinically active dose of VAL-083 (mOS = 7.9mo, 95% CI = 3.1-9.6mo) was superior to OS for pts receiving an inactive dose of VAL-083 (mOS = 2.9, HR = 0.341, p = 0.003); historical publications (mOS = 2.8mo, HR = 0.362, p = 0.0005); and EMR data (mOS = 2.9mo, HR = 0.399, p = .011). There was no statistical difference between the control groups. Pts receiving a clinically active dose of VAL-083 demonstrated an OS benefit compared to an aggregate of the controls (mOS = 2.9mo, HR = 0.395, p = .0003). **Conclusions:** The results suggest a statistically significant and meaningful OS benefit for BEV-rGBM pts treated with a clinically active dose of VAL-083. While small sample size and retrospective nature of the analyses is limiting, the results warrant further exploration via a randomized trial. Clinical trial information: NCT01478178.

2062 Poster Session (Board #220), Sat, 1:15 PM-4:45 PM

Neurological death in patients with EGFR-mutant non-small cell lung cancer. *First Author: Matthew Ramotar, Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Patients with EGFR mutant non-small cell lung cancer (EGFRmNSCLC) have a high incidence of brain metastases (BM). We sought to determine the rate of neurologic death in EGFRmNSCLC patients diagnosed with brain metastases. **Methods:** A single-institution prospectively managed database identified 204 patients with EGFRmNSCLC treated for brain metastases between 2000 and 2016. We estimated actuarial survival rates using the Kaplan-Meier method. The incidence of neurologic death (ND) was determined using a competing risks analysis. ND was correlated to clinical and treatment variables using Fisher's exact test. Survival was calculated from the date of BM diagnosis. We defined neurologic death as death due to brain metastases or leptomeningeal disease **Results:** Fifty-six percent of patients had BM at the time of initial diagnosis. The initial BM treatment was up front stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or tyrosine-kinase inhibitor (TKI) alone in 22, 60, and 18 percent of patients, respectively. Two-year rates of OS in these subgroups were 64%, 38%, and 50%, respectively (p = 0.016). The 5-year rate of neurologic death was 38%. Thirty-four percent died of non-neurologic causes, 8% died of unknown causes, and the remaining patients were alive at last follow-up. Median survival (MS) was 19 months; MS in patients who died of non-neurologic causes and neurologic causes was 23, and 15 months, respectively. Of age, staging, BM at diagnosis, history of TKI therapy, initial treatment of BM, staging at diagnosis, and leptomeningeal disease at diagnosis (LMD), only LMD was significantly associated with ND (p = 0.047). **Conclusions:** Neurologic death due to EGFRmNSCLC BM was more common in our cohort than has been previously reported, highlighting the need for dedicated studies focused on the best management of BM in this population.

2063 Poster Session (Board #221), Sat, 1:15 PM-4:45 PM

Impact of prior systemic therapy on lymphocytic infiltration in surgically resected breast cancer brain metastases. *First Author: Andrew Bacotti, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor infiltrating lymphocytes (TILs) have been positively correlated with response to systemic therapy and for triple negative and HER2+ subtypes and clinical outcomes in early breast cancer (BC) (Denkert C et al., Lancet Oncol 2018). Less is known about TILs in metastatic sites (Cimino-Mathews A et al., Hum Pathol 2016; Ogiya R et al., Cancer Sci 2016), particularly brain (BM), where unique immune regulation governs stromal composition (Duchnowska R et al., Breast Can Res 2016; Harter PN et al., Oncotarget 2015). Reactive glial cells actively participate in cytokine-mediated T cell stimulation (Fitzgerald DP et al., Clin Exp Met 2008). The impact of prior medical therapy (chemotherapy, endocrine therapy, and HER2-targeted therapy) on the presence of TILs and gliosis in human BCBMs has not been previously reported. **Methods:** In order to determine the impact of prior medical therapy on the presence of TILs and other histopathologic variables, we examined prior treatment data for 133 patients who underwent craniotomy for resection of BMs from the electronic medical record. We examined the relationship between prior systemic therapy exposure and the histologic features of gliosis, necrosis, hemorrhage, and lymphocyte infiltration (LI) assessed by hematoxylin and eosin stain in BCBMs resected at subsequent craniotomy in uni- and multivariate analyses (Prince G et al. Proc ASCO 2017, abstract 2072). **Results:** Complete treatment data were available for 122 patients. 36 of 114 patients (31.6%) who had received prior systemic treatment had BCBM LI while BCBM LI was observed in 6 of 8 patients (75%) who had not received systemic treatment {significant by Fisher's exact test p = 0.02}. There were no statistically significant relationships between prior systemic therapy and the three other histologic variables examined. **Conclusions:** This observation suggests that systemic therapy may interfere with the immune response to BCBMs. This motivates clinical investigation of strategies to enhance LI for therapeutic benefit to improve outcomes for patients with BCBMs. Analysis of these tissue samples to address the potential significance of the pattern of LI as well as relevant biomarkers is ongoing.

2064 Poster Session (Board #222), Sat, 1:15 PM-4:45 PM

Outcomes of lung cancer patients with leptomeningeal metastases in the targeted therapy era. *First Author: Kathryn Sara Nevel, Memorial Sloan Kettering Cancer Center - Fellowship (GME Office), New York, NY, US*

Background: Recent improvements in detection and molecular characterization of leptomeningeal metastasis from lung cancer (LC-LM) coupled with cerebrospinal fluid (CSF)-penetrating targeted therapies have substantially altered the management of this disease. In this new era, outcomes of patients harboring LC-LM are not well defined. This study identifies molecular and clinical characteristics of LC-LM and correlates these with clinical outcome. **Methods:** We retrospectively reviewed charts of 171 patients diagnosed with LC-LM between June 2009 and June 2017 at Memorial Sloan Kettering Cancer Center. Presence of targetable mutations (TM) in the primary tumor and CSF was determined by MSKCC IMPACT. Extent of radiographic involvement was scored by number of gadolinium-enhancing sites in eight locations. CSF studies included cytopathology, quantification of circulating tumor cells (CTCs), and cell free DNA (cfDNA) analysis. Kaplan-Meier survival curves were compared by log-rank analyses. **Results:** Median overall survival (OS) after LC-LM diagnosis (dx) was 125 days; 80/171 patients harbored a TM. At one year, 29% of patients with a TM were alive versus 12% of those without. Treatment of LC-LM with targeted therapies (TTx) was associated with improved OS (0 TTx = 70 days, 1 TTx = 109 days, 2+ TTx = 507 days; $p < 0.0001$). A subset of 93/171 patients underwent MRI brain, spine and CSF studies within 30 days of LM dx. Extent of radiographic involvement correlated with OS: 0-2 sites of disease OS = 113 days, 3+ sites OS = 75 days; p = 0.015. CTCs were analyzed in 15/171 patients. Fewer than 50 CTCs/3 mL correlated with OS of 377 days, versus OS 66 days for $>$ 50 CTCs/3mL. cfDNA was extracted from 20/171 patients. cfDNA concentration correlated with outcome; cfDNA < 0.025 ng/μl = OS of 231 days, vs cfDNA > 0.025 ng/μl OS of 60 days p = 0.022. **Conclusions:** In this largest study of LC-LM, presence of a TM and treatment with TTx were associated with improved OS. Extent of radiographic involvement at dx was also a prognostic indicator. These findings support complete molecular characterization and CNS staging for clinical management, prognostication and clinical trial stratification of LC-LM.

2065 Poster Session (Board #223), Sat, 1:15 PM-4:45 PM

Impact of apolipoprotein E (APOE) genotype on neurocognitive function (NCF) in patients with brain metastasis (BM): An analysis of NRG Oncology's RTOG 0614. *First Author: Jeffrey Scott Wefel, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Whole brain radiotherapy (WBRT) is a common treatment for BM and is associated with decline in NCF. The APOE e4 allele is associated with increased risk of Alzheimer's disease, and NCF decline after chemotherapy for non-CNS cancer, treatment for primary brain tumor, and in irradiated mouse models. APOE carrier status has not been evaluated as a risk factor for impaired NCF in patients with BM before and after WBRT. **Methods:** RTOG 0614 treated adult patients with BM with 37.5 Gy of WBRT (+/- memantine), performed NCF testing (HVLT-R, TMT, COWA) at baseline, 8, 16, 24, and 52 weeks, and included an optional blood draw for APOE analysis. APOE alleles were evaluated by real-time PCR based SNP analysis using TaqMan genotyping. NCF test results were compared at baseline and over time with mixed effects models adjusted for baseline score, treatment arm, time, and interaction between time and APOE carrier status. A cause-specific Cox model for time to NCF failure was performed to assess the effects of treatment arm (memantine versus placebo) and APOE carrier status (e4 versus no e4). **Results:** APOE results were available for 45% (n = 227/508) of patients. No pretreatment differences were detected between patients with APOE available versus not available. APOE e4 carrier status was evenly distributed between treatment arms (e4 positive = 29.5%). NCF test results did not differ by APOE e4 carrier status at baseline, but e4 carriers were less often white and had started WBRT at study entry more often. Mixed effects modeling showed that patients without an APOE e4 allele had better memory after WBRT compared to patients with an APOE e4 allele (HVLT-R Total Recall [estimate = 2.44, p = 0.026], Delayed Recognition [estimate = 1.15, p = 0.024]). For time to NCF failure, treatment arm was significant (HR = 0.715, 95% CI: 0.513-0.998, p = 0.0487) in favor of memantine; however, APOE e4 status was not (HR = 0.865, 95% CI: 0.606-1.233, p = 0.422). **Conclusions:** Patients with an APOE e4 allele exhibited worse memory function after treatment with WBRT (+/- memantine), but no difference in time to NCF failure. APOE carrier status was not associated with NCF in patients with BM prior to WBRT. Clinical trial information: NCT00566852.

2066 Poster Session (Board #224), Sat, 1:15 PM-4:45 PM

Incidence of treatment effect and characteristic MRI findings in immunotherapy-treated melanoma patients with brain metastases receiving stereotactic radiosurgery. *First Author: Justin Lin Sovich, University of Michigan, Ann Arbor, MI*

Background: Melanoma brain metastasis (MBM) treated with stereotactic radiosurgery or stereotactic body radiation therapy (SRS/SBRT) and immunotherapy may have higher rates of treatment-related injury including radiation necrosis, which can be difficult to differentiate from disease progression. Little is known about characteristic radiographic findings to guide decision-making. **Methods:** We identified all patients (pts) with MBM from the University of Michigan from 2012-2017 who were treated with SRS/SBRT. Pts receiving immunotherapy were compared to those who had not. Overall incidence of treatment-effect (TE) (pathologically confirmed or inferred by $>$ 6 mos stable imaging) were calculated. We reviewed MRIs in pts with TE for conventional metrics including enhancement, T2 hyperintensity, and apparent diffusion coefficient (ADC) and perfusion parameters including calculated blood volume (rBV), blood flow (rBF), time to maximum (tMAX), and leakage (K2). **Results:** 104 pts received SRS/SBRT and immunotherapy and 29 pts had not. Among the immunotherapy group, 16 had TE (6 pathologically confirmed, 10 by serial imaging) (15.4%). Of the 29 who did not receive immunotherapy, one had TE (pathologically confirmed) (3.45%). The observed risk difference was 12.0% (95% CI 2.4% to 21.6%). We reviewed MR findings for 18 lesions in 15 pts with TE, all of which had enhancement with T2 hyperintensity. Reliable ADC values were calculated for 14 lesions, averaging 112.8 (range 72 to 192). Perfusion imaging was available for 9 lesions, with average rBV 1.63 (range 0.63 to 3.6), rBF 23.86 (9 to 55.4), tMAX 5.71 (0.99 to 27), and K2 -266.78 (-111to -636). **Conclusions:** SRS/SBRT and immunotherapy resulted in higher absolute risk of treatment-related changes. MRI findings were consistent with existing data on radiation necrosis in glioblastoma multiforme which could help guide decision making in MBM. Comparative analysis on tumor progression in this population is ongoing and will be presented.

2067 Poster Session (Board #225), Sat, 1:15 PM-4:45 PM

Mutational complexity increases in lung adenocarcinoma (LADC) with the development of brain metastasis (BM). *First Author: Matthew K Stein, Department of Hematology-Oncology, West Cancer Center/University of Tennessee Health Science Center, Memphis, TN*

Background: Up to 40% of LADC patients (pts) develop BM but little is known about the inciting molecular events. **Methods:** We compared mutational profiles of LADC BM pts with primary (P) LADC submitted to Caris Life Sciences from 2015-2017. Testing included next-generation sequencing (NGS) of 592 cancer-related genes, PD-L1 IHC and tumor mutational burden (TMB). NGS aberrations were test-defined as pathogenic (PATH), variants of undetermined significance or unclassified mutations (VUS). TMB was defined as: high (H; $\geq$17 mutations/megabase), intermediate (I; 7-16) and low (L; 0-6). **Results:** 145 BM (57% female (f)) and 1145 P (58% f) cases were identified; BM median age was 64 (range 31-86) vs. 70 (25-90) in P pts. BM had 55 PATHs (38% pts) in *KRAS*, 34 *STK11* (23%), 17 *EGFR* (12%), 5 *BRAF* (3%); 3 were *MET*-amplified (2%), 3 *ALK* (2%) and 1 *ROS1*-rearranged (1%). Compared to P, more BM pts harbored *STK11* PATHs (23% vs. 11%, P $<$ 0.0001); no other difference in PATHs was observed. 143 BM and 1102 P pts had TMB data. BM cases were more-frequently TMB-H compared to P (39% (N = 56) vs. 12% (132), P $<$ 0.0001) and less likely to be TMB-L (8% (12) vs. 33% (366), P $<$ 0.0001). 131 (92%) BM pts were TMB-I or H. Of 142 BM and 1060 P with PD-L1 testing, incidence of $\geq$1% (46% BM vs. 49% P) and $\geq$50% (24% vs. 23%) cases were similar. 327 VUS in 28 receptor tyrosine kinases (RTK) were observed in 117 BM (median 1 (0-12)) vs. 1648 VUS in 807 P pts (median 1 (0-13); 79% vs. 70%, P = 0.007). RTK VUS more frequently observed in BM included: 51 *EPHA3* VUS (17% pts vs. 8%. P = 0.0002), 25 *EPHA5* (15% vs. 8%, P = 0.004), 26 *NTRK3* (14% vs. 6%, P = 0.0002), 22 *EPHB1* (13% vs. 6%, P = 0.0001) and 17 *PDGFRA* (12% vs. 5%, P = 0.0001). No significant difference was observed between BM specimen site and *EGFR*, *KRAS*, TMB and PD-L1 status. **Conclusions:** While classic LADC biomarkers including PD-L1, *EGFR* and *KRAS* were similar between BM and P cases, nearly 40% BM pts were TMB-H ($\geq$25% more than P) and $>$ 90% either TMB-I or H, indicating an increased mutational complexity in BM development, suggesting immune checkpoint inhibitor use. In addition to *STK11* PATHs, RTK VUSs including *NTRK3*, *EPHA3*, *EPHA5* and *EPHB1* were more-frequently mutated and warrant further evaluation as biomarkers or targets in BM.

2068 Poster Session (Board #226), Sat, 1:15 PM-4:45 PM

Discovery of a predictive protein biomarker for leptomeningeal disease after craniotomy and radiation. *First Author: Michael Henry Soike, Wake Forest Baptist Medical Center, Winston-Salem, NC*

Background: Leptomeningeal disease (LMD) is a common but morbid disease progression after craniotomy for resection of brain metastases (BrM). LMD has been observed most commonly with breast cancer BrM, but the cellular mechanisms facilitating LMD have not been elucidated. We sought to identify a protein associated with a higher risk of developing LMD. **Methods:** At our institution, patients (2005-2016) who had craniotomy for BrM followed by adjuvant radiation therapy were eligible for this IRB approved study. Frozen BrM samples were reduced with trypsin digestion, pelleted by centrifugation, and analyzed by liquid chromatography–mass spectrometry. Mass spectra were searched with Sequest HT algorithm in Proteome Discoverer v2.1 (Thermo Scientific). Patient outcomes were obtained from the medical record and overall survival (OS) and time-to-event were calculated with Kaplan-Meier and Competing Risk. To identify proteins of interest, we used empirical Bayes based linear models (limma) and the Benjamini–Hochberg false discovery rate analysis (FDR). Univariate (UVA) and multivariate (MVA) analyzed patient characteristics and proteins associated with LMD. **Results:** Proteomic expression data for 39 patients were included. The median OS was 13 months. Eleven (28%) developed LMD. 6407 proteins were analyzed. After FDR, only collagen type 1 alpha 1 chain (COL1A1) and collagen type I alpha 2 chain (COL1A2) were associated with a higher risk of LMD (FDR 0.045 and 0.089, respectively). On UVA and MVA analysis, COL1A2 was associated with a statistically significant higher risk of LMD (Table). **Conclusions:** COL1A2, a component of type I collagen, is associated with a higher risk of LMD development, even when accounting for breast histology. COL1A2 may be a protein of interest in the mechanism facilitating LMD progression.

UVA and MVA for proteins of interest developing in LMD progression.

Variable	UVA Hazard Ratio (confidence interval)	MVA Coefficient and p-value
Previous systemic therapy	7.8 (1.6-38)	1.24 p = 0.15
Smoking at diagnosis	0.4 (0.1-1.3)	
Age	1.0 (0.9-1.0)	
Gender	0.3 (0.1-1.5)	
Breast vs other histology	4.4 (1.5-12.8)	0.08 p = 0.89
COL1A1	1.3 (1.2-1.4)	-0.002 p = 0.98
COL1A2	1.3 (1.1-1.4)	0.20 p = 0.03

2069 **Poster Session (Board #227), Sat, 1:15 PM-4:45 PM**

MRI texture features and outcomes to immune checkpoint inhibitors in melanoma brain metastases. *First Author: Ankush Bhatia, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Brain metastases (BM) in patients (pts) with melanoma historically portend a dismal prognosis, but immune checkpoint inhibitors (ICI) are associated with durable responses in a subset of pts. There are no validated imaging biomarkers associated with outcomes in pts with melanoma BM receiving ICI. We hypothesized that texture analysis of contrast T1-weighted magnetic resonance images (MRI) could identify "higher order" features associated with progression-free (PFS) and overall survival (OS). **Methods:** Between 2010 and 2017, we retrospectively reviewed pts with measurable ($>$ 1.0cm) melanoma BM on MRI who received ICI with or without concurrent radiation therapy (RT). Volume-of-interests were drawn around up to 5 BM per pt, and Haralick textures (n = 5), and Gabor edge features (n = 4) at angles (0°, 30°, 45°, 90°) and a bandwidth (γ = 2) were extracted for each lesion. Progression for BM was determined using RANO-BM; pts who died without repeat MRI were considered to have progressed. OS was calculated from date of ICI receipt. Cox regression was performed for each texture feature. **Results:** 88 pts with 196 total BM were identified. Median age was 63.5 (19-91), ECOG (0-54%, 1-34%, 2-3 12%), 38% had elevated LDH, and 42% had prior systemic treatment. ICI was CTLA-4 monotherapy in 77%, PD-1 monotherapy in 9%, and PD-1 + CTLA-4 in 14%. 79% received concurrent RT (38% focal, 62% whole brain). Median OS was 5.4 months (0.3-80.9). Increased energy (HR = 1.04, 95%CI 1.01-1.07, p = 0.02) was associated with a poorer progression-free (PFS) and OS (HR = 1.04, 1.00-1.07, p = 0.03). Increased entropy was associated with an improved PFS (HR = 0.82, 0.69-097 p = 0.02) and OS (HR = 0.84, 0.72-.99, p = 0.03). Both features remained significantly associated with OS (Energy HR = 1.15, 1.03-1.20, p = 0.02; Entropy HR = 0.84, 0.71-0.98, p = 0.03) after adjusting for receipt of RT and ICI (PD-1 vs. CTLA-4 vs. PD-1+ CTLA-4). **Conclusions:** In the first ever analysis of higher order MRI features in pts with melanoma BM receiving ICI, Haralick texture features are associated with both PFS and OS. Further research is required to determine whether these features are independently associated with OS in a multivariate analysis.

2070 **Poster Session (Board #228), Sat, 1:15 PM-4:45 PM**

Timing, presentation, and patterns of failure of leptomeningeal disease after surgical resection and radiosurgery for brain metastases: A multi-institutional analysis. *First Author: Roshan Sudhir Prabhu, Levine Cancer Institute and Southeast Radiation Oncology Group, Charlotte, NC*

Background: Postoperative (post-op) radiosurgery (SRS) has been proposed as a standard of care based on 2 phase III trials, but has been associated with up to 30% risk of leptomeningeal disease (LMD). The specifics of timing, presentation, and patterns of LMD failure have not been well described. **Methods:** The records of patients (pts) with brain metastases (BM), of which 1 was resected and treated with post-op or pre-op SRS, and who subsequently developed LMD were combined from 7 tertiary care centers. Pts with classically radiosensitive tumors or prior or planned whole brain radiotherapy were excluded. LMD pattern was categorized as either nodular or linear ("sugarcoating"). **Results:** The study cohort consisted of 147 pts. The most common primary sites were lung (40%), breast (24%), and melanoma (16%), and most pts received post-op SRS (94%). Pts with breast primary were enriched for HER-2 positivity (60%). The majority of resected BM (82%) extended to within 5 mm of the pial surface. Median time from initial SRS to 1st LMD was 5.6 months (interquartile range [IQR] 3.2 – 11). The majority of LMD events were nodular (60%), of which 64% were within 5 cm of the surgical corridor. The median number of nodules was 2 (IQR 1 – 4), with a median distance of 2.5 cm from the surgical corridor (IQR 1.1 – 5.2). Most pts (60%) were symptomatic at time of LMD diagnosis, of which the most common symptoms were headache (58%), cranial nerve deficit (28%), and dizziness/balance issues (24%). Of the pts who received LMD treatment and had follow-up imaging (n = 101), 50% experienced 2nd LMD at a median of 5.5 months after 1st LMD (IQR 2.8 – 9.4). Of these, 68% were symptomatic at the time of 2nd LMD diagnosis, 58% had nodular LMD with a median of 1 nodule (IQR 1-3), and 70% underwent salvage therapy. **Conclusions:** LMD failure is an increasingly recognized event after surgery and SRS for BM. Pts who experience LMD are enriched in HER-2 positive disease and superficial location of the resected BM. Nodular LMD is the predominant pattern of LMD failure in this pt population, with most LMD events being symptomatic. 2nd LMD is common after initial salvage therapy and also has a predominantly nodular pattern.

TPS2071 **Poster Session (Board #229a), Sat, 1:15 PM-4:45 PM**

A randomized, multicenter phase 2 study of DSP-7888 dosing emulsion in combination with bevacizumab (Bev) versus Bev alone in patients with recurrent or progressive glioblastoma. *First Author: John Frederick De Groot, The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX*

Background: Glioblastoma (GBM) is the most frequently diagnosed high-grade glioma with an incidence of 3-4/100,000 in the US. Although treatments have improved, median survival remains 15–18 months for newly diagnosed patients. DSP-7888 is an investigational peptide cancer vaccine comprised of peptides derived from the Wilms' Tumor 1 (WT1) protein, with immunomodulating and antineoplastic activities. DSP-7888 may induce a WT1-specific cytotoxic T-lymphocytes against WT1-expressing tumor cells in HLA-A*02:01+, HLA-A*02:06+, and HLA-A*24:02+. DSP-7888 may induce a helper T-lymphocyte–mediated immune response against WT1-expressing tumor cells. **Methods:** This phase 2, active-controlled, multicenter, open-label randomized study (NCT03149003; WIZARD201G) is randomizing patients with recurrent or progressive GBM 1:1 to treatment with DSP-7888 + Bev or Bev alone. A screening phase of $\leq$28 d determines eligibility. DSP-7888 is administered intradermally at 10.5mg every 7 d ($\pm$1 d) for 5 doses (induction phase), then every 14 d ($\pm$3 d) for 6–15 doses (consolidation phase), then every 28 d ($\pm$7 d) for each additional dose (maintenance phase). Bev is administered every 14$\pm$3 d IV at 10mg/kg. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, response rate, and 12-month survival. Safety will be evaluated based on adverse events (AEs) recorded at each visit, physical examinations, and laboratory test results. The severity of AEs or abnormal laboratory results will be based on the CTCAE V4.03. About 200 patients will be enrolled. The study has 2 parts. In part 1, 3 patients are to receive DSP-7888 + Bev in a single-arm manner. If no patients experience a dose limiting toxicity (DLT), the study proceeds to part 2. If $\geq$1 patient experiences DLT, 3 more patients will be treated in the same manner. If $\geq$1 patient again experiences a DLT, the dose is reduced to 3.5mg. In part 2, new patients are randomized to one of the 2 treatment arms. Treatment continues in the absence of clear progression, clinical neurologic deterioration, or until 150 deaths have occurred. Study funding: Boston Biomedical, Inc. Clinical trial information: NCT03149003.

TPS2073 **Poster Session (Board #230a), Sat, 1:15 PM-4:45 PM**

A phase II, open label, single arm study of nivolumab for recurrent or progressive IDH mutant gliomas with prior exposure to alkylating agents. *First Author: Laura Donovan, Columbia University Medical Center, New York, NY*

Background: Gliomas are the most common malignant primary brain tumors in adults. Mutations in Isocitrate dehydrogenonase 1 (IDH1) or IDH2 genes are associated with longer survival. These mutations are found in over 70% of WHO Grade II and III astrocytomas and are now required for the diagnosis of oligodendroglioma. Upfront standard of care treatment for high grade gliomas includes a combination of radiation with alkylating agents including temozolomide or procarbazine and lomustine. Unfortunately, independent of initial grade or IDH mutation status, recurrence after first line therapy is nearly universal. Currently, there is no standard of care therapy for recurrent disease. Trials of PD1 and PD-L1 inhibitors in recurrent high grade gliomas and IDH inhibitors in IDH mutant gliomas have been disappointing. Multiple studies in other solid tumors have shown that high mutational burden is associated with response to immune checkpoint inhibitors. In comparison to other cancers, gliomas have a low mutational burden. However, there is evidence suggesting that IDH mutant gliomas are more prone to develop a hypermutated phenotype after exposure to alkylating agents. This subgroup of patients may be more likely to benefit from treatment with nivolumab, an anti-PD1 agent. **Methods:** Design This is a Phase 2, open label, single arm study. We will enroll 37 evaluable subjects. The primary endpoint is ORR based on RANO criteria. Secondary endpoints are PFS, OS, and duration of response. Exploratory endpoints include evaluation of mutational burden, 2HG spectroscopy, spatial profiling of PD-1/PD-L1 interaction and NANO scale. Eligibility Adult patients with recurrent or progressive IDH mutant high-grade gliomas who have received prior treatment with alkylating agents with no prior bevacizumab or other immune checkpoint inhibitors. Treatment All subjects will be treated with nivolumab 240mg IV every 2 weeks for 8 cycles. Beginning with cycle 9, nivolumab 480mg IV will be administered every 4 weeks until completion of the study.

TPS2074 **Poster Session (Board #230b), Sat, 1:15 PM-4:45 PM**

Phase I/II study of laser interstitial thermotherapy (LITT) combined with checkpoint inhibitor for recurrent glioblastoma (rGBM). *First Author: Andrew E. Sloan, University Hospital Case Medical Center, Cleveland, OH*

Background: Glioblastoma (GBM) has a survival of only 3-5 months at recurrence.. Salvage chemotherapy has been largely ineffective with PFS-6 rates of 10-15%. Bevacizumab's impact on OS is modest at best.· Thus, there is a pressing need for minimally invasive, approaches to debulk rGBM such as laser interstitial thermotherapy (LITT). **Methods:** Rationale for treating rGBM with LITT: Laser interstitial thermotherapy (LITT) is a minimally invasive technique for ablating tumors percutaneously using thermal radiation which has demonstrated efficacy in several non CNS tumors. Subsequent studies reproduced the efficacy of LITT for glioma demonstrating that survival was consistently related to tumor volume and a minimal dose threshold. This suggested the possibility of an *abscopal effect* mediated by unmasking of tumor antigens by LITT as has been previously demonstrated for ionizing radiation (radiotherapy). Rationale for Immunotherapy for rGBM: GBM patients are known to have elevated levels of immunosuppressive cells such as T_{reg}, M2 macrophages and MDSC, both in the tumor as well as in the systemic circulation. *Rationale:* Immunotherapy targeting co-inhibitory checkpoints such as CTLA-4 and PD-1 have proven highly effective for some solid tumors. The first trial targeting CTLA + PD-1 in rGBM demonstrated evidence of safety. Interestingly, targeting PD-1 concurrent with RT appeared to be synergistic and was effective in preclinical models. However, patients with rGBM have typically received maximum tolerated radiotherapy and are thus not candidates for additional RT off trial. We hypothesize that thermal radiation delivered using LITT technology interferes with tumor microenvironment, minimizing immunosuppression and re-introducing tumor neoantigens. The primary objective of this phase II trial is to estimate radiological response to LITT + pembrolizumab and compare this to that observed for LITT alone. Each patient will undergo a stereotactic biopsy followed by 200 mg pembrolizumab at various times before or after LITT. Secondary endpoints include a putative serum biomarker for GBM. Here we present the concept and the outcomes of the first patients in the study. Clinical trial information: NCT 03277638.

2500 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Single agent activity of ZW25, a HER2-targeted bispecific antibody, in heavily pretreated HER2-expressing cancers. *First Author: Funda Meric-Bernstam, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ZW25, a novel Azymetric bispecific antibody, targets HER2 domains ECD2 and ECD4, resulting in multiple differentiated mechanisms of action including increased tumor cell binding, blockade of ligand-dependent and independent growth, and improved receptor internalization and down-regulation relative to trastuzumab (T). *In vivo* studies demonstrate anti-tumor activity in HER2-low to high expressing models. This Phase 1 study evaluated ZW25 single agent safety and anti-tumor activity. **Methods:** Part 1 (P1) evaluated ZW25 5, 10 and 15 mg/kg weekly and 20 mg/kg biweekly using a 3+3 design to identify a recommended dose (RD) for further study. Part 2 (P2) is ongoing and evaluating safety and efficacy in separate expansion cohorts, including HER2-high (IHC 3+ or 2+/FISH+) breast (BC), gastric/esophageal (GE), and other cancers. Pts had to have progressive disease after standard of care, including HER2-targeted agents. Adverse events (AE), PK, and response per RECIST 1.1 (every 8 wks in pts with measurable disease) were assessed. **Results:** 33 pts have been treated in P1 and P2: 17 BC, 11 GE and 5 other cancers. HER2-high BC pts had prior T and T-DM1 (100%), pertuzumab (82%) and lapatinib (53%), with a median of 6 HER2-targeted regimens for metastatic disease. All GE pts had received prior T, with a median of 4 systemic tx. Safety and anti-tumor activity were similar across dose levels with no DLTs. The RD for Part 2 was 10 mg/kg weekly or 20 mg/kg biweekly. The most common AEs were diarrhea and infusion reaction, all Gr 1 or 2, with no tx-related discontinuations. Time on study is 14-348 days with 9 pts still active. 23 pts are response evaluable, with 3 pts not yet restaged. **Conclusions:** ZW25 has been well tolerated with promising single agent anti-tumor activity in pts with heavily pretreated HER2-expressing cancers that have progressed after standard of care, including multiple HER2-targeted regimens. These data support the therapeutic potential of ZW25 and suggest that its unique MOA may overcome mechanisms of resistance to other HER2-targeted agents. Clinical trial information: NCT02892123.

Partial response (PR) and disease control rates DCR = PR or SD anytime on study.

	PR	DCR
BC n=13	46%	54%
GE n=7	43%	57%
Other n=3	—	33%
Total n=23	39%	52%

2501 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: Long-term results of a large phase 1 study with multiple expansion cohorts. *First Author: Hiroji Iwata, Aichi Cancer Center, Nagoya, Japan*

Background: DS-8201a is a HER2-targeted antibody drug conjugate with novel topoisomerase I inhibitor payload and linker technology. **Methods:** This ongoing phase 1 study (NCT02564900) enrolls subjects (sbj) with HER2+ breast cancer (BC) post T-DM1, HER2+ gastric cancer (GC) post trastuzumab, HER2 low BC (IHC 1+ or 2+, ISH-), and other HER2-expressing solid tumors (IHC ≥1+). **Results:** [Results will be updated for presentation at meeting] From Sep 2015–Dec 2017, 212 sbj received ≥1 dose of DS-8201a; 200 at 5.4 or 6.4 mg/kg. Median (mdn) age was 59 y with mdn of 4 prior regimens. At data cutoff, 121/200 (60.5%) sbj remain on treatment (tx). Mdn duration of tx was 10.3 mo (range 0.7+, 21.2+ mo). Overall, RECIST-confirmed overall response rate (ORR) in the evaluable sbj was 81/160 (50.6%) with the highest ORR in HER2+ BC (64.2%). Mdn duration of response was not reached (NR, range 0.03+, 15.2+ mo). 155/181 (85.6%) of sbj with ≥1 postbaseline scan (ps) experienced tumor shrinkage (92.3% of them at 1st ps at 6 weeks). Major reasons for tx discontinuation were progressive disease (PD; 50/200; 25.0%) and adverse event (AE; 18/200; 9.0%); 93/200 (46.5%) experienced a grade ≥3 AE. Common AEs included nausea 73.5% (3.5% grade ≥3), decreased appetite 59.5% (4.5% grade ≥3) and vomiting 39.5% (1.5% grade ≥3). Two grade 5 cases of interstitial lung disease were reported. **Conclusions:** DS-8201a shows antitumor activity in multiple tumor types with high ORR and durable responses in heavily pre-treated sbj. Clinical trial information: NCT02564900.

	Confirmed ORR (95% CI)*	DCR (95% CI)	DOR, Mdn (95% CI), mo	Duration of FU, Mdn Min, Max, mo	PFS, Mdn (95% CI), mo	OS, Mdn (95% CI), mo
HER2+ BC	43/67, 64.2% (51.5, 75.5)	63/67, 94.0% (85.4, 98.3)	7.6 (NA)	6.0 0.7, 21.2	10.4 (NA)	NR
HER2+ GC	19/43, 44.2% (29.1, 60.1)	34/43, 79.1% (64.0, 90.0)	7.0 (NA)	5.6 1.2, 17.8	5.8 (3.0, 8.3)	NR
HER2 low BC	10/26, 38.5% (20.2, 59.4)	23/26, 88.5% (69.8, 97.6)	NR	4.9 0.5, 16.1	13.6 (NA)	NR
Other HER2 expressing solid tumors	8/22, 36.4% (17.2, 59.3)	18/22, 81.8% (59.7, 94.8)	NR	8.1 0.7, 15.0	NR	NR

*Sbj who received 5.4 or 6.4 mg/kg with 2 ps (N=141), or PD prior to 2nd ps (N=19), excluding 40 sbj too early to evaluate. Two low-HER2 GC sbj are not included in the Table; 1 had a confirmed response.

2502 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A multi-histology basket trial of ado-trastuzumab emtansine in patients with *HER2* amplified cancers. *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human epidermal growth factor receptor 2 (*HER2*, *ERBB2*) amplification occurs in 2-5% of non-breast non-gastric cancers. Ado-trastuzumab emtansine is a HER2 targeted antibody drug conjugate that may have activity against a variety of cancers driven by *HER2* amplification. **Methods:** Patients with *HER2* amplified cancers were enrolled into a multi-histology basket trial of ado-trastuzumab emtansine, treated at 3.6mg/kg IV every 3 weeks. The primary endpoint was overall response rate (ORR) using RECIST v1.1 or PERCIST. A Simon two stage optimal design was applied to each histology cohort with type I error rate under 2.7%, power of 89%, H0 10%, H1 40%. Other endpoints include duration of response (DOR), progression-free survival (PFS) and toxicity. *HER2* amplification was identified by next generation sequencing (NGS), and tumors with adequate tissue were subsequently tested by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). **Results:** 58 patients were treated across 8 cohorts of advanced lung, endometrial, salivary gland, biliary tract, ovarian, bladder, colorectal and other cancers. The median age was 63 (range 34-90 years), 72% were female. The median lines of prior systemic therapy was 2 (range 1-7). ORR was 26% (14/53 confirmed, 95% CI 15-40%), including 50% (3/6) for lung cancers, 22% (4/18, 2 CR) for endometrial cancers, 100% (5/5, 3 CR) for salivary cancers, 17% (1/6) for biliary cancers, 17% (1/6) for ovarian cancers, not including partial responses awaiting confirmation. Median DOR was 6 months (range 2-22+), median PFS was 3 months (95% CI 2-6). There was 1 (2%) grade 3 febrile neutropenia, but no treatment related deaths. The degree of *HER2* amplification (NGS fold change 1.7 to 27.9) did not predict response. *HER2* amplification by NGS correlated well with HER2/CEP17≥2 by FISH (40/41 tested) or IHC3+ (31/40 tested), and tumor shrinkage was seen in 2 patients who were tested IHC negative. **Conclusions:** Ado-trastuzumab emtansine showed efficacy in patients with *HER2* amplified lung, endometrial, salivary gland, biliary tract and ovarian cancers as identified by NGS. This study has met its primary endpoint. Further development is warranted. Clinical trial information: NCT02675829.

2503 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Molecular analysis for therapy choice (MATCH) arm W: Phase II study of AZD4547 in patients with tumors with aberrations in the FGFR pathway. *First Author: Young Kwang Chae, Northwestern University, Chicago, IL*

Background: MATCH is a histology-agnostic signal finding trial targeting pathways in cancer. AZD4547 is a selective inhibitor of the fibroblast growth factor receptor (FGFR) 1-3 kinases. **Methods:** Patients (Pts) were screened by NGS for *FGFR* aberrations including amplification (≥7x), mutation, and fusion. 70/5558 (1.3%) of pts who underwent successful NGS evaluation were assigned to arm W. 52/689 (7.5%) of total pts enrolled in all treatment arms were in arm W (July 2016 to June 2017). 50 pts received treatment with AZD4547 80mg PO twice a day until progression of disease (PD) or drug intolerance. **Results:** 39/50 (78%) were female, 45/50 (90%) were Caucasian with a median age of 62 years (range: 22-80). 25/50 pts (50%) had received more than three prior lines of treatment. The most common histologies were breast (n = 16), urothelial (n = 7), and endometrial cancer (n = 4). Pts were divided into three groups: amplification (Amp) (n = 21), single nucleotide variant (SNV) (n = 20), or fusion (n = 9). Best confirmed response for the three groups are shown in the table below. Of 41 evaluable pts, the objective response rate was 5% (all partial response, PR), 51% stable disease (SD), and 44% PD. All pts with PR had tumors harboring FGFR fusions; one with urothelial transitional cell carcinoma (FGFR3-TACC3 F17T8) and the other with squamous cell carcinoma of cervix (FGFR3-TACC3 F17T11). Six cases [2 PR and 4 SD (2 SNV, 1 Amp, 1 fusion)] out of 41 achieved a duration of response greater than 24 weeks (disease control rate, 15%). The 6-month progression-free survival rate is 17% (90% CI: 8.6-34%): Amp 15% (90% CI: 4-58%), SNV 8% (90% CI: 2-38%), and fusion 42% (90% CI: 19-94%). Of 49 pts evaluable for adverse events (AEs), 39 experienced any AEs (80%) with 19 having grade 3/4 AEs (49%). Common AEs were fatigue, anorexia, dry mouth, nausea/vomiting, diarrhea, constipation, oral mucositis, anemia and liver function tests abnormality. **Conclusions:** AZD4547 demonstrated modest activity across various solid tumors with aberrations in FGFR pathway with acceptable toxicities. Further trials are warranted in tumors harboring FGFR fusions. Clinical trial information: NCT02465060.

	Amp	SNV	Fusion	Total
PR	0	0	2	2
SD	10	6	5	21
PD	7	9	2	18
Not Evaluable	4	5	0	9
Total	21	20	9	50

2504 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Biomarker-driven access to crizotinib in ALK, MET, or ROS1 positive (+) malignancies in adults and children: The French National AcSé Program. *First Author: Gilles Vassal, Gustave Roussy, Villejuif, France*

Background: Crizotinib (czb) is registered for the treatment of patients (pts) with ALK+ or ROS1+ lung cancer. Czb targets (ALK, MET, ROS1) are also altered (translocation [tlc], amplification [amp], mutation [mut]) in a wide range of malignancies (malg.) in adults and children. To generate high evidenced-based knowledge and to prevent off-label use, the French National Cancer Institute (INCa) launched the AcSé Program: equal access to tumor molecular diagnosis along with an exploratory phase II trial, to allow for a nationwide safe and controlled access to czb outside its indication. **Methods:** Biomarker identification was proposed to pts ≥ 1 year old (yo) with an advanced disease among more than 15 malg. known to harbor a czb target alteration. If not eligible for any other trial, pts may enter one of the 22 cohorts defined by the type of tumor and target. Tumor response was evaluated every 2 months (mo) using RECIST criteria v1.1. The primary endpoint is the objective response rate (ORR) at 2 mo [complete + partial response]. A two-stage Simon design is applied to each cohort. **Results:** From 08/2013 to 12/2017, 12836 pts from 186 centers have entered the biomarker program. Alterations found in pts were: ALK tlc, mut, amp in 14/2053, 8/306, 10/1846; MET amp (> 6 copies/diploid genome) in 392/7847 [250/4127 NSCLC, 60/1232 glioblastomas, 28/939 colon, 33/546 esogastric, 7/635 ovarian, 3/82 kidney cancers]; MET mut in 98/2697; ROS1 tlc in 80/4625 [NSCLC, cholangiocarcinoma, inflammatory myofibroblastic tumor (IMT)]. Clinical trial information: NCT02034981. Overall, 235 pts (median age, 58 yo [1–92]) received czb (adult 250 mg bid; child 280 mg/m^2 bid). **Conclusions:** Czb displayed a wide antitumor activity in several MET, ALK and ROS1+ malg. Equal and safe access across France to molecular testing and targeted therapies outside their approved indication is feasible.

Positive cohorts	Pts analyzed	CR/PR	ORR % [IC95%]
ALCL ALK tlc	22	12	54 [34-75]
NSCLC MET amp	25	6	24 [7-40]
ROS1 tlc	37	20	54 [40-70]
MET mut	27	6	22 [7-38]
Esogastric MET amp	8	3	37 [10-74]
IMT ALK tlc / ROS1 tlc	7	1	28 [5-70]

2505 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

First-in-human phase 1 study of the PARP/tankyrase inhibitor 2X-121 (E7449) as monotherapy in patients with advanced solid tumors and validation of a novel drug response predictor (DRP) mRNA biomarker. *First Author: Elizabeth Ruth Plummer, Northern Centre for Cancer Care, Newcastle-upon-Tyne, United Kingdom*

Background: A phase I study was done to establish the safety, MTD and anti-tumour efficacy of the novel PARP 1/2 and Tankyrase 1/2 inhibitor, 2X-121 (E7449). A novel tumor agnostic molecular biomarker, 2X-121 DRP, was developed to identify responders and non-responders. **Methods:** Patients (pts) with advanced solid tumors were eligible. 2X-121 was administered orally, once daily (QD), continuously. Archival tumor samples were obtained from consenting patients. Following completion of the study the 2X-121 DRP was applied in a blinded manner following a pre-specified analysis plan. This biomarker is based on expression of 414 genes predictive of response to 2X-121. **Results:** 41 pts were treated at 6 dose levels: 50, 100, 200, 400, 800 and 600 mg QD. Tumor types were pancreatic (n = 13), ovarian (n = 5), breast (4), lung (n = 4), colorectal (n = 4) and other (n = 11). Fatigue is the dose limiting toxicity. The MTD is 600 mg QD. The most frequently reported (> 30% of pts) TEAEs were fatigue, chromaturia, decreased appetite, nausea, diarrhea, constipation, and vomiting. No significant hematological toxicity and no Gr4 or 5 AEs were reported. Two pts had partial response (PR, both ovarian cancer), 13 pts had stable disease (SD), with 8 of these > 24 weeks; 7/8 were pancreatic cancer pts. Sustained PARP inhibition of ~90% is seen at doses over 600mg QD in PBMCs. The 2X-121 DRP was applied to 13 patients from which adequate biopsy material was available evaluating the 414 gene signature. Patients with PR and durable SD were correctly identified. It divided patients in two groups, sensitive (N = 6) or resistant (N = 7) to 2X-121. The median time to progression was 296 and 155 days, respectively (HR = 0.29, P = 0.14). Overall survival (OS) differed between the two groups, with a median survival in excess of 800 days and 208 days, respectively (HR = 0.26, P = 0.07). **Conclusions:** 2X-121 was generally well tolerated at the MTD of 600 mg QD, with evidence of antitumor activity. The 2X-121 DRP predicted the responders irrespective of BRCA mutation status. Clinical trial information: NCT01618136.

2506 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

First-in-human phase 1 study of TAK-931, an oral cell division cycle 7 (CDC7) inhibitor, in patients (pts) with advanced solid tumors. *First Author: Toshio Shimizu, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan*

Background: TAK-931 is an oral selective inhibitor of CDC7, a protein kinase with key roles in DNA replication and DNA damage response. TAK-931 has demonstrated potent antitumor activity in various preclinical models. **Methods:** We evaluated safety, dose limiting toxicity (DLT), maximum tolerated dose (MTD), and preliminary antitumor activity of TAK-931 in pts with advanced solid tumors. Four schedules are being tested, and we report data from Schedule A: TAK-931 QD for 14 days on/7 days off in 21-day cycles. A Bayesian logistic regression model with overdose control was used to guide dose escalation and MTD estimation. **Results:** As of 14-Nov-2017, 25 Japanese pts (60% male; median age 59 [range 42–75] years) were treated with TAK-931 30 mg (n = 3), 40 mg (n = 3), 60 mg (n = 3), and 50 mg (n = 16: 7 pts in dose escalation, 9 pts in expansion). Pts received a median of 3 cycles (range 1–12). Most common any-grade adverse events (AEs) were nausea (n = 15), neutropenia (n = 12), decreased white blood cells (WBCs) (n = 8), decreased appetite, vomiting, and diarrhea (each n = 7). Most common grade ≥3 AEs were neutropenia (n = 11), decreased WBCs (n = 3), leukopenia, and decreased appetite (each n = 2). DLTs (grade 4 neutropenia) were observed in 2 of 3 pts at 60 mg; 50 mg was considered the MTD. Preliminary pharmacokinetics (PK) showed increased systemic exposure of TAK-931 in a dose proportional manner between 30 and 60 mg, with minimal accumulation and mean terminal elimination half-life of 5.4 hours (15% CV). Dose-dependent inhibition of pMCM2, a direct substrate of CDC7, was observed in skin biopsies from most pts treated with TAK-931, which correlated well with drug exposure (R^2= 0.6598). Partial responses were observed in pts with duodenal, esophageal, and cervical cancers (1 pt each) as well as prolonged stable disease of ~6 months in a bladder cancer pt and ~9 months in a pancreatic cancer pt. **Conclusions:** TAK-931 demonstrated an acceptable safety profile with early signs of clinical antitumor activity. Isolated neutropenia was the DLT with the tested schedule. Strong pharmacodynamic (PD) effects and PK-PD correlation provide clinical evidence of target engagement of TAK-931 in pts. Clinical trial information: NCT02699749.

2507 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase I dose escalation study of the first-in-class selective PTEFb inhibitor BAY 1251152 in patients with advanced cancer: Novel target validation and early evidence of clinical activity. *First Author: Jennifer Robinson Diamond, University of Colorado, Aurora, CO*

Background: PTEFb/CDK9 mediated transcription of short-lived anti-apoptotic survival proteins and oncogenes like MYC and MCL-1 plays a critical role in a variety of cancers. We present findings from a phase I study of BAY 1251152 in pts with solid tumors and aggressive NHL. **Methods:** Patients with advanced or metastatic solid tumors or aggressive NHL and refractory to available therapies were eligible. BAY 1251152 was administered once weekly as a 30-minute IV infusion on Days 1, 8 and 15 of a 21-day cycle. Tumor response was assessed according to RECIST v1.1 and the revised Cheson criteria (2007). **Results:** A total of 31 pts were enrolled and evaluable for safety, including subjects with breast cancer (n = 6), pancreatic adenocarcionoma (5), ovarian cancer (4), and colorectal cancer (3). No DLTs were reported in the first 3 cohorts (5 mg, 10 mg and 15 mg). There was one DLT in the 22.5 mg cohort (grade 4 [G4] neutropenia), which was then expanded to 6 pts without subsequent DLTs. At 30 mg, neutropenia became the most prominent AE, with one G3 febrile neutropenia and two G4 neutropenia's reported as DLTs in 9 evaluable pts. Three additional pts were enrolled in the 22.5 mg cohort, with one DLT (G3 neutropenia) but no other G3 or G4 drug-related AEs. The 30 mg dose was deemed the MTD. There were 4 deaths on study, none of which was attributed to study drug. Pharmacodynamic biomarker analysis showed significant dose-dependent reduction of MYC, PCNA, and MCL-1 RNA. PK was generally linear over the dose range. Antitumor activity consisted of stable disease (SD) in 9 subjects and durable SD in 3 pts: one relapsed pancreatic adenocarcinoma pt treated for 15 cycles, one double-hit DLBCL (GCB subtype, 2 prior lines) pt was treated > 22 cycles with a 40% reduction in tumor size and complete metabolic response, and a salivary gland carcinoma pt treated for > 24 cycles with a 21% reduction in tumor size; the latter 2 pts remain on treatment. **Conclusions:** PTEFb inhibitor BAY 1251152 had a manageable safety profile, apparent dose-proportional PK, on-target pharmacodynamic activity and signs of antitumor activity. Clinical trial information: NCT02635672.

2508 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A first-in-human phase 1 dose-escalation trial of the oral HIF-2a inhibitor PT2977 in patients with advanced solid tumors. *First Author: Kyriakos P. Papadopoulos, START, San Antonio, TX*

Background: Hypoxia-inducible factor (HIF)-2α is a transcription factor that plays a central role in the hypoxic response pathway in tumors. HIF-2α heterodimerizes with HIF-1β and binds to hypoxic response elements in target genes. The first-in-class HIF-2α inhibitor, PT2385, demonstrated clinical activity in patients (pts) with clear cell renal cell carcinoma (ccRCC). PT2977 is a novel, orally administered selective small molecule HIF-2α inhibitor with improved potency compared to PT2385. PT2977 inhibited expression of HIF-2α target genes in tumor cells and induced regression in mouse xenograft models. **Methods:** Pts with advanced solid tumors who had received at least 1 prior therapy were treated with PT2977 once daily (QD) in a Phase 1 dose-escalation trial to determine the recommended Phase 2 dose (RP2D) and evaluate safety, pharmacokinetics (PK) and pharmacodynamics (PD). Plasma PK were measured on days 1 and 15 and PD weekly. **Results:** 29 pts were treated at doses of 20 - 160 mg QD in the dose-escalation. As of January 15, 2018, no treatment-related dose-limiting toxicities have been observed. The most common all-grade AEs have been anemia (35%), fatigue (24%), edema (17%), headache (17%), and nausea (17%). Anemia (11%) was the most common Grade 3 AE; there have been no Grade 4 events. Exposure increased with dose along with dose-dependent reductions in erythropoietin (PD marker) consistent with the pharmacology of PT2977. At the RP2D of 120 mg, PT2977 was rapidly absorbed (T_{max} = 3.1 h) with a C_{max} of 1.83 mg/mL, a C_{min} of 0.71 mg/mL, and a $T_{1/2}$ of 20 h. A pt with SDHB mutant paraganglioma has had stable disease (SD) $>$ 25 weeks with sustained decrease in normetanephrine levels. Of 6 pts with ccRCC treated at 120 mg or 160 mg, there was one PR and 4 SD with tumor reductions from 8%-26%. **Conclusions:** PT2977 is well tolerated and has a favorable safety and PK/PD profile. Early evidence of clinical activity shows promise for HIF2a inhibition in the treatment of ccRCC. PT2977 is currently under evaluation in an expansion cohort of 50 pts with previously treated advanced ccRCC at a dose of 120 mg QD. Clinical trial information: NCT02974738.

2509 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Preliminary results of a first-in-human, first-in-class phase I study of MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/EBP-α in patients with advanced liver cancer. *First Author: Debashis Sarker, King's College London, London, United Kingdom*

Background: MTL-CEBPA is a liposomal formulation of saRNA targeting the transcription factor C/EBP-α, which acts as a master regulator of liver homeostasis and multiple oncogenic processes including cell cycle control, proliferation and angiogenesis and inhibits hepatocellular cancer (HCC) tumor growth in preclinical models. MTL-CEBPA is the first saRNA and the first drug targeting C/EBP-α entering clinical trials. **Methods:** Patients (pts) with advanced HCC (Child-Pugh A/B) or secondary liver cancer, were enrolled in a 3+3 dose escalation study. MTL-CEBPA is administered as a 1-hr IV infusion on Day 1, 8 and 15 of a 28 day cycle. The primary endpoint was safety and the secondary endpoints included PK, liver function improvement and anti-tumor activity. Correlative studies include C/EBP-α mRNA levels in PBMCs and tumor tissue, evaluation of C/EBP-α downstream target genes (e.g.TGFβ) and distal target engagement in WBCs (e.g.IL-6, NF-κB). **Results:** 19 participants have been treated across 5 dose levels (28-130 mg/m^2): 13M/6F, median age 67 yrs (range 27 - 80), ECOG PS 0/1: 9/10. Tumour types include HCC (13), colorectal (4) and fibrolamellar (2). The most common treatment-related AEs (all grades/grade 3) include fatigue (9/1), diarrhoea (5/0), AST increase (5/1), low platelets (2/1) hyperbilirubinaemia (5/1) and hypophosphataemia (4/1). Maximum tolerated dose has not yet been reached. Serum PK analysis shows a terminal half life of $>$ 24 hrs, with dose proportional C_{max} and AUC. Analysis of WBCs showed a significant increase of C/EBP-α expression during treatment providing evidence of target engagement. Of 10 evaluable pts with HCC, 4 pts have had SD$\geq$ 4months, with one patient having an ongoing PR for 18 months associated with 73% decrease in tumour volume and reduction in IL-6, NF-κB and IFN-γ. **Conclusions:** Once weekly MTL-CEBPA therapy was well tolerated, shows promising PD and initial clinical response in patients with advanced HCC. Updated results for the dose escalation will be presented. Clinical trial information: NCT02716012.

2510 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Results of the first-in-human study of ABBV-075 (mivebresib), a pan-inhibitor of bromodomain (BD) and extra terminal (BET) proteins, in patients (pts) with relapsed/refractory (R/R) solid tumors. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BDs are protein domains that bind to acetylated histone tails, leading to upregulation of target genes driving oncogenesis. Inhibition of the BET family prevents assembly of the macromolecular complex and its transcriptional response. ABBV-075 is a pan-BET inhibitor that induces death in cell lines and tumor growth inhibition in xenograft models. This first-in-human, phase 1, two-part study (NCT02391480) assessed the safety and pharmacokinetics of ABBV-075 in pts with advanced tumors. Results from the dose escalation part in pts with solid tumors are reported. **Methods:** The dose escalation part of this open-label study enrolled adult pts with R/R solid tumors in a 3+3 fashion. Endpoints included maximum tolerated dose, recommended phase 2 dose (RP2D) at different ABBV-075 dosing schedules (daily, Monday/Wednesday/Friday [MWF], or 4 days on/3 off [4/7]), safety and preliminary efficacy. **Results:** As of Dec 2017, 72 pts with solid tumors enrolled in the dose escalation cohort. Most common tumors were: uveal/choroidal melanoma (n = 10); breast (n = 8); pancreatic (n = 6); head and neck (n = 5); and prostate (n = 3). Median age was 61.5 years (range 23–83); median treatment duration was 7.6 weeks (range 0.9–39.6). In total, 23, 27, and 22 pts entered the daily, MWF and 4/7 schedules. Overall, 71 pts (98.6%) reported ≥1 treatment-emergent adverse events (TEAEs); thrombocytopenia (56.9%), dysgeusia (48.6%), fatigue (43.1%) and nausea (34.7%) were most common. Grade 3/4 TEAEs were reported in 52 pts (72.2%); thrombocytopenia (30.6%) and anemia (15.3%) were most common; 11 pts died (none considered study drug related). Dose-limiting toxicities included thrombocytopenia, fatigue, aspartate aminotransferase elevation, gastrointestinal bleed and hypertension. The RP2D is 1.5 mg for the daily schedule, 2.5 mg for 4/7 and 3 mg for MWF. Of 65 evaluable pts, 25 pts (38.5%) had stable disease and 40 pts (61.5%) had progressive disease. Median progression-free survival was 1.8 months (95% CI: 1.8, 1.9). **Conclusions:** ABBV-075 has a tolerable safety profile and led to stable disease in some pts with malignant solid tumors. Clinical trial information: NCT02391480.

2511 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Ph 1 study of MRG-106, an inhibitor of miR-155, in CTCL. *First Author: Francine M. Foss, Yale Cancer Center, Woodbridge, CT*

Background: MRG-106 is an inhibitor of miR-155, a microRNA with a strong link to CTCL pathogenesis. The goals of this FIH study are to evaluate the safety, tolerability, PK, and efficacy of MRG-106 in mycosis fungoides (MF) patients (pts). **Methods:** This Ph 1 trial evaluated MRG-106 given via intralesional injection (75 mg/dose), subcutaneous or IV rapid bolus injection, or 2-hour IV infusion (300, 600 or 900 mg/dose). Pts must have MF stage I-III with plaques and/or tumors and could remain on concurrent stable CTCL therapy. Pts received 6 doses (SC/IV) in the first 26 days of the study followed by weekly or bi-weekly doses. Safety was monitored by physical exams, clinical lab tests, and reported adverse events (AEs). Efficacy was assessed by CAILS and by the modified Severity Weighted Assessment Tool (mSWAT). The effect of MRG-106 on quality of life was assessed by Skindex-29. **Results:** 36 subjects (20M/16F, median age 63 yrs) have been on study for up to 17 months (as of 25Jan2018). No serious AEs have been attributed to MRG-106. Most common AEs in ≥ 15% of subjects were: fatigue, neutropenia, injection site pain, nausea, pruritus, and headache. Two AEs were deemed DLTs: Gr3 worsening pruritus and Gr 3 tumor flare. MTD has not yet been reached. In the SC/IV cohorts, 26/29 evaluable subjects had improvement in mSWAT score. Skin improvements were observed as early as the first assessment (Day 17). Best improvements were after ≥ 1 month. All 8 pts (across all doses with SC or IV infusion) who achieved ≥ 50% reduction in mSWAT and received $>$ 2 treatment cycles, maintained response for ≥ 4 months. 4/5 pts treated at the 300 mg IV infusion dose had ≥ 50% mSWAT improvement. The overall skin response in pts who received MRG-106 as monotherapy or MRG-106 with concurrent stable therapy were not significantly different. Reductions in Skindex-29 total score correlated to reductions in mSWAT score during the treatment phase. **Conclusions:** These preliminary results suggest that MRG-106 is well-tolerated, has clinical activity, and has potential to impact MF quality of life. These encouraging data support the continued investigation of MRG-106 in this population. The study is expanded to enroll pts with other hematologic malignancies in which miR-155 is elevated and relevant, including CLL, DLBCL, ATLL. Clinical trial information: NCT02580552.

2512 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Single agent activity of U3-1402, a HER3-targeting antibody-drug conjugate, in breast cancer patients: Phase 1 dose escalation study. *First Author: Takahiro Kogawa, Department of Breast and Medical Oncology, National Cancer Center Hospital East, Chiba, Japan*

Background: U3-1402 is a human epidermal growth factor receptor 3 (HER3)-targeting antibody-drug conjugate (ADC) of high drug-to-antibody-ratio (DAR: 7 to 8) with a novel linker and topoisomerase I inhibitor payload. HER3 is overexpressed in a variety of cancers, including breast, lung, colorectal, ovarian, prostate and urothelial cancer. This ongoing, Phase 1/2 study (NCT02980341) of U3-1402 in HER3-expressing metastatic breast cancer (MBC) is divided into three parts: dose escalation (Part 1), dose finding (Part 2), and dose expansion (Part 3). **Methods:** In Part 1 of the ongoing study, the dose of U3-1402 was escalated based on dose-limiting toxicity data, guided by the modified Continuous Reassessment Method (mCRM). U3-1402 was administered via intravenous (IV) infusion in 21-day cycles. The primary objectives are to determine safety and tolerability of U3-1402, the maximum tolerated dose (MTD), and the recommended dose for Phase 2. AEs, PK, ORR per RECIST v1.1, and durability of responses were assessed. Efficacy-evaluable patients (pts) received at least one dose of U3-1402 and had pre- and post-treatment tumor assessments. **Results:** As of December 28, 2017, 21-evaluable pts (female, median age 59 years, ECOG 0-1, and $\geq$ 2 previous treatment regimens) have received U3-1402 at dose levels between 1.6 mg/kg to 8.0 mg/kg. Reversible Grade 3/4 thrombocytopenia, and Grade 3/4 liver enzyme increase as dose-limiting toxicities were observed in 4 (19%) and 2 (9.5%) pts respectively. The most common treatment-related adverse events were nausea (71.4%), vomiting (47.6%), and decreased appetite (47.6%). ORR was 33% and DCR (CR+PR+SD) was 95%. Three pts (14%) discontinued due to PD and 1 pt discontinued due to Grade 2 pneumonitis. Seventeen pts (80%) remain on treatment, including 6 pts (28%) who have remained on treatment for more than 6 months. HER3 IHC has been evaluated in 294 breast cancer pts, 87 (30%) showed high levels of HER3 expression. **Conclusions:** In a preliminary analysis of 21 pts, U3-1402 exhibits antitumor activity in previously treated HER3 expressing MBC pts and treatment is associated with a manageable safety profile. Clinical trial information: NCT02980341.

2513 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase 1 study of the next-generation ALK/ROS1/TRK inhibitor ropotrectinib (TPX-0005) in patients with advanced *ALK/ROS1/NTRK+* cancers (TRIDENT-1). *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pts with *ALK*/*ROS1*/*NTRK* fusion-positive cancers can develop on-target TKI resistance [e.g. solvent front mutations (SFMs)] and/or central nervous system (CNS) relapse. Ropotrectinib is a potent next-generation *ALK/ROS1/TRK* TKI designed to inhibit SFMs in addition to most clinically relevant resistance mutations. **Methods:** Phase I eligible pts had *ALK*, *ROS1*, or *NTRK1-3* fusion-positive advanced solid tumors and were TKI-naïve or TKI pre-treated. Pts with treated/untreated asymptomatic brain mets were allowed. Dose escalation followed a 3+3 design. **Results:** As of Jan 2, 2018, 65 pts (28 *ALK+,* 29 *ROS1+,* and 8 *NTRK+*) received at least 1 dose of ropotrectinib. The most common tumor was NSCLC (83%). The median # of prior chemo- or immune-therapy was 1 (range 0-9). Many pts were TKI pre-treated (86% of *ALK+* had $\geq$ 2 prior TKIs, 66% of *ROS1+* and 50% of *NTRK+* had $\geq$ 1 prior TKIs). 23 pts (35%) had baseline CNS metastases, including 52% with untreated CNS disease. Pts were treated over 5 dose levels/schedules (40–240 mg QD & 160 mg BID). The majority of AEs were G1-2. Treatment-related AEs ($>$ 10% of pts) included: dysgeusia (38%), dizziness (35%), paresthesia (24%), nausea (12%), anemia, constipation, fatigue, and oral numbness (11% each). DLTs occurred in 2 NSCLC pts: G3 dizziness at 240 mg QD (resolved with dose reduction) and G3 dyspnea/hypoxia at 160 mg BID (resolved with drug discontinuation). The MTD has not been reached. Dose escalation is ongoing. Confirmed partial responses (cPR, RECISTv1.1, n = 8) were observed in TKI-naïve or TKI pre-treated ROS1+/NTRK+ pts at all dose levels. These include pts with acquired SFM+ tumors (1 entrectinib-refractory NTRK3 G623E+, 1 crizotinib-refractory ROS1 G2032R+ pt with untreated CNS mets). The median duration on study of cPRs was 6.7 mos (range 2.6-9.9+ mos), and 88% (7/8) of responses are ongoing. Of the 16 ALK+ pts completed 2 cycles of ropo, 4 had confirmed SD (4 cycles) as best response at data cutoff. **Conclusions:** Ropotrectinib was well-tolerated and exhibited both intra- and extra-cranial clinical activity in TKI-refractory *ROS1+* and *NTRK+* pts with SFM-containing tumors. Clinical trial information: NCT03093116.

2514 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

First-in-human study of DS-6051b in patients (pts) with advanced solid tumors (AST) conducted in the US. *First Author: Kyriakos P. Papadopoulos, South Texas Accelerated Research Therapeutics, San Antonio, TX*

Background: DS-6051b is an oral, small molecule receptor tyrosine kinase inhibitor with high affinity for ROS1 and NTRK kinases. Preclinical studies demonstrated activity against tumors harboring ROS1 or NTRK fusion genes. We report results from the dose escalation (ESC) and food effects (FE) portion of a phase 1/1b study of DS-6051b with follow-up through October 2017. **Methods:** Pts aged $\geq$18 y with ASTs harboring ROS1 and NTRK mutations/fusion genes or with neuroendocrine tumors (NET) or with tumor-induced pain (TIP), regardless of ROS1/NTRK status, were eligible. Pts with ROS1 non-small cell lung cancer (NSCLC) progressing on crizotinib (CRZ) or $>$ 1 ROS1 inhibitor were included. Primary objectives: determine the maximum tolerated dose (MTD), assess safety/tolerability (ESC) and determine FE on the pharmacokinetics (PK) of a single 400-mg daily (QD) DS-6051b dose with/without food. PK and antitumor activity were also assessed. A design of accelerated titration followed by modified continuous reassessment method and escalation with overdose control was used (50–1200 mg QD or 400 mg twice daily). Tumor assessments were every 3 cycles by RECIST 1.1. **Results:** In ESC, 35 pts (n = 14 NET; n = 9 TIP; n = 2 NET/TIP; n = 10 AST with ROS1/NTRK [n = 1 NTRK fusion; n = 9 ROS1 fusion including 7 NSCLC with prior CRZ]) enrolled, with 31 tumor evaluable. Dose-limiting toxicities (grade [G] 3 increased transaminases) occurred in 2 pts (1200 mg QD dose); 800 mg QD was the MTD. TEAEs G $\geq$3 occurred in 69% (overall) and 31% (drug-related) and all serious TEAEs in 20% (overall) and 9% (drug-related) of pts. Most common TEAEs were gastrointestinal disorders (89%); the majority (71%) G1/2. Peak concentration (C_{max}) and AUC increases were generally dose-proportional. Of 6 tumor evaluable NSCLC ROS1 pts with prior CRZ, 2 had partial response (PR) and 2 had stable disease (SD). Two other pts (n = 1 NTRK fusion thyroid cancer; n = 1 NET) had PR. Prolonged SD (6.9–27.2 months) was observed in 4 (40%) of 10 tumor-evaluable NET pts. In FE (n = 11), food intake had a modest PK effect: C_{max} and AUC increased by 30-45%. **Conclusions:** DS-6051b was well tolerated up to 800 mg QD. The observed efficacy signal in targeted populations warrants further evaluation. Clinical trial information: NCT02279433.

2515 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase I study of AL101, a pan-NOTCH inhibitor, in patients (pts) with locally advanced or metastatic solid tumors. *First Author: Anthony B. El-Khoueiry, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Notch signaling can be deregulated in human cancer. AL101 (formerly BMS-906024), a gamma secretase inhibitor that potently inhibits all Notch receptors, was evaluated. The primary objective was safety and tolerability of multiple IV doses of AL101 and to establish a RP2D. **Methods:** Pts with advanced tumors refractory to standard therapies were included. Primary and secondary endpoints included safety, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity. Cohorts were administered escalating doses of AL101 IV weekly (QW) or q 2 weeks (Q2W) using a 3+3 design, with expansion at the MTD in TNBC, NSCLC, and selected other tumors with reported Notch activation. The DLT period was 4 weeks (4 doses QW or 2 doses Q2W). PD markers of Notch activity, including HES1 mRNA, were evaluated in serial whole blood. **Results:** As of 1Feb2018, preliminary data are available on 94 pts dosed at 0.3 mg to 8.4 mg QW, and 4 mg to 6 mg Q2W. The MTD for QW was 4 mg with 0 DLTs in 7 evaluable pts; DLTs occurred at 8.4 mg QW (Gr 3 infusion reaction, Gr 3 vomiting, Gr 5 liver failure) and 6 mg in de-escalation (Gr 3 vomiting/lipase elevation, Gr 3 diarrhea [n = 3]). The MTD for Q2W was 6 mg, with 1 DLT in 6 evaluable pts (Gr 3 diarrhea). In escalation/expansion at the QW MTD (n = 43), Gr 3 or higher related AEs were: hypophosphatemia (42%), diarrhea (16%), hypokalemia (7%), and anaphylaxis, anemia, AST increase, nausea, pruritus, and vomiting (2% each). There were dose related increases in exposures over 0.3 to 8.4 mg, and the mean plasma half-life following 4 doses QW was 67 - 148 hours, supporting QW dosing. Dose related reduction of HES1 mRNA was seen with $>$ 80% peak inhibition and $>$ 50% inhibition sustained over several days at QW doses of 4 mg and higher. Objective responses were seen in 4 pts (RECIST v1.1): gastroesophageal junction adenocarcinoma (n = 1, 1 cCR ongoing $>$ 1 y), desmoid tumor (n = 3, 2 cPR, ongoing $>$ 1 y, $>$ 3 y), adenoid cystic carcinoma (n = 2, 1 cPR with PD at 8 m). SD was best response in 9 pts (9.6%). **Conclusions:** AL101 at the RP2D was generally well-tolerated and demonstrated sustained Notch inhibition as well as clinical activity across different tumor types. Future trials will evaluate AL101 in tumors with Notch activating mutations. Clinical trial information: NCT01292655.

2516 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Phase I trial of z-endoxifen with estrogen receptor imaging in adults with advanced hormone receptor–positive solid tumors including desmoid and gynecologic tumors. *First Author: Naoko Takebe, NCI/ NIH, Elkridge, MD*

Background: Differential response to tamoxifen observed in patients (pts) with hormone receptor-positive cancer may be due to variations in tamoxifen metabolism from CYP2D6 genetic polymorphisms that limit exposure to the active metabolite, z-endoxifen (Z). We conducted a phase 1 clinical trial (3+3 design) with estrogen receptor imaging to determine the safety, MTD, and pharmacokinetics (PK) of oral Z. **Methods:** Adults with refractory gynecologic tumors, hormone-positive breast or other solid tumors, or desmoid tumors were eligible with ECOG performance status of 0-2 and adequate organ functions. Z was administered at 20, 40, 60, 100, 140, 200, 280, and 360 mg q day on a 28-day cycle. Estrogen receptor imaging with 16 alpha-[^{18}F]-fluoro-17 beta-estradiol (FES)-PET was performed before dosing and, if positive, repeated during C1W1. **Results:** Median age of the 40 pts enrolled was 60 (range 21-80 yr) and 90% were female. MTD was not reached up to the targeted maximum dose of 360 mg/day. Of the 38 pts evaluable for response, 2 (fallopian tube and breast) had partial responses and 9 had 6+ cycles of stable disease. Pts stayed on study for 1-47+ cycles (average, 6 cycles; median, 2.5 cycles); two pts remain on treatment. Grade 3/4 adverse events occurring in ≥5% of pts were hypertension (13%), hyponatremia (8%), hypophosphatemia (8%), neutropenia (8%), dehydration (5%), and elevated ALT (5%). Mean Z plasma levels increased linearly with administered dose. Increases were seen in mean D1 C_{max} (68.6 to 1309 ng/mL) and $AUC_{0\text{-}24}$ (1084 to 20546 ng/mL•hr) between doses of 20 and 360 mg/day. The elimination $t_{1/2}$ was 30.6-55.9 hr, based on the AUC accumulation ratio of 2.4-3.9 over the 28-day dosing period. FES-PET from 9 pts with FES-positive lesions demonstrated a 2%-76% reduction in average FES standard uptake values following 2-5 days of Z. **Conclusions:** We established a targeted maximum dose of 360 mg/day Z and evidence of antitumor activity was observed. Oral Z administration produces Z plasma exposures well above those obtained after therapeutic doses of tamoxifen. Clinical Trial Information: NCT01273168. Supported in part by NCI Contracts CM52206 and HHSN261200800001E. Clinical trial information: 01273168.

2517 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

First-in-human, first-in-class phase 1a study of BXQ-350 for solid tumors and gliomas. *First Author: Olivier Rixe, University of New Mexico Cancer Center, Albuquerque, NM*

Background: BXQ-350 is a novel agent composed of the multifunctional, lysosomal activator protein Saposin C and phosphatidylserine. BXQ-350 demonstrated antitumor effects *in vitro* and *in vivo*, particularly in glioma and pancreatic cancer models. **Methods:** A phase 1a dose-escalation trial (NCT02859857; Phase 1b ongoing) was conducted in refractory solid tumors/high-grade glioma (HGG) patients (Pt) by administering escalating IV BXQ-350 doses of 0.7, 1.1, 1.4, 1.8, or 2.4 mg/kg on days 1-5, 8, 10, 12, 15, 22 (cycle 1) and at 28-day cycles thereafter. Response was assessed at day 113 by RECIST or RANO. **Results:** 17 Pt (age 24-67) with a median 7 (range, 2-12) prior systemic therapies completed a median 2 (range, 1-6) cycles without DLTs or treatment-related serious adverse events (AEs). Moderately severe related AEs occurred in 3 (100%), 1 (33%), 1 (33%), and 2 (25%) Pt at 1.1, 1.4, 1.8, and 2.4 mg/kg cohort doses, respectively. The most common treatment-related AEs was transient fatigue ($n = 4$, 23.5%). At 2.4 mg/kg, 1 Pt had moderate blood pressure elevation. Best response in 7 Pt completing to day 113 was 1 PR (appendiceal carcinoma) at 2.4 mg/kg, and 6 SD (1 HGG Pt at 0.7 mg/kg had stable disease >12+ months, and 6 had improved day 113 RANO/RECIST). BXQ-350 pharmacokinetics was dose proportional with half-life and Cmax, consistent with preclinical data. **Conclusions:** BXQ-350 showed clinical activity in heavily pre-treated patients with advanced solid and brain tumors. BXQ-350 has a tolerable safety profile with no significant DLT at the highest planned dose, supporting continued monotherapy dose expansion at 2.4 mg/kg. Clinical trial information: NCT 02859857.

DOSE (mg/kg)	0.7	1.1	1.4	1.8	2.4
N	1	3	3	3	8
Mean Age, F:M	64, 0:1	53, 0:3	58, 2:1	49, 1:2	54, 2.2
Prior systemic therapy, # cycles, *range*	7, 6	5-7, 2-4	2-12, 1-3	3-8, 2-6	4-12, 1-4
Solid Tumor *n*, Improved RANO *n/N D 113*	1, 0	2, 1/1	1, 1/2	1, 0	5, 0
HGG *n*, Improved RECIST, *n/N D 113*	1, 1/1	1, 0	2, 0	2, 0	3, 2/2
Adverse Event (*n case, n event*)	1, 15	3, 54	3, 37	3, 32	8, 80
Moderate severity related		3, 6	1, 1	1, 2	2, 2
Fatigue		2, 2		1, 2	1, 1
Neutropenia, EKG, Balance, Nerv, Dysarthria, Urin, BP		3, 4			
Serious non-related – GI, hyponatremia, weak	1, 1	1, 4	1, 3	1, 3	3, 5

2518 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase Ia/Ib trial of the DNA-PK inhibitor M3814 in combination with radiotherapy (RT) in patients (pts) with advanced solid tumors: Dose-escalation results. *First Author: Baukelien Van Triest, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: DNA-dependent protein kinase (DNA-PK), regulates one of the major pathways responsible for repair of DNA double-strand breaks. The combination of RT and DNA-PK inhibition (DNA-PKi) has been shown to be synergistic in preclinical studies. The purpose of this phase I trial is to explore the safety, tolerability, pharmacokinetic (PK) profile, and clinical activity of M3814 administered together with RT (Arm A) and chemo-RT (CRT; Arm B). Results for Arm A are reported. **Methods:** Pts with tumors or metastases in the head and neck region or thorax in need of palliative RT (30 Gy in 10 factions) are enrolled in the dose escalation part Ia of Arm A to receive M3814, starting dose 100 mg. Dose escalation is aided by a Bayesian logistic regression model. Dose-limiting toxicity (DLT) is evaluated up to 3 weeks after RT. Rich PK sampling is taken during treatment. Tumor evaluation is performed every 6 weeks up to 6 months and every third month thereafter. **Results:** 16 pts had been enrolled, 100 mg (N = 7), 200 mg (3) and 400 mg (6). The most frequent adverse events (AEs) were fatigue (n = 12), nausea (8), constipation, decreased appetite, dysphagia, mucosal inflammation/stomatitis (6), vomiting (5), back pain, chest pain, diarrhea, radiation skin injury, and weight decreased (4). All pts completed treatment (> 80% of specified dose) and no pts discontinued due to DLTs. Four DLTs were reported: grade 3 mucositis lasting > 7 days in 3 pts (100 and 400 mg) and odynophagia in one pt (400 mg). All pts with DLTs recovered without sequelae. One fatal suspected unexpected serious AE considered as radiation pneumonitis occurred. Preliminary efficacy: in field response: one pt had pCR, 4 PR, 7 SD, and 3 have not yet been evaluated one pt was not evaluable. PK was like an earlier first-in-man study, including high inter-subject variability. **Conclusions:** M3814 is well tolerated at doses of 100 and 200 mg QD as part of a palliative treatment combination with RT. Since 2 DLTs were seen at 400 mg QD, the therapeutic window will be further evaluated based on toxicity profile and PD data. Currently, M3814 300 mg QD is being explored. Updated safety and efficacy data will be presented Clinical trial information: NCT02516813.

2519 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

First-in-human phase I study of JPH203, L-type amino acids transporter 1 inhibitor, in patients with advanced solid tumors. *First Author: Naohiro Okano, Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan*

Background: The uptake of amino acids is essential for cancer growth. The L-type amino acid transporter 1 (LAT1) is overexpressed in various cancers, and the LAT1-mediated uptake of plasma-free amino acids (PFAA) plays a critical role in cancer growth. JPH203 is a novel, selective LAT1 inhibitor. **Methods:** A first-in-human phase I study of JPH203 was designed to determine the safety, maximum-tolerated dose (MTD), and recommended phase II dose (RP2D) of JPH203. This study evaluated the anti-tumor effects, progression-free survival, pharmacokinetics (PK), and pharmacodynamics (PD) of JPH203 and analyzed PFAA levels. JPH203 was administered intravenously for seven days, at planned doses ranging from 12–110 mg/m^2, followed by a 21-day rest, in patients with advanced solid tumors that were refractory to standard therapies. Before treatment, we confirmed the safety of a single dose of JPH203. Dose-limiting toxicity was evaluated during the first cycle, using a 3+3 design. **Results:** Seventeen patients were enrolled. One patient discontinued JPH203 after a single dose because of tumor progression. Grade 3 liver dysfunction occurred in one of six patients who received 60 mg/m^2 and the first patient received 85 mg/m^2. Although we determined that the MTD was 60 mg/m^2, the PK/PD profile and anti-tumor effects supported an RP2D of 25 mg/m^2. Common treatment-related adverse events were increased ALT/AST, malaise, nausea, hypertension, and grade 1 or grade 2 fevers. A partial response was achieved in a patient with biliary tract cancer (BTC) who continued JPH203 for two years without disease progression. Disease control was observed in three of five patients with BTC, and in two of six with colorectal cancer. LAT1 substrates, PFAA and branched-chain amino acids (BCAA), were higher in patients with BTC than in those with other cancers. All patients with disease control had a body mass index (BMI) greater than the median BMI of 20.5 kg/m^2. Furthermore, BCAA levels were associated with BMI. **Conclusions:** At the RP2D of 25 mg/m^2, JPH203 was well tolerated and showed promising results against BTC. This phase I study also suggests that BMI and BCAA might predict the efficacy of targeted cancer chemotherapy. Clinical trial information: UMIN000016546.

2520 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

First-in-class phase I study evaluating MP0250, a VEGF and HGF neutralizing DARPIN molecule, in patients with advanced solid tumors. *First Author: Analia Azaro, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: The VEGF/VEGFR and HGF/c-MET pathways are key mediators of the growth of solid tumours. MP0250 is a first-in-class, tri-specific DARPin compound neutralizing VEGF-A and HGF as well as binding to human serum albumin to increase plasma half-life and potentially enhance tumour penetration. **Methods:** Patients with advanced solid tumours were enrolled in a 3+3 dose escalation part (cohorts 1-5) and then in a single-arm dose expansion part (cohorts 6-7) (NCT02194426). The primary objectives were to evaluate safety, tolerability, the recommended biological dose, the maximum tolerated dose (MTD), the dose-limiting toxicities (DLTs) and the pharmacokinetics of MP0250. The secondary objective was to characterize the immunogenicity of MP0250. **Results:** From August 2014 until January 2018, 45 patients were enrolled in 7 different cohorts: cohort 1 to 5 (3 hr infusion, q2w): 0.5 mg/kg; 1.5 mg/kg; 4 mg/kg; 8 mg/kg, and 12 mg/kg; dose expansion cohorts: cohort 6 (1 hr infusion, q2w): 8 mg/kg and cohort 7 (1 hr infusion, q3w): 12 mg/kg. Patients were heavily pre-treated with a median of 3.6 lines of previous treatment (1-13). Median number of MP0250 infusions were 6.5 (1-31). Most common any-grade TEAEs were: hypertension 67% (grade 3: 37%), proteinuria 49% (grade 3: 4.4%), diarrhoea 36% (grade 3: 2.2 %), nausea 36% and fatigue 31% (grade 3: 2.2%). Two out of 5 patients in the 12 mg/kg q2w had a DLT (hypertension, nephrotic syndrome, GI bleeding). Additional DLTs (1 patient per cohort) occurred at 4 mg/kg q2w (left ventricular failure), 8 mg/kg q2w (creatinine and urea increase and thrombocytopenia), 8 mg/kg 1 hr infusion q2w (nephrotic syndrome) and 12 mg/kg q3w (nephrotic syndrome). Based on these data, the MTD for MP0250 was determined to be 8 mg/kg q2w or 12 mg/kg q3w. Two patients achieved a partial response, 44 % of patients were on MP0250 treatment for 3 months, 9 % for 6 months and 1 patient for over 1 year. **Conclusions:** In this FIH study, MP0250 was well tolerated with most AEs being consistent with profound inhibition of the VEGF pathway. Signs of single agent antitumour activity were observed and MP0250 is being further developed in lung cancer and multiple myeloma. Clinical trial information: NCT02194426.

2521 Poster Session (Board #347), Mon, 8:00 AM-11:30 AM

Can VEGFA and ICAM1 polymorphisms predict response to bevacizumab? *First Author: Apostolos Papachristos, Laboratory of Pharmacokinetics, Department of Pharmacy, School of Health Sciences, University of Patras, Rio-Patras, Greece*

Background: Most targeted treatments are associated with biomarkers, predictive of drug response. Although bevacizumab is widely used, there are still no available biomarkers. Given the need of individualized treatment approaches and the high cost of Bevacizumab, it is necessary to find biological predictors of response. The present study investigated the role of selected single nucleotide polymorphisms (SNPs) in *VEGFA* (Vascular Endothelial Growth Factor) and *ICAM1* (Intracellular Adhesion Molecule 1) genes as response biomarkers. **Methods:** 46 patients with metastatic colorectal cancer (mCRC) treated with Bevacizumab and chemotherapy (fluoropyrimidines/oxaliplatin or irinotecan) as first-line treatment were enrolled. Selected *VEGFA* (rs2010963, 1570360, rs699947) and *ICAM1* (rs5498, rs1799969) SNPs were detected using PCR-based Sanger sequencing (KAPABIOSYSTEMS, MA, USA). Statistical analysis was done using ANOVA and Kaplan-Meier Survival Analysis on SPSS software. Ethical committee of University Hospital of Patras approved study. **Results:** 61% of patients were males and 39% females, mean age was 64.5 years (31-86). *ICAM1* genotype analysis was available in 27 patients. For rs699947 (A > C), the % genotype frequencies were 29.8% AA, 23.4% A C , and 46.8% CC, while the rs1570360 (A > G) ones were determined to be equal to 10.6% AA, 23,4% A G , and 66% GG. For rs2010963 (C > G), 12.7% CC, 27.7% CG , and 59.6% GG were obtained. In the case of ICAM1, rs5498 AA, rs5498 AG and rs5498 GG were present with % frequencies of 37%, 37% and 26% , respectively. For rs1799969 (G > A) , 85% GG, and 15% AG. Mean Progression Free Survival (PFS) and Overall Survival (OS) were 14 and 44 months, respectively. PFS was significantly longer in rs699947 AA (27.1 months, p = 0.039) and rs5498 GG (27.8 months, p = 0.018) carriers. Moreover, OS was significantly increased in rs2010963 GC carriers (59.5 months, p = 0.03). **Conclusions:** Our findings suggest that rs699947, rs5498, and rs2010963 serve as candidate response biomarkers. All three might be able to stratify patients, who may gain a long-term benefit towards the optimization of Bevacizumab therapy and achieving better-informed therapeutic outcomes.

2522 Poster Session (Board #348), Mon, 8:00 AM-11:30 AM

A phase I dose escalation study of hPV19, a novel humanized monoclonal antibody against vascular endothelial growth factor (VEGF), in patients with advanced solid tumors refractory to standard therapy. *First Author: Dongmei Ji, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: hPV19 is a novel inhibitory mAb against VEGF with unique binding site different from that of Bevacizumab. This phase 1 study aimed to determine its dose-limiting toxicity (DLT), maximum tolerated dose (MTD), safety and pharmacokinetics (PK) in patients with advanced solid tumors. **Methods:** This is a first-in-human study with a 3+3 design. Eligible patients received hPV19 on day 1 and were observed for DLTs for 21 days. Subsequent treatment was every 14 days until disease progression or toxicity. DLTs were defined as occurrence of grade 3 or above non-hematological or grade 4 hematological toxicities. Response was evaluated at week 8 and then every 8 weeks using RECIST criteria. Extension enrollment (n = 5) was planned at dose levels 2.5 mg/kg and 6 mg/kg. **Results:** From 08/23/2016 to 01/25/2018, 24 patients were enrolled (22 for toxicity study) to 6 dose levels: 0.3 mg/kg (n = 3), 1 mg/kg (n = 3), 2.5 mg/kg (n = 8), 4mg/kg (n = 3), 6mg/kg (n = 4) and 10mg/kg (n = 3, not included in PK or response assessment). The median age was 46.5 years old (range 29-70). No DLTs have been observed and MTD has not been reached. Common grade 3 toxicities were hypertension 22.7%, proteinuria 9%, and LFT abnormalities 9%. Common grade 1 or 2 toxicities were hypertension 13.6%, proteinuria 59%, epistaxis 22.7%, dysphonia 18.2%, LFT abnormality 59%, renal abnormality 27.3%, anemia 22.7%, leukopenia 18.2% and thrombocytopenia 18.2%. A linear AUC dose response with elimination mean serum half-life ($t_{1/2}$) of 66.88-156.09h (2.78-6.50 days) and C_{max} of 4.06 to 132.01μg/ml were observed between doses 0.3 mg/kg to 6 mg/kg. Low titres of anti-hPV19 antibody were detected in 3 patients at 0.3 mg/kg (n = 1) and 1 mg/kg (n = 2). Six patients (27.2%) had clinical response, including 1 PR (breast ca, 2.5mg/kg), and 5 SDs (colon ca x2, renal ca x2 and breast ca x1, at all dose levels). The median duration of response was 27 weeks (range 17-57 weeks). **Conclusions:** hPV19 is safe and tolerable with promising durable single agent activity in refractory solid tumors. The dose selected for phase Ib /phase II is 4 mg/kg every 2 weeks or 6 mg/kg every 3 weeks. Clinical trial information: CTR20160585.

2523 Poster Session (Board #349), Mon, 8:00 AM-11:30 AM

PK/PD properties of BI 836880, a vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang-2)-blocking nanobody, in patients (pts) with advanced/metastatic solid tumors. *First Author: Christophe Le Tourneau, Institut Curie, Paris, France*

Background: BI 836880 (q3w or qw, iv) was evaluated in two first-in-human, Phase I trials in pts with advanced/metastatic solid tumors. We report exploratory PK/PD analysis of these studies to support dose selection for further clinical development of BI 836880. **Methods:** PK/PD analysis used evaluable data from 23 pts treated over ≥1 cycle (14 q3w; 9 qw [pt accrual ongoing in the qw schedule to confirm the maximum tolerated dose]). Analytes were systemic BI 836880, free VEGF, free Ang-2 and total Ang-2. Levels of BI 836880 in plasma were analyzed using a LC-MS/MS method, via monitoring a unique peptide of BI 836880 (lower limit of quantification [LLOQ] 0.5 mg/L). Total and free systemic Ang-2 were analyzed using ELISAs (LLOQ 0.1 and 0.08 ng equivalents [ngeq]/mL). Free systemic VEGF was analyzed using ECLIA with LLOQ 2.7 pgeq/mL. Development of an assay for total VEGF is ongoing. DCE-MRI data, as PD markers, were evaluated in 8 pts. **Results:** BI 836880 plasma kinetics appeared dose-proportional over 40–1000 mg q3w and 40–180 mg qw, with accumulation ratios between 1 and 2.The geometric mean half-life of BI 836880 in the q3w schedule over all dose groups was 8.2 days (cycle 1; n = 12), 9.9 days (cycle 2; n = 7) and 14.3 days (cycle 4; n = 4). Required trough values (20 mg/L; predicted based on preclinical experiments) were achieved at doses ≥720 mg q3w.Predose free VEGF levels were 0.022 to 0.669 ngeq/mL. Predose free Ang-2 levels were 0.72 to > 15 ngeq/mL. Individual pt PK/PD profiles showed that free VEGF was below LLOQ at the lowest dose; free Ang-2 was blocked dose-dependently and was below LLOQ at doses ≥360 mg q3w or 120 mg qw. Both analytes remained below LLOQ at these doses even before the next treatment cycle. Total Ang-2 (the majority bound to BI 836880) increased 100- to 1000-fold above predose levels and for some samples to the upper LOQ (1000 ngeq/mL). K_{trans} (capillary permeability) decreases ≥20% were observed in 5/7 pts at the 720 mg q3w dose, including 3 with K_{trans} reduction > 40%. **Conclusions:** PK/PD analysis supported BI 836880 720 mg q3w as the biologically relevant dose. DCE-MRI analysis confirmed anti-angiogenic activity in the tumor at this dose. Clinical trial information: NCT02674152; NCT02689505.

2524 Poster Session (Board #350), Mon, 8:00 AM-11:30 AM

Evaluation of fixed-dose regimens of seribantumab in patients with solid tumors. *First Author: Bambang Adiwijaya, Merrimack Pharmaceuticals, Inc., Cambridge, MA*

Background: Seribantumab (MM-121) is an anti-ErbB3 human monoclonal antibody being tested as an anti-cancer therapy for patients with high expression of heregulin mRNA in NSCLC (SHERLOC study, 3g every 3 weeks [Q3W]+docetaxel) and in and in HR+/ HER2- metastatic breast cancer (mBC) (SHERBOC study, 3g every 2 weeks [Q2W]+fulvestrant). Here we aimed to evaluate seribantumab dose regimens based on PK and safety. **Methods:** Pharmacokinetics (PK) and safety were evaluated for fixed and weight-based dose: in NSCLC, 3 g Q3W vs. 20 mg/kg Q2W; in mBC, 3 g Q2W vs. 40 mg/kg loading dose, followed by 20 mg/kg QW. PK was quantified using nonlinear mixed effect with the following covariates: sex, race, age, weight, dose, study, and hepatic functions. Adverse events (AEs) were evaluated for associations to PK and weight: Grade 1+ and 3+ diarrhea, fatigue, hypokalemia, hypomagnesemia, nausea, pulmonary embolism, rash, stomatitis, and vomiting. **Results:** Seribantumab PK from 499 patients in 7 previous trials identified associations with sex and weight. Fixed and weight-based doses showed similar variability. With higher weight, weight-based dose resulted in higher exposure (average concentration [Cavg] and maximum concentration [Cmax]), and fixed dose resulted in lower exposure. Steady-state Cmax were higher with 3 g than with 20 mg/kg; these values were comparable to Cmax with 40 mg/kg. Steady-state Cavg were equal to or higher for fixed dose than comparable weight-based dose. All doses tested had minimum concentrations (Cmin) higher than the nonclinical target concentration of 100 mg/L. Among AEs evaluated, significant associations with seribantumab exposure were observed for G1+ diarrhea, fatigue, nausea, rash, and stomatitis. Weight-based dose showed higher AE rates with increasing weight. Fixed dose is predicted to reduce AE rates in high-weight patients and to increase AE rates in low-weight patients, with the latter rates still lower than those in patients with high weight dosed by weight. **Conclusions:** The recommended dose of seribantumab is 3 g Q3W+docetaxel in NSCLC and 3 g Q2W+fulvestrant in mBC. The fixed dose of seribantumab allows acceptable concentrations and safety profiles and potentially reduces drug waste and dosing errors.

2525 Poster Session (Board #351), Mon, 8:00 AM-11:30 AM

Pharmacokinetics of Hu5F9-G4, a first-in-class anti-CD47 antibody, in patients with solid tumors and lymphomas. *First Author: Balaji Agoram, Forty Seven, Inc., Menlo Park, CA*

Background: Hu5F9-G4 is a humanized monoclonal antibody targeting CD47, a "don't eat me" signal on cancer cells, that stimulates tumor cell phagocytosis and activates an anti-tumor T-cell response. The objectives of this analysis were to characterize the pharmacokinetics (PK) and anti-drug antibody (ADA) incidence of Hu5F9-G4 after single and multiple doses in patients with solid tumors and lymphomas. **Methods:** Data from a first-in-human Phase 1 study in 58 patients with advanced solid tumors and lymphomas (NCT02216409) were used for this analysis. Multiple intravenous (IV) doses in the range 0.1 – 30 mg/kg were given at once or twice weekly frequencies. Serum samples were collected in all subjects at various timepoints after first and subsequent doses. PK data were analyzed by a noncompartmental approach using the PKNCA package in R; population modelling analysis was done with NONMEM software. Presence of ADA was analyzed using a 3-tiered - screening, confirmatory, titre - approach. **Results:** At doses of 0.1 – 10mg/kg increases in maximum serum concentration (C_{max}) and area under concentration curve (AUC) of Hu5F9-G4 were greater than dose-proportional indicating nonlinearity in PK. The PK parameters were consistent with the presence of a CD47 antigen sink, which was saturated at doses ≥ 10 mg/kg. Above this dose level, increases in C_{max} and AUC were dose proportional and the half-life of the antibody was ~14 days – typical of human IgG4. Simulations with the model predicted that a maintenance dosing regimen of 30 mg/kg every other week from cycle 2 onwards would result in serum concentrations ≥200 μg/mL, a level where full CD47 receptor occupancy on blood cells was observed in this study and where preclinical efficacy has also been previously reported. ADA were confirmed in 2 subjects (3.4%) in this study but had no observable impact on the PK parameters. **Conclusions:** Hu5F9-G4 has PK properties typical of antibodies directed towards cell-surface receptors. Hu5F9-G4 exhibits nonlinear PK, typical of a receptor-targeted antibody, with doses ≥10 mg/kg saturating the antigen sink. The PK profile of Hu5F9-G4 is suitable for every other week maintenance dosing in solid tumor and lymphoma patients in Phase 2.

2526 Poster Session (Board #352), Mon, 8:00 AM-11:30 AM

A phase I study to evaluate safety, tolerability, pharmacokinetics and activity of oraxol in patients (pts) with advanced malignancies. *First Author: Wen Wee Ma, Mayo Clinic, Rochester, MN*

Background: Oraxol is an oral formulation of paclitaxel (PTX) co-administered with the potent, selective, poorly absorbed, P-glycoprotein inhibitor HM30181A (HM) that enhances the absorption of PTX. PK modelling of prior data showed fixed dose administration was feasible. The objectives were to determine the MTD and PK of Oraxol administered as a fixed dose for up to 5 consecutive days. **Methods:** Eligible pts had advanced solid tumors, ECOG PS ≤ 1 and adequate organ function. The dose escalation utilized the standard 3+3 design (Part 1) and then expanded to enroll additional pts at the MTD (Part 2). The treatment consisted of sequential administration of HM oral 15 mg then PTX oral 270 mg daily while fasting. Dose escalation was achieved by increasing the number of dosing days per week (2 to 5 days per week x 3 weeks then 1-week rest, per 4-week cycle). Pts were monitored for dose limiting toxicity (DLT) during the first cycle for dose escalation/de-escalation decisions. Adverse events (AEs) were assessed per CTCAE v4.03 and response by RECIST v1.1. **Results:** A total of 34 pts received treatment and were AEs evaluable. Twenty-one of 24 pts in Part 1 were DLT evaluable and 1 DLT (febrile neutropenia) occurred at the 5-day dose level. Ten additional patients were treated at the 5-day dose level in Part 2. The most common (≥30%) treatment-related AEs (TRAEs) were nausea, diarrhea, anorexia and vomiting. Serious TRAEs included febrile neutropenia, pneumonia and dehydration. Pre-medication with steroids/anti-histamines was not required and hypersensitivity reactions were not observed. Partial responses occurred in 2 pts at the 5-day dose level (salivary gland, ovarian cancers). The median Tmax was 1 to 2 hrs. PTX exposure (Cmax and AUC) was comparable following 2-5 days of treatment; with a Day 1 C_{max} ranging from 147 to 246 ng/mL and $AUC_{0\text{-}8hr}$ ranging from 369 to 800 ng*hr/mL. Plasma levels of HM/metabolite were minimal. **Conclusions:** The MTD was not reached and the highest planned dose level (HM 15 mg/PTX 270 mg x 5-day) was selected for expansion. Sequential oral administration of HM and PTX achieved clinically efficacious PTX level and showed evidence of anti-tumor activity. Clinical trial information: NCT01967043.

2527 Poster Session (Board #353), Mon, 8:00 AM-11:30 AM

A phase I clinical trial of hepatic arterial infusion of oxaliplatin and oral capecitabine, with or without systemic bevacizumab, for patients with advanced cancer and liver involvement. *First Author: Elena Fountzilas, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Hepatic arterial infusion (HAI) of chemotherapy is a treatment option for patients (pts) with cancer metastatic to the liver. We investigated HAI oxaliplatin combined with capecitabine +/- bevacizumab, in advanced cancer with liver involvement. **Methods:** Pts received HAI oxaliplatin (140 mg/m^2) and escalating doses of capecitabine (500, 750, and 1000 mg/m^2), with (Arm A) or without (Arm B) bevacizumab (10 mg/kg IV). A 3+3 dose design was used, followed by an expansion phase. **Results:** From 9/2009 to 2/2014, 61 pts (34 men, 27 women) were enrolled (Arm A = 44; Arm B = 17). Pts were treated in Arm B if they had contraindications to bevacizumab (n = 13) or if there was no spot available in Arm A (n = 4). The median age was 60 yrs (range, 20-88). The most common cancers were colorectal (22 pts), liver (13), pancreas (7), breast (4), and biliary tract (4). The median number of prior therapies was 3 (range, 1-12); 32 (53%) pts had previously oxaliplatin. Grade 3 diarrhea was the only DLT and occurred in 2 pts receiving 1000 mg/m^2 capecitabine. Thus, the MTD was HAI oxaliplatin 140 mg/m^2, capecitabine 750 mg/m^2, and bevacizumab 10 mg/kg. Common toxicities were anemia, thrombocytopenia, neutropenia, hypomagnesemia, and nausea/vomiting. Outcomes are shown in Table. Eleven (18%) pts remained on treatment for ≥6 months, including 4 (6.6%) pts who remained on treatment for ≥1 year. **Conclusions:** HAI oxaliplatin combined with capecitabine +/- bevacizumab was well-tolerated and was associated with favorable outcomes in selected pts. Clinical trial information: NCT01213238.

	Oxaliplatin HAI, Capecitabine, Bevacizumab	Oxaliplatin HAI, Capecitabine	Total
No. of pts	44	17	61
No. of evaluable pts	36	11	47
CR+PR (%)	8 (22)	1 (9)	9 (19)
SD (%)	26 (72)	9 (81)	35 (75)
SD≥4 months (%)	14 (39)	0	14 (30)
Median TTF, months (95% CI)	3 (2.27-3.73)	1.5 (1.0-2.0)	2.7 (2.4-3.0)
Median OS, months (95% CI)	7.1 (5.46-8.8)	6.2 (3.16-9.17)	7 (5.57-8.56)
Median time on Rx, months (95% CI)	3 (2.35-3.65)	2 (1.56-2.47)	3 (2.48-3.53)
(Range)	(1-21)	(1-15)	(1-21)

* CR complete response, OS: overall survival, PR: partial response, Rx: treatment, SD: stable disease, TTF: time to treatment failure

2528 Poster Session (Board #354), Mon, 8:00 AM-11:30 AM

Plinabulin (Plin), a small molecule with anti-cancer activity and a novel mechanism of action (MoA) in docetaxel (Tax)-induced neutropenia: Phase (φ) 2 results from a head-to-head comparison with Pegfilgrastim (Peg). *First Author: Douglas W. Blayney, Stanford Cancer Institute, Stanford, CA*

Background: Plin has clinical anticancer activity in combination with Tax (Mohanlal ASCO-SITC 2017,18). Plin prevented Tax-induced neutropenia in a post-hoc analysis of a φ 2 trial (Blayney ASH 2016). Plin is being studied in the prevention of chemotherapy(chemo)-induced neutropenia (CIN) induced by Tax/ adriamycin/ cyclophosphamide in BC, by gemcitabine/ abraxane in PC, by carboplatin/ pemetrexed/ pembrolizumab in NSCLC , and irinotecan in CRC. We report final results of the φ 2 portion of a prospective φ 2/3 trial of Plin for CIN compared with Peg (NCT03102606; Study BPI-2358-105). The 105 study is designed to demonstrate non-inferiority (NI) of Plin vs Peg for duration of severe neutropenia (DSN) in φ 3. **Methods:** Patients (Pts; n = 55) with lung cancer (NSCLC) were randomized to Tax 75 mg/ m2 day (D)1, and either Peg 6 mg D2 or Plin 5, 10, or 20 mg/ m2 D1. Plin was dosed on the same day of (30 min after) chemo. Absolute Neutrophil Count (ANC) was collected D1,2,3,6,7,8,9,10,15 and 21. Primary endpoints were DSN and grade (Gr) 4 neutropenia to establish recommended phase 3 dose (RP3D). The NI margin for DSN is 0.65 D. Hypertension (HT) was evaluated by semi-continuous BP measurement on D1. **Results:** DSN for Peg was 0.51 D and for Plin 0.54 D. Gr 3 HT was transient and not different among all groups ($p < 0.18$). Bone Pain occurred in 33% of pts with Peg and 11% with 20 mg/ m2 Plin. Clinical trial information: NCT03102606. **Conclusions:** Plin 20 mg/ m2, given 30 min after chemo is well tolerated, has less bone pain, and has similar myeloprotective effect vs Peg. Its post chemo recovery curve is shallower, broader and later than Peg, with median ANC staying within normal range, suggesting a different MoA to prevent CIN. Plin 20 mg/m2 is the RP3D based upon its protection against Gr 4 neutropenia and safety profile.

			Median ANC (cell count x10E9/L)*							
	Dose	Pts	D1	D6	D7	D8	D9	D10	D15	Gr 4 CIN %
Peg	6 mg	14	9.43	4.65	5.82	12.1	15.7	16.7	11.4	14
Plin	20 mg/m^2	14	7.39	4.25	3.57	2.69	2.25	2.41	3.97	14
Plin	10 mg/m^2	13	7.93	4.13	1.91	1.76	1.94	2.30	4.69	23
Plin	5 mg/m^2	14	7.63	3.57	1.73	1.33	1.42	1.95	3.21	21

* Normal range of ANC: 1.8 to 7.7 X 10^9 cells/L

2529 Poster Session (Board #355), Mon, 8:00 AM-11:30 AM

Phase 1/2a study of BAL101553, a novel tumor checkpoint controller (TCC), administered as 48-hour infusion in adult patients with advanced solid tumors. *First Author: Markus Joerger, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

Background: BAL101553 is the prodrug of BAL27862, a small molecule TCC that binds microtubules and promotes tumor cell death by activation of the spindle assembly checkpoint. In a study of BAL101553 administered as a 2-h infusion on Days 1, 8 and 15 of a 28-day cycle (NCT01397929, Lopez et al. JCO 34, 2016; 2525), vascular toxicities were observed and appeared to be C_{max} related. Nonclinical models indicate that the antiproliferative effects of BAL27862 are AUC driven; this trial was intended to determine whether prolonged infusion reduces C_{max}-related toxicity and increases the AUC at the recommended phase 2 dose (RP2D) (NCT02895360, Joerger et al. JCO 2017; TPS2602). **Methods:** Patients with advanced solid tumors received 48-h infusions of BAL101553 using an elastomeric pump on Days 1, 8 and 15 of consecutive 28-day cycles using a 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD). During Cycle 2, patients received BAL101553 orally QD (Days 15–21) instead of IV in order to assess oral bioavailability. Adverse events (AEs) were assessed by CTCAEv4.03 grade (G); tumor response by RECIST 1.1 every two cycles; pharmacokinetics were assessed during the first two cycles. **Results:** Phase 1 enrollment was completed with 20 patients (7M/13F; median age 60 years; median 3 prior chemotherapies) receiving IV BAL101553 at doses of 30, 45, 70 or 90 mg/m^2. Dose-limiting toxicities included transient G3 hypotension at 70 mg/m^2 and reversible G3 hyponatremia, G3 neutropenia, G2 hallucinations and ataxia at 90 mg/m^2. There were no relevant vascular toxicities. Of 16 evaluable patients, one had a confirmed partial response (ovarian cancer) and one had stable disease for 6 months (endometrial cancer). BAL27862 exposures (AUC) were near dose-proportional. At 70 mg/m^2, the BAL27862 Cycle 1/Day 1 C_{max} was 144 ng/mL and AUC was 8580 ng.h/mL. Oral bioavailability was estimated to be > 80%. **Conclusions:** The MTD/RP2D of BAL101553 48-h infusion was 70 mg/m^2. At this dose the AUC/C_{max} ratio was ~4× higher compared to the 2-h infusion regimen at the RP2D of 30 mg/m^2. There were indications of potential clinical benefits in patients with ovarian and endometrial cancers. Clinical trial information: NCT02895360.

2530 Poster Session (Board #356), Mon, 8:00 AM-11:30 AM

Phase 1/2a study of once daily oral BAL101553, a novel tumor checkpoint controller (TCC), in adult patients with advanced solid tumors. *First Author: Juanita Suzanne Lopez, The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom*

Background: BAL101553 is the prodrug of BAL27862, a small molecule TCC that binds microtubules and promotes tumor cell death by activation of the spindle assembly checkpoint. In a study of BAL101553 administered as 2-h infusions on Days 1, 8 and 15 of a 28-day cycle (NCT01397929, Lopez et al. JCO 34, 2016; abstr 2525), vascular toxicities (troponin increases/ ECG changes suggestive of microvascular myocardial injury and hypertension) were observed and appeared to be C_{max} related. Nonclinical models indicate that the antiproliferative effects of BAL27862 are AUC driven; this trial was designed to determine whether oral once-daily (QD) administration of BAL101553 reduces C_{max}-related toxicity and increases the AUC at the Recommended Phase 2 Dose (RP2D) (NCT02490800, Kristeleit et al. JCO 35, 2017; abstr 2532). **Methods:** Adult patients with advanced solid tumors received QD oral BAL101553 (28-day cycles) in a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD). Adverse events (AEs) were assessed by CTCAEv4.03 grade (G); tumor response by RECIST 1.1 every 2 cycles; pharmacokinetics on Day 1 of Cycles 1 and 2. **Results:** Phase 1 enrollment completed with 26 patients (10M/16F; median age 62 y; median 3 prior chemotherapies) receiving oral BAL101553 at doses of 2–30 mg QD. BAL101553 was generally well tolerated at doses ≤16 mg, with one G3 event of increased alkaline phosphatase not considered clinically significant and G1/G2 events that did not show organ-specific patterns. Dose-limiting toxicities were seen at doses ≥20 mg: G3–4 hyponatremia, G3 hypokalemia and G2 hallucinations (all reversible). Of 19 efficacy-evaluable, 7 patients treated for ≥4 cycles (range 4-10) had stable disease (5/10 at ≥16 mg). BAL27862 exposure (AUC) was dose-related, almost dose-proportional. C_{max} levels were below those seen with 2-h infusions at the RP2D and there were no effects on blood pressure. At 16 mg, the BAL27862 Cycle 1/Day 1 C_{max} was 120 ng/mL and the estimated weekly exposure was 8400 ng.h/mL. **Conclusions:** The MTD of daily oral BAL101553 was 16 mg. At this dose, the weekly AUC is ~2-fold higher than that achieved at the RP2D for the weekly 2-h infusion. Vascular side effects were absent. Clinical trial information: NCT02490800.

2531 Poster Session (Board #357), Mon, 8:00 AM-11:30 AM

Investigation of profile-related evidence determining individualized cancer therapy (I-PREDICT) in heavily pre-treated patients: A role for combinatorial precision cancer therapy. *First Author: Jason K. Sicklick, Department of Surgery, University of California San Diego, San Diego, CA*

Background: With the increasing availability of large gene panels and cognate agents, we hypothesized that offering individualized combination therapies to patients with refractory cancers would improve outcomes. **Methods:** I-PREDICT (NCT02534675) is a prospective navigation trial (two centers: UC San Diego and Avera Cancer Institute). Comprehensive genomic profiling (CGP, Foundation Medicine; 315 genes), and, if possible, PD-(L)1 immunohistochemistry, tumor mutational burden and circulating tumor DNA were performed. A molecular tumor board discussed results immediately upon receipt, and emphasized use of customized, matched targeted/ immunotherapy combinations. Final decisions were the treating physician's choice. **Results:** Overall, 149 patients with advanced cancers were enrolled: 83 (55.7%) have been treated [73 matched (49.0%); 10 unmatched (16.7%)]. Diverse malignancies including gastrointestinal, hepatobiliary, gynecologic, and brain were represented. Median number of prior therapies = 2; median (range) of genomic alterations per patient = 4 (1-20). Each tumor had a unique genomic profile. The median (range) number of agents given was 2 (1-5), dosed individually on an N-of-1 basis. There were no drug-related deaths. We classified the patients based upon their treatment regimens' molecular Matching Score [number of genomic alterations matched/total number of characterized DNA alterations (> 50%: "high," n = 28; ≤50%: "low," n = 55 (includes unmatched (score = 0))]. High vs low Matching Scores independently correlated with better outcomes: SD≥ 6 months/PR/CR, 50% versus 22% (P = 0.03); median PFS (6.5 vs 3.1 months; P = 0.0004); median OS (not reached vs 10.2 months; P = 0.04) (all multivariate). **Conclusions:** The use of customized, multi-drug combinations targeting > 50% of identified genomic alterations recommended by timely molecular tumor boards and based on CGP was safe and associated with improvements in all outcome parameters. These findings underscore the feasibility and the importance of designing precision oncology trials that emphasize tailored combinations rather than monotherapies. Clinical trial information: NCT02534675.

2532 Poster Session (Board #358), Mon, 8:00 AM-11:30 AM

Palbociclib (P) in patients (Pts) with pancreatic cancer (PC) and gallbladder or bile duct cancer (GBC) with *CDKN2A* alterations: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Tareq Al Baghdadi, Michigan Cancer Research Consortium, Ypsilanti, MI*

Background: The TAPUR Study is a phase II multi-basket study that evaluates the anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations known to be drug targets. Results in two cohorts of PC and GBC pts each with *CDKN2A* loss or mutation treated with P are reported. **Methods:** Simon's optimal two stage design was used to test the null hypothesis of 15% response rate versus the alternative of 35%. Power and alpha were set at 85% and 10%, respectively. Response was assessed per RECIST v1.1. This design requires 10 pts in stage 1 and if < 2 pts have objective response (OR) or stable disease (SD) at 16-weeks (wks), the cohort is closed. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. Genomic testing was performed using commercially available tests selected by clinical sites. Treatment was determined according to protocol matching rules based on pre-defined genomic inclusion criteria. **Results:** Twelve pts were enrolled in the PC cohort from July 2016 to April 2017, but 2 were subsequently found to be ineligible due to minor deviations from inclusion criteria. Ten pts were enrolled in the GBC cohort from August 2016 to November 2017. All pts are included in the data analysis for demographics, safety, PFS and OS (Table 1). No ORs or SD at 16 wks were observed in the PC or GBC pts and both cohorts were therefore closed. The most common toxicity from P was thrombocytopenia. **Conclusions:** Monotherapy with P does not have clinical activity in PC or GBC pts with *CDKN2A* loss or mutation. Toxicity is similar to previous experience with P. These pts should be offered other treatments, including clinical trials. Clinical trial information: NCT02693535.

Baseline demographics, clinical characteristics and outcomes by cohort.

	Palbociclib targeting *CDKN2A*	
Tumor Type	PC (N = 12)	GBC (N = 10)
Median age, yrs (range)	62 (52, 70)	63 (54, 81)
Male%	67	50
ECOG Performance Status, %	25	10
0		
1	67	60
2	8	30
Median PFS, wks (90% CI)	7.2 (4.0, 8.0)	7.4 (4.0, 8.4)
Median OS, wks (90% CI)	12.4 (4.7, 23.1)	11.9 (5.1, 14.0)
Drug-related AEs, grades 3-4 (% of pts)	8	40

2533 Poster Session (Board #359), Mon, 8:00 AM-11:30 AM

Enrolling patients in clinical trials: Advice from close family and friends. *First Author: François Eisinger, Institut Paoli-Calmettes, Marseille, France*

Background: Clinical research is a major aspect of drug development and requires patient participation. Family and friends are known to play a role in medical decision-making, the extent of which depends on factors such as timing (onset or end of the disease), type of disease, the legal situation (e.g., patients under guardianship, or minor), and cultural aspects. The role of the close circle in inciting patients to enroll in clinical trials therefore warrants further study. **Methods:** The French nationwide observational survey, EDIFICE 6, was conducted online from 26 June-28 July 2017 on a core sample of 12 046 individuals (age, 18-69 years). Representativeness was ensured by quota sampling on age, gender, profession, and stratification by geographical area and type of urban district. Multivariate stepwise logistic regression analysis was conducted to identify factors likely to incite close relatives of cancer patients to urge them to enroll in a clinical trial. The present analysis included 11 307 individuals with no history of cancer and focused on the question "If a person you are close to had cancer and was invited to take part in a clinical trial, would you encourage them to participate?" **Results:** Most respondents declared they would very likely (22%) or likely (61%) encourage someone close to enroll in a clinical trial. Of the 21 significant explanatory factors affecting this opinion, two were predominant: believing that clinical research leads to important advances (OR = 2.75; 95% CI [2.33-3.24], $p < 0{,}001$) and that progress is made rapidly (OR = 2.18; 95% CI [1.95-2.43], $p < 0{,}001$). Other factors related to the "advice-giver" were also significant though less so: male gender (OR = 1.29), being married (OR = 1.20), not being socially vulnerable (OR = 1.17), former smoker (OR = 1.16), and having short-term perspectives (OR = 0.96). **Conclusions:** A large proportion (83%) of close family and friends of cancer patients were seen to encourage them to take part in clinical trials. Greater awareness and a clear understanding of the numerous benefits of clinical research would likely further increase the number of individuals who are in favor of clinical trials.

2534 Poster Session (Board #360), Mon, 8:00 AM-11:30 AM

AUCtox: A new method to evaluate the safety of anticancer drugs. *First Author: Vincent Launay-Vacher, Pitié-Salpêtrière Hospital, Paris, France*

Background: The evaluation of anticancer drugs safety currently relies on the NCI-CTCAE classification. Most often in clinical trials, attention is focused on severe adverse events (AE) *i.e.* grade 3 or more. However, AE of lower grades can have a significant deleterious impact, especially when recurrent or permanent. We aimed at defining a new method to better describe the impact of treatment on quality of life (QoL). **Methods:** The oncology patient monitoring program OptiSoins prospectively records treatment, number of cycles, and toxicities (NCI-CTCAE). Patients with castration-resistant metastatic prostate cancer treated with either docetaxel (DOC) or cabazitaxel (CABA) were identified in the database. For each patient, toxicities and their grade reported in medical records were plotted against time under treatment, to calculate the area under the curve of toxicities (AUCtox) that takes into account both the intensity and duration of toxicities, and the number of events. AUCtox was calculated for any toxicity reported at least once. The association with QoL, evaluated by EQ-5D-3L was determined. **Results:** In total, 146 patients were evaluable [DOC 85 (58%), CABA 61 (42%)]. Median age was 70.5 years (Q1-Q3: 64.7; 76.0). Median follow-up was 4.0 months. Patients underwent a median number of 6 cycles, with a median number of 15.0 evaluations (monitoring calls). At least one grade $\geq$3 AE was reported by 45.2% of patients, most frequently fatigue (20.6%) and pain (12.3%). A negative impact on global health status, assessed by the VAS of EQ-5D-3L, was identified for 3 AEs based on grade alone vs. 8 when considering AUCtox. **Conclusions:** Current evaluation of toxicity, based on grade alone, underestimates the impact of anticancer drugs on QoL. Our method, using AUCtox, can better detect this impact, allowing a more patient-oriented evaluation of drug safety.

Adverse events significantly associated with a negative impact on VAS, univariate analysis ($p \leq 0.05$).

Type of AE	AUCtox	≥Grade 3
Alopecia	+	-
Anorexia	+	+
Dyspnea	+	+
Fatigue/Asthenia	+	+
Tearing/Watering eye	+	-
Nausea	+	-
Peripheral sensory neuropathy	+	-
Nail loss/Onycholysis	+	-

2535 Poster Session (Board #361), Mon, 8:00 AM-11:30 AM

Trends in oncology trials termination due to toxicity over a period of 16 years. *First Author: Laura Vidal, Syneos Health, Barcelona, Spain*

Background: Pre-clinical studies may not fully determine the safety profile of an investigational agent resulting in the need to terminate studies due to safety concerns. Additionally, the development of effective new anti-cancer agents may undermine the risk-benefit ratio. We sought to determine the number of oncology studies indicated as terminated for safety reasons over the past 16 year period. **Methods:** Oncology and hematology trials listed as terminated due to safety or adverse event, between January 1 2002 and December 31 2017, and sponsored by biopharmaceutical industry were identified on the Citeline® Trialtrove database. Two periods were compared, prior to 2010 and from 2010. **Results:** 380 oncology trials were listed as terminated due to safety or adverse effects; 184 phase I and I/II, 147 phase II and II/III and 48 phase III and IV. 233 trials were terminated due to safety during 2002 – 2009 and 147 during 2010 - 2017. Considering the total number of trials terminated for all reasons, 10% of all terminations were due to safety reasons; 11% versus 9% in the early versus late 8 year period, respectively. For phases and period of time, 44% vs 57% phase I and I/II, 42% vs. 32% phase II, and 13% vs 10% phase III studies were terminated due to safety during 2002 – 2009 and 2010-2017 respectively. For trials performed in the elderly population, 33 trials (31 for $>$ 65 years old and 2 for $>$ 70 years old) were terminated for all reasons during the sixteen-year period: 21 trials terminated during 2002 – 2009 and 12 during 2010-2017. Of all 33 studies, 3 (9%) terminated due to safety (2 trials for $>$ 70 years old). Despite small numbers, the percentage is similar to safety terminations in all trials - nonage specific. **Conclusions:** The percentage of trials terminated due to safety has decreased very slightly. When examined as a proportion of trials by phase, the overall trend toward improvement seems to be result for decrease in late phase study terminations, indicating toxicity profile is better characterized at earlier stages. Although few studies focus on elderly cancer patients, there appears to be no increased risk for discontinuation due to safety reasons in this population.

2536 Poster Session (Board #362), Mon, 8:00 AM-11:30 AM

Systematic review of pediatric oncology phase I trials: Toxicity and outcomes in the era of targeted therapies. *First Author: Julia Wanda Cohen, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Historically, objective response rates (ORR) (CR/CRi + PR) in pediatric phase I oncology trials have been $< 10\%$. With an increased emphasis on targeted treatment approaches, safety profiles and response rates may have changed. We analyzed outcomes of recent phase I pediatric oncology trials. **Methods:** Peer-reviewed phase I pediatric oncology trials published from 2012 through 2017 were identified through a PubMed search. Selection criteria included a pediatric population (median age ≤ 25 years), diagnosis of cancer (including CNS tumors), and a clear dose-escalation schema. Each publication was evaluated for therapy type (cytotoxic versus targeted, combination vs. single agent), trial design, patient characteristics, toxicity, and response. **Results:** Of 242 publications identified, 89 articles met the inclusion criteria. 46 (52%) incorporated targeted therapies. Total enrollment was 2187 patients; median age at enrollment/trial was 10 years (range 3-25 years). 1990 patients (91%) were evaluable for toxicity, of whom 256 (12.9%) experienced dose-limiting toxicity (DLT) with 3 study-related deaths (0.15%). Of 1708 patients evaluable for response in 78 trials, 287 (16.8%) demonstrated a response (188 CR, 15 CRi, 84 PR). 31 (40%) of trials had no objective responses. Sixteen trials (21%) had an ORR $\geq 25\%$ (leukemia trials = 9, solid tumor trials = 7), of which 8 were combination cytotoxic trials and 8 were targeted trials, the majority enrolling patients with the relevant target (e.g. CD19-directed therapy for CD19+ disease). Comparison between the 46 targeted trials and the 43 cytotoxic trials demonstrated similar pooled rates of DLT (11.1% vs. 15.4%) and ORR (16.9% vs. 16.7%). **Conclusions:** Our systematic review of recent pediatric oncology phase I trials demonstrated a higher pooled ORR than rates previously reported without increased toxicity. A subset of trials with substantially higher ORR included combination cytotoxic trials and targeted trials with target specific enrollment, supporting earlier introduction of combinatorial approaches and inclusion of pediatric patients with the relevant target in early phase targeted trials.

2537 Poster Session (Board #363), Mon, 8:00 AM-11:30 AM

A randomized Bayesian phase 1 design combining an MPS-1 inhibitor with paclitaxel: A strategy to improve determination of the incremental toxicity of a novel compound over a known backbone therapy. *First Author: Florence Atrafi, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Here we present a study combining BAY1217389 (BAY), a potent MPS-1 kinase inhibitor with a backbone chemotherapy paclitaxel. Since we expected overlapping toxicities we sought to improve determination of the maximal tolerated dose (MTD) using a randomized phase 1 design with Bayesian dose modeling. We hypothesized that this approach may determine the MTD of BAY more accurately by limiting the effect of variability of dose limiting toxicities (DLTs) related to paclitaxel. **Methods:** Patients ($\geq$18 years) were randomized to receive oral BAY with intravenous paclitaxel (experimental arm) or paclitaxel monotherapy (standard arm) in cycle 1. Dose escalation was guided by Bayesian modeling targeting a DLT-rate in the experimental arm of 10% over DLT-rate in the standard arm. PK profiles were determined for both BAY and paclitaxel. Simulations were performed to estimate MTD for several scenarios. **Results:** We were able to establish an MTD of 65 mg BAY using 50 patients in the dose-escalation part. As expected the main DLTs were hematologic toxicity. Grade ≥ 3 neutropenia was predominantly observed in the experimental arm and was related to higher BAY AUC0-12 on D8 ($p<0.001$) and not to paclitaxel AUC0-24 ($p>0.1$). To determine whether the randomization adds value to the study design we ran simulations comparing our randomized strategy using variable toxicity rate (5, 10, 20, 40%) for paclitaxel monotherapy with the 3+3 design. These data showed that the randomized design outperformed the 3+3 design. The 3+3 design underestimated the MTD as dose escalation was terminated more frequently at first dose for higher paclitaxel toxicity rate. **Conclusions:** Randomized Bayesian phase 1 dose escalation design was feasible with BAY plus paclitaxel. A major advantage of this design is the precise determination of an exposure-toxicity relation for the experimental drug. Moreover, simulations support our hypothesis that the randomized design was able to determine the MTD accurately regardless of variable toxicity rate for paclitaxel. This approach may improve dose determination in phase I combination trials. Clinical trial information: NCT02366949.

2538 Poster Session (Board #364), Mon, 8:00 AM-11:30 AM

Successes and challenges faced by tissue collection during trials by oncology translational sciences. *First Author: Martine P Roudier, Oncology Translational Science, IMED Biotech Unit, AstraZeneca, Cambridge, United Kingdom*

Background: Knowledge of the success rates in obtaining baseline and on treatment tumour biopsies with sufficient evaluable tumour tissue is valuable in guiding strategies for evaluation of PD biomarker analysis in future clinical trials. **Methods:** We present a 12 month translational experience collecting patient paired-biopsies for pharmacodynamic (PD) biomarker evaluation in a multi-centre, multi-trial context. We analysed - 152 specimens, 72 pairs, for tumour content success rate and pair biopsy success rate in 8 investigational clinical trials. The tumour content was defined as successful when the biopsy contained greater than 100 tumour cells. All biopsies were formalin fixed paraffin embedded at the clinical sites and blocks or unstained slides were sent to a central pathologist for evaluation of tumour content and relevant PD biomarkers. **Results:** Tumour organ sites were per pair: bone (n = 14), lung (n = 16), prostate (n = 11), liver (n = 11), and no organ site (n = 20). Tissue size was an average of 17.25 mm^2 (range: 2-88 mm^2). Tumour content in skin biopsies was 42.7% (range 0-80%) and yielded the best tumour content sampling as compared to deep organ biopsies: bone:2.2% (range 0-20%); prostate: 20.3% (range 0-80%), liver: 27% (0.1-60%; lung: 28.1 % (0-60), no indication of organ site: 42.6% (range 1-90%). There was no correlation between tissue size and tumour content (r = - 0.083). Tumour content success rate was globally 40%. **Conclusions:** In summary, paired biopsies were 40% successful in sampling patient tumour. However 30% of them were evaluated without indication of primary or metastatic tumour status or initial tumour histopathology diagnosis. Processes to link meta-data collection (organ site or pathology report) with biopsies are in progress as well as encouragement to bone scan guiding when bone metastasis biopsies are necessary.

2539 Poster Session (Board #365), Mon, 8:00 AM-11:30 AM

Prospective assessment of tumor biopsies as part of clinical trials: Patients' (pts) perspectives. *First Author: Sunu Lazar Cyriac, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Despite the increased inclusion of mandatory biopsies for clinical trials, there are scant data related to the perceptions and acceptability by pts. This study assessed the pre and post biopsy perceptions among gynecological cancer pts. **Methods:** A prospective study was conducted at Princess Margaret Hospital for pts with gynecological cancers. The study was approved by local ethics committee and enrolled pts planned for core tumors biopsies as part of clinical trials. A questionnaire was completed by pts prior to and 1 week post biopsy. The questionnaire assessed the Hospital Anxiety and Depression Scale (HADS), pts' perceptions and experience. **Results:** 42 women completed the questionnaire at both time points. Median age was 63 years. Sites of biopsies were peritoneal nodules in 45%, liver in 24%, superficial lymphnodes (LN) in 17%, retroperitoneal LN in 7% and abdominal wall in 7%. 88% were Ultrasound guided, 8% was CT, and 4% as blind procedure. A risk threshold of less than 2% was considered acceptable for major complications, major bleeding or infection by 71%, 60% and 55% of pts, respectively. While 50% (21/42) of the pts reported that the biopsy didn't impact their care, but helps research; only less than 10% felt it would impact their care. 71% (30/42) of the pts would allow their specimen to be used for future research. Most pts (98%) were agreeable for genetic testing of their specimen and wanted to be informed of significant findings. Table 1 shows the HADS result. The baseline score was normal in 81%. 91% (38/42) felt that the side effects and risks of biopsy were adequately explained before the procedure. One week after the biopsy, only 1 pt had major pain. 91% (38/42) of pts did not feel any embarrassment during the procedure. The majority of pts (91% [38/42]) were agreeable for a repeat biopsy for research. Table 1 **Conclusions:** Core biopsies for correlative studies for research purpose are well accepted and tolerated by patients. Patients were well informed and importantly willing to undergo further biopsies in the future if necessary. This is critical with the growing integration of biopsies in clinical trial design.

HADS (Anxiety)(n = 42)	Pre Biopsy	1 week post Biopsy
Normal	34	39
Borderline abnormal	2	1
Abnormal	6	2

2540 Poster Session (Board #366), Mon, 8:00 AM-11:30 AM

Accelerated vs. regular approval: Lessons learned from U.S. FDA oncology approvals. *First Author: Ihid Carneiro Leao, U.S. Food and Drug Administration, Silver Spring, MD*

Background: This work categorizes the justifications for accelerated and regular approvals (AA and RA) of oncology products granted by U.S. FDA, based on endpoints other than overall survival (OS) that supported RA and pathways for AA conversion to RA. **Methods:** We reviewed FDA databases for approved oncology products for specific indications from January 2006 to November 2017. For each product and its indication, we reviewed the trial that supported its approval with respect to study population, trial design, endpoints, magnitude of the treatment effect and benefit-risk assessment. **Results:** Two hundred twenty-six new indications were granted, 159 (70%) received RA and 67 (30%) AA. OS was the primary endpoint supporting 40% of RAs. Non-OS endpoints that supported RA (60%, n = 95) included PFS (n = 51), response and response rate (n = 34), TTP (n = 4), DFS (n = 2), RFS (n = 2) and EFS (n = 2). The disease settings where non-OS endpoints were used included advanced breast cancer, multiple myeloma, chronic lymphocytic leukemia, acute lymphoblastic leukemia, advanced solid tumors such as thyroid, renal cancer, NSCLC and rare cancers. Of the 67 indications granted under AA, response including hematologic response endpoints and pathological complete response was the basis for most of AA (88%, n = 59). Eight approvals were based on a time to event endpoint (12%; PFS, n = 7 and DFS, n = 1). We identified two pathways for AA to RA conversion based on 33 out of 67 AAs converted: (1) longer follow-up of the same trial that supported the AA demonstrating the sustained treatment effect (18%) and (2) additional confirmatory trial with primary endpoint that represented clinical benefit in the intended indication (82%). **Conclusions:** Our results provide clarity of FDA oncology approvals and useful information to stakeholders for efficient development of oncologic products.

2541 Poster Session (Board #367), Mon, 8:00 AM-11:30 AM

A phase I molecular adaptive clinical study to evaluate safety and tolerability of BPM31510-IV in advanced solid tumors: Final study results. *First Author: Niven R. Narain, BERG, LLC, Framingham, MA*

Background: BPM31510-IV is an Ubidecarenone (CoQ10) containing IV nanodispersion targeting metabolic machinery in cancer, shifting bioenergetics from lactate dependency towards mitochondrial OxPhos and reversing the Warburg effect. This study evaluated the safety & tolerability of BPM 31510-IV alone or in combination with chemotherapy. The study design included PD sampling for multi-omic analysis to identify predictive markers of clinical benefit and patient stratification. **Methods:** Eligible patients were relapsed/refractory to standard therapy. The monotherapy arm received IV BPM 31510 for 6 d in continuous infusion in 28-d cycles, and combination arms (gemcitabine, 5-FU or docetaxel) were primed for 3 wks with BPM31510 prior to chemotherapy regimen followed by weekly dosing in a 6 wk cycle. Endpoints were safety, pharmacokinetics (PK) and pharmacodynamics (PD). Tumor response was evaluated at cycle 1 and then after every 2 cycles. **Results:** A total of 98 pts were enrolled. Thirty of 66 evaluable pts (45%) achieved stable Disease, for $\geq$ 2 cycles and 16/66 (24%) maintained a minimum of SD for $\geq$ 4 cycles. 99% patients receiving $\geq$ 1 treatments with BPM31510 experienced a TEAE. The most frequently experienced TEAEs were asymptomatic elevated APTT in 80% of pts, INR increased in 74%, PTT prolonged 64%, Anemia in 41%, fatigue in 24% and both AST increase & platelet decrease in 16% of pts. Molecular predictors of coagulation-related events prior to and 24h after 1st treatment with IP were identified. Biomarker candidates correlating with favorable clinical response & safety identified were independent of tumor type and prior therapy, suggesting a broad anti-tumor effect. Novel multi-omic panels with potential to stratify response before and 24h post treatment with AUC $>$ 0.85 were identified. **Conclusions:** BPM31510-IV is well tolerated as monotherapy and in combination with several standard chemotherapeutic agents. Molecular signatures with predictive potential of the safety and clinical response have been identified that will guide Phase 2/3 clinical development. Clinical trial information: NCT01957735.

2542 Poster Session (Board #368), Mon, 8:00 AM-11:30 AM

Adverse events (AEs) in early phase cancer clinical trials. *First Author: Grace Mishkin, National Cancer Institute, Rockville, MD*

Background: AE reporting is required in the conduct of clinical trials for patient safety and to understand the toxicities from treatment interventions. This analysis used a uniquely comprehensive dataset of AEs from early-phase NCI trials to describe overall clinician-reported AE frequency and prevalence, as well as changes in frequency and prevalence over time. **Methods:** Data were used from early phase trials using NCI-sponsored agents with complete AE reporting. Patients ages 25+ with at least one AE were included. These AEs were collected for treatment courses started 2000-2016 and standardized to CTCAE v4.0. R was used for analysis. **Results:** Over this 17-year period complete AE reporting was available for 1,594 early phase clinical trials representing a wide range of disease areas and agents. There were 1,417,529 total AEs reported for 59,023 patients. There are 790 CTCAE terms, but the 15 most frequently reported AEs represented 48% of all AEs reported (Table 1). Grade 3 AEs represented 13.1% of the AEs for 2000-2003, but decreased to 9.9% for 2012-2016. **Conclusions:** These initial results from an extensive AE database show a small number of AE terms represent most AEs reported. The proportion of AEs which were grade 3 decreased over time, potentially due to changes in agents and improvements in supportive care. As more trials which include patient reporting of AEs are completed, joint analysis could lead to more comprehensive understanding of the tolerability of lower grade AEs. Analysis by agent class, patient age, and disease is ongoing.

15 most commonly reported ctcae terms.

CTCAE Term	# AEs	% AEs (n = 1433896)	# Patients	% Patients (n = 59802)
Fatigue	105012	7.4%	36645	62.1%
Anemia	78350	5.5%	27746	47.0%
White blood cell decreased	58984	4.2%	21114	35.8%
Nausea	56993	4.0%	27456	46.5%
Platelet count decreased	56157	4.0%	21497	36.4%
Diarrhea	52412	3.7%	22696	38.5%
Neutrophil count decreased	50901	3.6%	20145	34.1%
Hyperglycemia	32542	2.3%	13650	23.1%
Anorexia	32510	2.3%	17360	29.4%
Peripheral sensory neuropathy	30533	2.2%	10166	17.2%
Lymphocyte count decreased	27904	2.0%	11724	19.9%
Aspartate aminotransferase increased	27057	1.9%	13564	23.0%
Alopecia	25679	1.8%	8379	14.2%
Rash maculo-papular	25547	1.8%	12303	20.8%
Vomiting	24186	1.7%	15576	26.4%

2543 Poster Session (Board #369), Mon, 8:00 AM-11:30 AM

Violations of the proportional hazards assumption in randomized phase III oncology clinical trials. *First Author: Rifaquat Rahman, Harvard Radiation Oncology Program, Boston, MA*

Background: The hazard ratio is the most common measure of treatment effect in oncology trials, but many trials commonly violate the underlying Cox proportional hazards assumption. We aimed to evaluate the prevalence of non-proportionality of hazards in phase III oncology clinical trials. **Methods:** We performed a PubMed search for randomized phase III trials in breast cancer, lung cancer, prostate cancer and colorectal cancer published in high-impact journals between 2014 and 2016. To be included, studies were required to report on a cancer-directed intervention and provide Kaplan-Meier (KM) curves of a time-to-event outcome. We generated individual patient data for time-to-event outcomes for overall survival (OS) and non-survival endpoints. We reanalyzed trials with our reconstructed individual patient data and evaluated for evidence of violation of the proportional hazards assumption with the Grambsch-Therneau test with a p-value threshold of $<$ 0.1. **Results:** We identified 157 publications with 115 KM curves of overall survival (OS) and 139 KM curves of a non-survival time-to-event outcome. There was evidence of non-proportionality of hazards in a total of 62 (24%) time-to-event outcomes including 20 of 115 (18%) OS KM curves and 42 of 139 (30%) non-survival KM curves. Immunotherapy (50%) and endocrine/hormonal therapy (50%) trials had the highest prevalence of KM curves with evidence of non-proportional hazards, and this was less common in KM curves of targeted therapy (25%), radiation therapy (19%), and chemotherapy (15%) trials. **Conclusions:** A notable proportion of time-to-event outcomes reported in oncology clinical trials demonstrates evidence of violating the assumption of proportional hazards. Non-survival time-to-event outcomes were more likely to show evidence of non-proportionality of hazards. Consideration of violation of the proportional hazards assumption is warranted in designing clinical trials.

2544 Poster Session (Board #370), Mon, 8:00 AM-11:30 AM

FACTS: Factors affecting combination trial success. *First Author: Channing Judith Paller, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Experimental therapeutic oncology agents are often combined in an effort to circumvent tumor resistance to individual agents; most combination trials, however, fail to demonstrate sufficient safety and efficacy to advance to a later phase. The FACTS study collected survey data on phase 1 combination therapies to: 1) assess rates of advancement and regulatory approval, 2) identify factors associated with these rates, and 3) assess the degree that phase 1 trials were concordant with Clinical Trial Design Task Force (CTD-TF) Guidelines. **Methods:** A 13-question survey collected data on phase 1 trial design, predefined expectations and criteria to assess success, biomarker information, and questions about the trials' results and progress. Online surveys (N = 289, July-Dec. 2017) were emailed to PIs of early-phase NCI and/or industry trials; 263 emails (91%) were received and 114 surveys completed (43%). Two independent coders validated 10% of survey responses (N = 12) against manuscript publications (intercoder Reliability = 99%). **Results:** Phase 1 results indicated further investigation was warranted for 39.8% of combinations (95% CI: 30.8%, 48.8%). 24.9% of combination trials (95% CI: 15.3%, 34.4%) progressed to phase 2 or further. 18.7% (95% CI: 5.90%, 31.4%) progressed to phase 3 or FDA approval. 12.4% (95% CI: 0.00%, 25.5%) achieved regulatory approval. Trial results where "clinical promise was observed" in phase 1 of the combination study were associated with higher rates of progression past each milestone toward regulatory approval (cumulative OR = 11.9; p = 0.0002). The phase 1 study designs were concordant with CTD-TF Guidelines for 79.6% of the combinations (95% CI: 72.2%, 87.1%); most discordances occurred where no plausible pharmacokinetic or pharmacodynamic interactions were expected. **Conclusions:** "Clinical promise" of a combination may predict progress toward regulatory approval. Although concordance between study designs of phase 1 trials of combination therapies and CTD-TF Guidelines was relatively high, raising more awareness of the best study design to use when no plausible pharmacokinetic or pharmacodynamic interactions are expected may be beneficial.

2545 Poster Session (Board #371), Mon, 8:00 AM-11:30 AM

The rate of tumor growth during treatment accurately predicts the FDA gold standard of overall survival [OS] in a broad range of malignancies. *First Author: Julia Wilkerson, Columbia University Medical Center, New York, NY*

Background: Novel clinical trial endpoints that predict overall survival (OS) are needed to streamline anticancer drug development. **Methods:** We used a novel mathematical approach to estimate simultaneously occurring exponential rates of tumor growth [*g*] and regression [*d*] using data stored for $>$ 10,000 patients [pts] enrolled in clinical trials. Data were provided by investigators, pharmaceutical companies, or were downloaded from Project Data Sphere [PDS], a publicly available data sharing warehouse; and included imaging measurements and serum tumor markers [eg. PSA, CA19-9 and M-spikes]. Pts with multiple myeloma, prostate, pancreas, colorectal, breast, renal, and neuroendocrine (NET) cancers undergoing cytotoxic, targeted, or immune therapies were included in this analysis. **Results:** In 85-90% of pts enrolled in a clinical trial, *g* and *d* could be estimated with p-values for fits $<$ 0.1 in all and $<$ 0.001 in the majority. Greater than 95% of the data fit the exponential equations, with 14 other equations describing models of tumor growth from the literature unable to fit $>$ 5% of the data. Regression (*d*) rates are 3-4x faster than growth (*g*) but do not correlate with OS. *g* can estimate doubling time (dt), and is highly predictive of progression free survival (PFS) and OS even when analyzing combined data from disparate studies. Straightforward modeling shows *g* can distinguish whether an experimental therapy is associated with OS gain in as few as 30 pts. Estimated median *g* values ranged from $0.0057d^{-1}$ (dt 0.3y) for pancreatic adenocarcinoma to $0.00046d^{-1}$ (dt 4.1yr) for NETs on therapy. **Conclusions:** Estimates of *g* accurately predict OS in a broad range of cancers and *g* should be considered a valuable surrogate in assessing trial outcomes. *g* can be compared easily across settings and allows large clinical trials to serve as benchmarks for estimating efficacy of experimental therapy. Development of this valuable assessment tool has been made possible by the sharing of clinical trial data by pharmaceutical companies directly or through PDS. Housing both the data and soon the benchmark analyses in PDS will offer investigators new strategies for clinical trial assessment.

2546 Poster Session (Board #372), Mon, 8:00 AM-11:30 AM

Phase 1 dose escalation of XMT-1522, a novel HER2-targeting antibody-drug conjugate (ADC), in patients (pts) with HER2-expressing breast, lung and gastric tumors. *First Author: Erika Paige Hamilton, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: XMT-1522 is comprised of 10-15 molecules of the payload AF-HPA, an auristatin-derivative with two-step intra-tumor metabolism intended to optimize therapeutic index, conjugated to a novel anti-HER2 monoclonal antibody via the Dolaflexin ADC platform. **Methods:** In this ongoing Phase 1 study, pts with advanced HER2-expressing (IHC $\geq$1+) breast cancer (BC), gastric cancer (GC) and non-small cell lung cancer (NSCLC) progressing on standard therapy or for whom no standard therapy exists are treated with XMT-1522 administered intravenously every 3 weeks. Dose escalation uses a 3+3 design with a modified Fibonacci escalation and a 3 week dose limiting toxicity (DLT) evaluation period. Primary objectives in dose escalation are safety and tolerability and determination of maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). (ClinicalTrials.gov NCT02952729) **Results:** As of February 1, 2018 19 pts have completed the DLT evaluation period across 6 dose levels (2 to 21.3 mg/m^2). There have been no DLTs nor serious adverse events (SAEs) attributed to study drug. Treatment-related adverse events (TRAEs) have been Grade 1 or 2; the most common TRAEs included increased liver enzymes, fatigue, nausea, vomiting, headache, and anorexia. 18 patients have had post-treatment restaging scans. Disease control rate (DCR) was 5/6 (83%) for patients dosed at 16 or 21.3 mg/m^2 with 1 PR and 4 SD. The ongoing PR occurred at first assessment in a pt with HER2-positive BC previously treated with ado-trastuzumab emtansine. Two SD were seen in HER2-positive BC pts (ongoing 13+ and 12+ wks duration) and SD was seen in two GC pts (12 weeks and ongoing 6+ weeks duration). DCR in patients treated at doses less than 16 mg/m^2 was 3/12 (25%) with 3 SD (duration 23, 13 and 9 wks). The systemic exposure of total payload showed approximately dose-proportional increase. Plasma concentration of free drug payload and its active metabolite were low. **Conclusions:** XMT-1522 has been well-tolerated up to the 21.3 mg/m^2 dose level with early signs of anti-tumor activity. Neither MTD nor RP2D has been identified. Dose escalation continues in pts with advanced HER2-expressing BC, GC and NSCLC. Clinical trial information: NCT02952729.

2547 Poster Session (Board #373), Mon, 8:00 AM-11:30 AM

A phase 1b study of the safety, pharmacokinetics, and preliminary antitumor activity of citarinostat (ACY-241) in combination with paclitaxel (Pac) in patients (pts) with advanced solid tumors (AST). *First Author: Michael S. Gordon, HonorHealth, Scottsdale, AZ*

Background: Citarinostat is an oral, selective histone deacetylase 6 inhibitor that inhibits growth of solid tumor cell lines and exhibits potent synergy with Pac in preclinical studies. We conducted a phase 1b dose-escalation study evaluating the safety and preliminary antitumor activity of citarinostat plus Pac in pts with AST. **Methods:** Pts with AST, including those who progressed on prior taxane therapy, were enrolled in a 3+3 escalation study. Cohorts: 1) 180 mg, 2) 360 mg, or 3) 480 mg oral citarinostat d1-21, all plus 80 mg/m^2 Pac d1, 8, 15 in a 28-day cycle. If no maximum tolerated dose (MTD) was identified, an additional cohort was allowed. Primary endpoints: dose limiting toxicity (DLT), MTD, and citarinostat recommended phase 2 dose (RP2D). Key secondary endpoints: safety, efficacy, and pharmacokinetics (PK). **Results:** Of 20 pts enrolled (cohort 1 = 3 pts, cohort 2 = 5 pts, cohort 3 = 6 pts, additional 360 mg cohort = 6 pts), 15 had prior taxane therapy. No DLTs were observed; MTD was not identified. Citarinostat RP2D was established at 360 mg/day. At 480 mg, a higher incidence and severity of neutropenia were observed (1 grade 4; 1 grade 3; 1 grade 2) vs 360 mg (1 grade 1). Common ($\geq$ 25%) treatment-emergent adverse events (TEAEs): anemia (50%), alopecia (40%), hypomagnesemia (40%), decreased appetite (35%), fatigue (35%), diarrhea (30%), nausea (30%), leucopenia (25%), dehydration (25%), and vomiting (25%). Peripheral neuropathy was observed in 30% of pts (15% grade 3; 8 Pac-related events, 1 Pac/citarinostat-related). Twelve serious TEAEs were reported in 8 patients. No deaths were observed under treatment. Citarinostat did not modify the overall safety profile of Pac. Two pts had confirmed partial response (PR); of 14 pts with stable disease, 2 had unconfirmed PR. In preliminary PK analysis, citarinostat exposure increased in a dose-proportional manner from 180 mg to 360 mg; however, a decrease in exposure was observed after dosing at 480 mg **Conclusions:** Citarinostat plus Pac showed acceptable safety in heavily pretreated pts without any unexpected toxicities. Further investigations of efficacy are needed. Clinical trial information: NCT02551185.

2548 Poster Session (Board #374), Mon, 8:00 AM-11:30 AM

NCI9782: A phase 1 study of talazoparib in combination with carboplatin and paclitaxel in patients with advanced solid tumors. *First Author: Anita Ahmed Turk, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: Poly(ADP-ribose) polymerase (PARP) enzymes are involved in DNA repair and activated by DNA strand breaks. DNA damage from carboplatin is associated with activation of PARP. Preclinical data indicate that PARP inhibition and trapping potentiates the anti-tumor effect of platinum chemotherapy. Talazoparib (T) is an oral, selective PARP inhibitor. This phase I study combines T with carboplatin (C) and paclitaxel (P). **Methods:** Two dosing schedules are being investigated. C is administered on day 1 and P on days 1, 8, and 15 of a 21-day cycle. T (100-1000mcg) is dosed once daily for days 1-7 (schedule A) or days 1-3 (schedule B) starting on day 1. Dose escalation is by 3+3 design. Key eligibility criteria include age 18+ with a solid incurable malignancy. Patients (pts) must have tumor type that is expected to respond to C + P or have BRCA germline or somatic mutation and adequate organ function. After 4-6 cycles of combination therapy, pts may continue the combination, change to C and intermittent T without P or change to T alone with continuous dosing. Each schedule will have a 6 pt dose expansion at the MTD. The starting dose for schedule B is the MTD from schedule A. **Results:** Schedule A results are reported: 23 pts (median age 55 yrs [range 37-70]) have been enrolled. Primary malignancies include breast (9), ovarian (3), SCC of skin/oropharynx (4), pancreatic (1), and other (5). 10 pts have known gBRCA1/2 mutations. Dose level 3 (T 350mcg with C AUC 6 + P 80mg/m^2) exceeded the MTD with 2 of 3 pts experiencing hematologic dose limiting toxicities (DLTs). Expansion of dose level 2 (T 250mcg with C AUC 6 + P 80mg/m^2) confirmed this level as the MTD. Most common adverse events included neutropenia (grade 3-4: 73.9%), anemia (grade 3-4: 39.1%), and thrombocytopenia (grade 3-4: 30.4%). Pts were on study a median of 15 weeks (range 1-98+). Of 17 pts with measurable disease, 9 (52.9%) had PR and 5 (29.4%) had SD. 35% of patients changed to T alone after combination chemotherapy. PBMC analysis for RAD51 foci, dH2AX, and PAR levels will be reported. **Conclusions:** The schedule A MTD and RP2D is T 250 mcg with C AUC 6 and P 80mg/m^2. This combination was tolerated with prolonged responses seen at lower dose T in combination with C+P. Clinical trial information: NCT02317874.

2549 Poster Session (Board #375), Mon, 8:00 AM-11:30 AM

Phase I trial of the triplet M6620 (formerly VX970) + veliparib + cisplatin in patients with advanced solid tumors. *First Author: Geraldine Helen O'Sullivan Coyne, Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Ataxia-telangiectasia-related (ATR) protein kinase is central to the repair of damaged DNA through the homologous recombination (HR) pathway, activating phosphorylation cascades that culminate in cell cycle arrest to allow time for DNA damage repair (DDR). M6620 is an ATR inhibitor with antitumor activity across a range of cell lines. Veliparib (ABT-888), an oral poly (ADP-ribose) polymerase (PARP) 1/2 inhibitor, plays a pivotal role in DDR response through the base excision repair pathway, with clinical evidence of antitumor activity in combination with cisplatin in *BRCA* mutation carriers. As DNA damage and antitumor activity of platinum results from DNA cross-links that stall replication forks and halt transcription, this trial evaluates if veliparib together with M6620 impair DNA repair by inducing a "*BRCA* null"-like phenotype that potentiates the antitumor activity of cisplatin. **Methods:** Open label phase I trial of the M6620+veliparib+cisplatin combination; 3+3 design, 21-day cycle: cisplatin 40mg/m^2 intravenously (IV) Day 1 [Day 8 added from dose level (DL)3]; M6620 (M) IV Days 2+9; Veliparib (V) orally twice daily Days 1-3 and 8-10. Prior platinum, PARPi therapy permitted. Response: RECIST 1.1. **Results:** 23 patients(pts) enrolled, 22pts evaluable for response. 3/22pts confirmed partial responses (PR) lasting $>$ 4cycles (range 4-15): 1pt with *BRCA*-wildtype ovarian cancer (DL3), 1pt with esophageal cancer/biallelic loss of ATM (DL4); 1pt with NSCL cancer/ATM mutation (DL5); all remain on study. 12/22pts have stable disease: median time on study 5 cycles (range 3-10). DL3+4 expanded for dose limiting toxicity: grade 4 hypophosphatemia and thrombocytopenia respectively (1pt, 4%). Other adverse events: grade 3 thrombocytopenia (6pts, 27%), leucopenia (5pts, 22%), lymphopenia (4pts, 18%). Maximally tolerated dose (MTD) not reached for the combination, currently enrolling DL7: V 200mg, M 210mg/m2. **Conclusions:** combination is safe and shows antitumor activity in HR-compromised tumors. Planned biomarker assessment at MTD includes γH2AX, RAD51, pNbs1, and pATR in tumor biopsies and circulating tumor cells using a validated, quantitative immunofluorescence assay. Clinical trial information: NCT02723864.

2550 Poster Session (Board #376), Mon, 8:00 AM-11:30 AM

Phase ib/2a study of PLX51107, a small molecule BET inhibitor, in subjects with advanced hematological malignancies and solid tumors. *First Author: Amita Patnaik, South Texas Accelerated Research Therapeutics, San Antonio, TX*

Background: PLX51107 is an orally active small molecule inhibitor that exhibits low nanomolar potency in blocking interactions mediated by the four BET family proteins and a unique pharmacokinetic (PK) profile. **Methods:** We conducted a first-in-man 3+3 dose escalation study of PLX51107 in adult patients with relapsed or refractory solid tumors (lymphomas included) and AML to determine the recommended phase II dose (RP2D) (NCT02683395). Secondary endpoints included safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). Enrollment through Cohort 7 (160 mg QD) is ongoing as of January 2018. **Results:** 36 subjects with advanced solid tumors (median age 60.5 years) received PLX51107 in escalating doses from 20mg to 160mg QD and 60mg BID. Uveal Melanoma (n = 11) was the most common tumor type followed by sarcoma (n = 6), and NSCLC, Breast and CRPC (n = 2 each). Most common toxicities in $\geq$ 15% of pts: fatigue (33%), vomiting (25%), diarrhea (25%), nausea (19%), bilirubin increase (17%), and INR increase (17%). Most were grade (G) 1-2. There were 3 treatment-related serious AEs (1 each of G3 nausea, G2 vomiting, and G2 kidney injury). Subjects with extensive hepatic metastases ($>$ approx. 50% of the liver) demonstrated higher exposure and more AEs. Dose limiting toxicity (DLT) was observed at 20mg (1 G3 thrombocytopenia), 120mg QD (1 G3 nausea) and 160mg QD (1 G2 kidney injury). PK was dose proportional with t1/2 $<$ 2.5hr. Sixty mg BID dosing yielded same AUC as 120mg QD. RNA-seq analyses of peripheral blood mononuclear cells showed a dose-dependent induction of HEXIM1/WDR47 and reduction of CCR1/CCR2 gene expression within 3 hours of dosing. Eight pts achieved stable disease by RECIST (2 uveal melanoma, 3 sarcoma, 1 CRPC, 1 NSCLC), ranging from 4-14 months, and one subject with uveal melanoma demonstrated stable disease for 14 months. **Conclusions:** PLX51107 continues to enroll in dose escalation; patients with extensive hepatic metastasis are excluded going forward. Based on preclinical toxicology data, the expected Maximum Tolerated Dose will be in the 200-300 mg range. The BID dosing schedule will not move forward due to no increase in exposure observed. Clinical trial information: NCT02683395.

2551 Poster Session (Board #377), Mon, 8:00 AM-11:30 AM

Phase I trial of lurbinectedin (PM1183) in Japanese patients with advanced tumors: Results of the dose escalation part. *First Author: Shunji Takahashi, Cancer Institute Hospital of JFCR, Tokyo, Japan*

Background: PM1183 (lurbinectedin, Zepsyre) is a new anticancer agent that inhibits activated transcription, induces DNA double-strand breaks leading to apoptosis and modulates tumor microenvironment. The recommended dose (RD) in non-Japanese patients (pts) is 3.2 mg/m^2 on Day 1 every three weeks (q3wk), with reversible myelosuppression as dose-limiting toxicity (DLT). **Methods:** Japanese pts with solid tumors (excluding CRC or CNS primary tumors), adequate organ function and ECOG PS 0-2 were treated at 3 different dose levels (DLs), 1.5 mg/m^2, 2.5 mg/m^2 and 3.2 mg/m^2, using a 3+3 design. **Results:** Fifteen pts (10 female / 5 male) were treated and evaluated for safety and efficacy. Median age was 52 years (38-65), albumin 4 mg/dL (3.5-4.6) with 2 median previous lines (1-3). Tumors were, among others, biliopancreatic (3), esophageal (2), endometrial (2) and breast (1). 2 out of 4 pts on DL3 (3.2 mg/m^2) had a DLT consisting of a grade (G) 4 neutropenia and a G3 neutropenia lasting $>$ 7 days. Eight pts were treated at the RD established on 2.5 mg/m^2, with G2 neutropenia leading to dose reduction and dose delay in 1 pt each. Main adverse events at the RD were hematological with 1 pt (12.5%) presenting G3 neutropenia. Other G3/4 toxicities included a non-drug related G4 hypokalemia (12.5%). Non-hematological toxicities were exclusively G1/2, including G2 ALT increase (50%), AST increase (25%), anorexia (25%), nausea (25%), fatigue (12.5%) and dyspnea (12.5%). At RD, 1 pt (12.5%) with metastatic breast cancer achieved a durable partial response and 3 pts (37.5%) had confirmed stable disease. PK at RD (n= 6 pts) showed a similar behavior to non-Japanese pts, with a mean (standard deviation) total body clearance (CL) of 10.5 (4.5) L/h, half-life of 50.7 (18.1) h and volume of distribution at steady-state of 375.5 (172.0) L. **Conclusions:** The RD of PM1183 in Japanese pts is 2.5 mg/m^2 q3wk, with mild toxicity. Main DLTs were hematological. Hints of activity were observed in breast cancer. Japanese pts showed a similar CL to non-Japanese pts, but with a 26.5% lower distribution volume. A new cohort is exploring PM1183 3.2 mg/m^2 (non-Japanese RD) in Japanese pts receiving G-CSF support. Clinical trial information: NCT02210364.

2552 Poster Session (Board #378), Mon, 8:00 AM-11:30 AM

Abrogation of resistance against bevacizumab (Bev) by mitochondrial inhibition: A phase 0 randomized trial of Bev plus ME344 or placebo in early HER2-negative breast cancer (HERNEBC). *First Author: Miguel Quintela-Fandino, CNIO - Spanish National Cancer Research Center, Madrid, Spain*

Background: Our preclinical data show that one mechanism of acquired resistance to anti-angiogenic therapy involves hypoxia correction, measured by decreased SUV (↓ SUV) on FDG-PET followed by mitochondrial up-regulation. ME344 is a potent inhibitor of mitochondrial respiration. The aims of this study were to assess 1) the fraction of HERNEBC patients that show ↓SUV in response to single dose Bev and 2) if adding ME344 to Bev inhibits cell proliferation as determined by Ki67% decrease, a surrogate marker of efficacy in neoadjuvant breast cancer. **Methods:** Treatment-naïve HERNEBC patients (T > 1 cm, any N, M0) received 15 mg/kg Bev on d0 and were then randomized 1:1 to ME344 10 mg/kg IV d8, 15 and 21 (arm A) or placebo (arm B) followed by physician's choice of definitive therapy. FDG-PET was performed on d0 and d7 and tumor biopsy on day 0 and 28. The primary endpoint was Ki67% relative reduction from d0 to 28. A 40 patient sample size was powered to detect a 30% relative difference in Ki67% between arm A and B (alpha 0.05, beta 0.2). Threshold for hypoxia correction by PET was 10% ↓ SUV. A predefined interim analysis was planned when 20 patients had completed treatment. **Results:** 19 patients were randomized (arm A/B: 7/7 LumA, 2/2 LumB, 1/0 TNBC). Baseline characteristics: Ki67 by IHC: mean 10.3% (1%-48%), age: mean 56 (44-75), T (8 T1, 10 T2, 1 T3), N (14 N0, 5 N1) and G (4 G1, 12 G2, 3 G3) were balanced between arms. 31% of patients experienced ↓SUV > 10%. Mean absolute (relative) Ki67 decreases were 5.13 (29%) and 1.2 (9%) in arms A and B (P = 0.06). Patients with ↓ SUV > 10% experienced an absolute average Ki67 decrease of 16.6 vs. 2.3 in arms A and B (P = 0.19). Two G3 adverse events (high blood pressure) were reported (1 per arm) and deemed related to Bev. **Conclusions:** ME344 results in significant Ki67 reduction compared to placebo in HERNEBC patients exposed to single-dose Bev. This effect may be greater in those patients with Bev induced hypoxia correction. These clinical results are consistent with preclinical data suggesting that ME-344 can reverse resistance to anti-angiogenic therapy and warrant further studies to assess clinical efficacy of the combination. Clinical trial information: NCT02806817.

LBA2553 Poster Session (Board #379), Mon, 8:00 AM-11:30 AM

Precision medicine: Clinical outcomes including long-term survival according to the pathway targeted and treatment period: The IMPACT study. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

2554 Poster Session (Board #380), Mon, 8:00 AM-11:30 AM

A phase 1/2 study of relacorilant + nab-paclitaxel (nab-pac) in patients (pts) with solid tumors: The dose-finding phase. *First Author: Pamela N. Munster, University of California, San Francisco, San Francisco, CA*

Background: Glucocorticoid receptor (GR) expression has been linked with chemotherapy resistance. Nonclinical and clinical studies have suggested that a GR antagonist (GRA) can enhance the efficacy of chemotherapy. Relacorilant (formerly CORT125134), a potent selective GRA, is being evaluated in solid tumors in combination with nab-pac. **Methods:** This ongoing phase 1/2 study is evaluating the tolerability, anticancer activity, and Phase 2 dose of relacorilant + nab-pac. Nab-pac is administered weekly for 3 of 4 weeks of a 28-day cycle. The study includes assessment of 2 relacorilant dosing schedules: continuous (CON) daily dosing and intermittent (INT) dosing (the day before, of, and after nab-pac). Pts ≥18 y old with advanced solid tumors, up to 3 prior lines of therapy in the advanced setting, ECOG status 0-1, and adequate renal, hepatic, and marrow function are included. Prior treatment with nab-pac is allowed. **Results:** As of Jan 1, 2018, 25 pts were enrolled; 17 had prior taxane. In CON dosing, 16 pts received 100 mg relacorilant/80 mg/m^2 nab-pac and 1 received 100 mg relacorilant/60 mg/m^2 nab-pac. In INT dosing, 4 pts received 200 mg relacorilant/150 mg/m^2 nab-pac and 4 received 150 mg relacorilant/100 mg/m^2 nab-pac. Grade ≥3 AEs included neutropenia (40%), anemia (12%), pneumonia (8%), mucosal inflammation (8%), and leukopenia (8%). Dose-limiting toxicity included neutropenia; GCSF support was added to regimens subsequently. Among pts treated to date, 1 unconfirmed CR (ovarian CA), 2 confirmed PRs (pancreatic CA, vulvar CA), and 5 SDs (2 ovarian CA, 2 pancreatic CA, 1 carcinoid) were observed. Pancreatic CA pt with confirmed PR has remained on study 48 weeks, despite having progressed within 14 weeks on earlier gemcitabine/nab-pac. For the 6 pts with available tissue, all had GR IHC results with ≥50% staining (range 50%-100%); 4/6 pts were responders; all 4 had ≥60% GR staining. **Conclusions:** An efficacy signal has been observed in pts with pancreatic and gynecologic CA previously treated with taxane. Neutropenia is manageable with GCSF support and dose modification. Expansions are planned, including pancreatic and ovarian CA cohorts. Clinical trial information: NCT02762981.

2555 Poster Session (Board #381), Mon, 8:00 AM-11:30 AM

Real world results of liquid biopsy in stage 3/4 solid tumors and potential "clinical actionability." *First Author: Rebecca Christian Arend, University of Alabama at Birmingham, Birmingham, AL*

Background: Next-generation sequencing (NGS) of plasma circulating cell-free DNA (cfDNA) and cfRNA, also known as a "liquid biopsy", is a minimally invasive technique available in the clinic. Here we report initial liquid biopsy results from stage 3 and 4 solid tumors using the Circulogene Theranostics Personalized Gene Profile (CGP, 50-gene panel) on cfDNA and cfRNA. **Methods:** DNA mutations detected and, where available, PD-L1 expression, ALK, and ROS1 fusions in RNA were retrospectively compiled from CGP ordered at two centers. To be considered clinically actionable and commercially available (CA), the biomarker had to have demonstrated clinical efficacy in human cancer prospective trials using the biomarker and commercially available drug that can target that biomarker. To be considered a clinical trial possibility (CT), one of the biomarkers was required to have a drug in clinical development using the biomarker for the patient's cancer type and disease stage listing on clinicaltrials.gov during the time period that CGP was ordered. **Results:** One hundred forty-five patients (median age 66 years, range 25-95; 35 men and 110 women) underwent CGP testing between November 2015 and October 2017. The majority of cancer types were ovarian, breast, pancreatic, uterine, and prostate. Most common DNA mutations recorded were TP53, PTEN, PI3KCA, SMAD4, and BRAF. There was a median of 2 mutations/patient (range 0-11), with a 0.69% sample failure rate. Overall, 36 cases had no detectable mutations (24.8%). There were six samples with PD-L1 results, and one was positive (16.7%), in the range of expected PD-L1 positivity across solid tumors. In addition to the 36 mutation negative cases, 19 cases had no potential match for CA or CT (e.g. APC, GNAS, SMAD4 mutations). Thus, 89 (61.4%) of cases had the potential for CA and/or CT drug identified by liquid biopsy. CGP is priced at approximately $600 per sample comparable to current reimbursement rate. **Conclusions:** In this real world experience, despite the low plasma sample input, there was a 0.69% sample failure rate, suggesting CGP *in situ* enrichment is robust. More experience with this assay and linkage with clinical outcomes is warranted.

2556 Poster Session (Board #382), Mon, 8:00 AM-11:30 AM

A phase Ib study of ADI-PEG 20 plus pembrolizumab in advanced solid cancers. *First Author: Kwang-Yu Chang, National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan*

Background: Arginine deprivation with pegylated arginine deiminase (ADI-PEG 20) has been shown to upregulate tumor programmed death-ligand 1 (PD-L1) expression and T cell infiltration. Current phase Ib study is to explore the feasibility of combining ADI-PEG 20 with pembrolizumab in patients with advanced solid tumors. **Methods:** Eligibility criteria included treatment-failure patients with measurable lesions. Pre-treatment tumor biopsy was required. In the "3 + 3" designed dose-escalation part, patients were enrolled to receive ADI-PEG 20 36 mg/m^2 at day 1, 8 and 15, and pembrolizumab (1 mg/kg or 200 mg) at day 1, every 3 weeks to determine the maximum tolerated dose (MTD) of pembrolizumab for expansion cohort study. In the expansion cohort part, patients with platinum-failed HNSCC would receive both ADI-PEG 20 and pembrolizumab (at MTD) from day 1; while patients in translation cohort who were required to have $<$ 50% PD-L1 expressing tumors would receive 3 doses of weekly ADI-PEG 20 and a post-ADI-PEG 20 biopsy before the start of combination treatment. The primary endpoint was safety and tolerability. Secondary endpoints included progression-free survival, overall survival, response rate, and the changes of tumorous PD-L1 expression and T-cell infiltration after treatment with ADI-PEG 20 with and without pembrolizumab. **Results:** The recruitment of dose-escalation cohorts was completed between July 2017-January 2018. There was only one dose-limiting toxicity, grade 3 hepatitis, observed in a patient in 1 mg/kg dose level; while none in the 200 mg dose level. Among them, two (22.2%) had partial response (PR) and four (44.4%) had stable disease. The two PRs were in thymus cancer and nasopharyngeal carcinoma, with both having 100% tumor baseline PD-L1 expression. The most common grade 3/4 adverse event (AE) was neutropenia, which occurred in seven patients. For serious AEs, two had neutropenic fever lasting less than one week in the third week, and one had tumor bleeding because of tumor progression in the eighth week. The expansion cohorts are enrolling. **Conclusions:** Co-administration of ADI-PEG 20 and pembrolizumab is feasible. The major toxicity is neutropenia which is transient and manageable. Responses were observed with the regimen. Clinical trial information: NCT03254732.

2557 Poster Session (Board #383), Mon, 8:00 AM-11:30 AM

Phase 1 study of ANDES-1537: A novel antisense oligonucleotide against non-coding mitochondrial DNA in advanced solid tumors. *First Author: Mallika Sachdev Dhawan, University of California San Francisco, San Francisco, CA*

Background: New non-coding RNAs, which appear to be involved in cell proliferation in animal cells, have been discovered by L.Burzio and co-workers. Andes-1537 is a short single stranded phosphorothioate-deoxyoligonucleotide which binds by base pairing to one of these newly discovered non-coding RNAs, named Antisense non-coding mitochondrial RNA (ASncmtRNA). The resulting RNA-DNA hybrid is then hydrolyzed by two cellular RNases: RNase H and DICER resulting in microRNAs. In vitro experiments with cells have shown Andes-1537 affects cancer cells by: a) inducing apoptosis by lowering the expression of anti-apoptotic proteins such as survivin b) decreasing proliferative signaling through inhibition of the expression of proteins such as cyclin D1 and cyclin B1, and c) inhibition of tissue invasion/metastatic proteins such as n-cadherin, B-catenin and metastasis inducing factors. **Methods:** The safety, tolerability, maximum tolerated dose (MTD), pharmacokinetic (PK) characteristics and efficacy of Andes -1537 was assessed in a phase 1 study. Patients with all solid tumors were enrolled in 5 cohorts at 100 mg subcutaneous (SC), 200 mg SC, 400 mg SC, 600 mg SC and 800 mg SC twice weekly. **Results:** 22 patients (14 M: 8F) with heavily pretreated solid tumors were enrolled in 5 cohorts. Two dose-limiting toxicities occurred at the 800 mg dose level both of which were injection site reactions: one precluding full cycle 1 dose delivery, and one involving grade 3 skin necrosis due to vascular occlusion and inflammation. No other grade 3/4 toxicities were seen. Grade 2 toxicities including injection site reactions and erythema. The MTD has been determined to be 600 mg SC twice weekly. Two patients (one with pancreatic cancer and one with cholangiocarcinoma) had stable disease on scans beyond six months. No partial or complete responses were seen with Andes 1537. PK data reveals a linear PK profile. **Conclusions:** Andes-1537 is a well-tolerated drug with a novel mechanism. It was determined to be tolerable at 600 mg SC twice weekly. An efficacy signal in pancreatic cancer and cholangiocarcinoma was seen at 200 mg dose level and thus dose expansion is under consideration. Clinical trial information: NCT02508441.

2558 Poster Session (Board #384), Mon, 8:00 AM-11:30 AM

Characterization of *KEAP1-NRF2* genomic alterations across diverse tumor types: Co-occurring alterations, survival outcomes, and implications for targeting cancer metabolism. *First Author: Shiraj Sen, The University of Texas Southwestern Medical School, Dallas, TX*

Background: CRISPR–Cas9-based genetic screening and metabolomic analyses have revealed that *KEAP1-NRF2*-mutated cancers depend on increased glutaminolysis and are vulnerable to glutaminase inhibition. However, alterations in *KEAP1-NRF2* have yet to be clinically characterized. **Methods:** We analyzed clinical and next gen sequencing data from pts treated at MD Anderson Cancer Center and performed bioinformatic analyses of alteration frequency using TCGA data on cBio Portal to characterize *KEAP1-NRF2* alterations and used Kaplan-Meier analysis to identify associations with overall survival (OS). **Results:** Among 189 pts with *KEAP1* or *NRF2* alterations (alts) at MDACC (97 with each, 5 with both), median age was 65 yrs (range: 18-89), 52% were females, 80% Caucasian, 11% Hispanic, and 5% African-American. *KEAP1-NRF2* alts were most common in NSCLC (19%), cholangiocarcinoma (8%), breast (7%), and renal cell CA (7%). Mean number of co-occurring alts was 8 (range:0-73). We identified 69 unique alts in *KEAP*1, most commonly Q619del (11%) and V369A (9%), and 68 unique alts in *NRF2*, most commonly E79Q (6%) and G31A (6%). Median OS in the entire cohort was 966 days. Of the 1505 co-alts identified with *KEAP1*, most common were *TP53* (57%), *ARID1A/B/2* (55%), *PI3K*-encoding genes (37%), and *NOTCH1* (29%). Of the 817 unique co-alts identified with *NRF2* alts, most common were *TP53* (52%), *PI3K*-encoding genes (36%), *ARID 1A/B/2* (25%), and *BRCA1/2* (19%). Co-alts in *TP53,* SWI/SNF complex, mTOR pathway, and NOTCH pathway genes did not impact survival. In TCGA, *KEAP1-NRF2* alts were most common in NSCLC (26%), uterine (15%), breast (10%), and cholangiocarcinoma (9%). *KEAP1-NRF2* alts were associated with decreased survival in lung adenocarcinoma (LUAD), 49 vs 33 months, log rank p = 0.02. **Conclusions:** KEAP1-NRF2 alts are prevalent across diverse tumor types and associated with decreased survival in LUAD. They most frequently co-occur with alts in TP53, SWI/SNF complex, and mTOR pathway genes but these co-occurring alts did not impact survival in our cohort. A Basket trial of Glutaminase Inhibitor (BeGIN) CB839 in patients with *KEAP1/NRF2* aberrant tumors is planned.

2559 Poster Session (Board #385), Mon, 8:00 AM-11:30 AM

Identification of predictive and pharmacodynamic biomarkers associated with the first-in-class selective axl inhibitor bemcentinib across multiple phase II clinical trials. *First Author: Robert J Holt, BerGenBio ASA, Bergen, Norway*

Background: AXL expression is strongly associated with immunosuppression and therapy resistance in a wide range of cancers. Bemcentinib is a first-in-class, orally bioavailable, selective AXL TKI which is being evaluated in solid tumours and myeloid malignancies in multiple Ph II clinical trials. Evidence of immune activation and reversal of therapy resistance upon treatment with bemcentinib has been observed in vivo as well as pts treated across the clinical programme. Here we report results of the accompanying biomarker research that utilises both liquid and tissue biopsies for gene expression, immunohistochemistry (IHC) and protein based analysis. **Methods:** Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in a selection of pts pre-dose and at C2D1 across six clinical trials. Axl expression was measured in FFPE tissue samples together with an evaluation of distinct immune cell populations collected using multiplex IHC. Gene expression analysis was carried out by TaqMan qPCR. **Results:** Predictive and PD plasma biomarkers were identified in response to bemcentinib monotherapy in AML/MDS (NCT02488408), combination with pembrolizumab in NSCLC (NCT03184571), TNBC (NCT03184558) and melanoma (NCT02872259) as well as in NSCLC in combination with erlotinib (NCT02424617) and docetaxel (NCT02922777). Identified biomarkers include soluble AXL (sAXL) and other AXL regulated targets including angiogenin. A pharmacodynamic response of sAXL levels was observed after 1 cycle of treatment with bemcentinib which corresponded with the subset of pts that benefitted from treatment. Several biomarkers associated with treatment using bemcentinib + pembrolizumab across multiple different disease indications were also identified. AXL was detected by IHC in pt tumour tissue as well tumour associated immune cells. **Conclusions:** Results indicate the presence of predictive biomarkers which may be suitable for development into companion diagnostics to predict response to bemcentinib treatment. These biomarkers also confirm that bemcentinib has selective 'on-target' activity in a clinical setting.

2560 Poster Session (Board #386), Mon, 8:00 AM-11:30 AM

Interim results from a phase 1 trial of SL-801, a novel XPO-1 inhibitor, in patients with advanced solid tumors. *First Author: Judy Sing-Zan Wang, Florida Cancer Specialists and Research Institute, Sarasota, FL*

Background: SL-801 is a novel, oral, small molecule reversible inhibitor of Exportin-1 (XPO-1), a critical nuclear export protein overexpressed in many cancers. SL-801 has demonstrated potent in vitro and in vivo anti-tumor activity against a broad range of hematologic and solid cancers. SL-801's reversible inhibition of XPO-1 may translate to selective activity and potential safety benefits. Interim results from the dose-escalation study are reported. **Methods:** STML-801-0115 is a first-in-human, multicenter Phase 1 3x3 dose escalation study in patients with localized unresectable, or metastatic solid tumors resistant to or relapsed following standard therapy. Objectives are to evaluate safety and tolerability, identify maximum tolerated dose (MTD) or optimal dose/regimen for further evaluation, and assess pharmacokinetics and preliminary anti-tumor activity. SL-801 is orally administered on days 1-4 and 8-11 of a 21-day cycle. Starting dose was 5 mg and is currently 55 mg (escalation ongoing). **Results:** As of 1/6/18, 31 pretreated patients (range: 1-11 prior therapies; 71% ≥3rd line) received SL-801 (16 females, median age 63 years [range: 39-76]). No dose limiting toxicity (DLT) has been identified, and a MTD has not been reached. Median follow-up is 1.4 months (range: 0.2-8.5). Dose-dependent increases in C_{max} and AUC have been observed. The most frequent treatment-related grade 1-2 adverse events (TRAEs) were nausea (45%), vomiting (32%), diarrhea (19%), fatigue (26%) and decreased appetite (19%). Grade 3 TRAEs included nausea (n = 3; 40, 45, 50 mg), vomiting (n = 1; 45 mg), diarrhea (n = 2; 10, 50 mg), acute renal injury (n = 1; 30 mg), and neutropenia (n = 1; 10 mg). There were no grade 4 or 5 TRAEs. Nine patients had stable disease (SD) for 3-12+ cycles. Five patients, with GE junction, colon, neuroendocrine, basal cell, and breast cancer, had SD ≥4 months. Radiographic tumor shrinkage > 10% was noted in 3 patients. **Conclusions:** SL-801 appears to be well tolerated in advanced solid tumor patients, and 29% of patients achieved SD as best reponse. Enrollment and dose escalation continue in an effort to identify an optimal dose and regimen. Clinical trial information: NCT02667873.

2561 Poster Session (Board #387), Mon, 8:00 AM-11:30 AM

Phase I study of defactinib combined with pembrolizumab and gemcitabine in patients with advanced cancer. *First Author: Andrea Wang-Gillam, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Focal adhesion kinase (FAK) is consistently hyperactivated in multiple tumor types including pancreatic ductal adenocarcinoma (PDAC). Our preclinical work showed that FAK and PD-1 inhibitors elicit significant tumor regression, and a maximal response is achieved by combining FAK and PD-1 inhibitors with gemcitabine, suggesting the need for a cytotoxic agent to bolster antigen presentation (Jiang H et al, Nature Medicine 2016). **Methods:** Eligible patients are being treated according to the dose escalation schema (Table 1). A 3+3 design is being used. The study has an expansion portion for PDAC patients at the recommended phase 2 dose (RP2D). The primary endpoint is to determine the RP2D. Secondary endpoints include safety, toxicity, objective response rate, progression-free survival and overall survival. The exploratory endpoints include developing a molecular and immune profile for treatment response. **Results:** The dose escalation cohort has been completed with a total of 20 patients with refractory solid tumors. The common treatment-related adverse events included nausea (50%), vomiting (40%), diarrhea (35%), anorexia (30%), fever (25%), and myalgia (25%). No DLTs were observed, therefore the Level 5 dose was deemed to be the RP2D. Among the 15 patients evaluable for treatment response, 1 (7%) partial response, 8 (53%) stable disease and 6 (40%) disease progression were observed. The median time on treatment was 132 days for all evaluable patients, and 127 days in the 8 PDAC patients with the longest time on treatment being 290 days. Partial response was seen in a patient with PDAC who progressed on gemcitabine and nab-paclitaxel. Paired biopsies in PDAC patients showed increased proliferating CD8+ T cells and decreased macrophages with treatment. **Conclusions:** The combination regimen is well tolerated. Dose Level 5 is the RP2D dose. The expansion cohort (PDAC only) is ongoing. Efficacy and correlative data is forthcoming. Clinical trial information: 02546531.

Dose escalation schema.

Dose Level	Defactinib D1-21 (BID)	Pembrolizumab D1	Gemcitabine D1, 8
Level 1 (starting dose)	200 mg	200 mg	-
Level 2	400 mg	200 mg	-
Level 3	400 mg	200 mg	500 mg/m^2
Level 4	400 mg	200 mg	750 mg/m^2
Level 5	400 mg	200 mg	1,000 mg/m^2

2562 Poster Session (Board #388), Mon, 8:00 AM-11:30 AM

Phase I clinical trial of the glutaminase inhibitor CB-839 plus capecitabine in patients with advanced solid tumors. *First Author: Jennifer Rachel Eads, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: Colorectal cancers (CRCs) harboring a PIK3CA mutation demonstrate glutamine dependency in both *in vitro* and *in vivo* models, including those known to be fluoropyrimidine (FP) resistant. CB-839 (CB) is an oral inhibitor of glutaminase, a key enzyme in glutamine metabolism. Preclinical studies further show that the combination of CB and a FP is superior to either as a single agent, and can overcome FP resistance. We conducted a phase I trial to assess the maximum tolerated dose and dose limiting toxicities (DLTs) of CB when given with capecitabine (C). **Methods:** Patients with advanced solid tumors and disease progression on standard treatment, or for whom C is an acceptable treatment option, were enrolled. A standard 3+3 design was used to assess escalating doses of CB (400-800 mg) and C (750-1000 mg/m^2) in four dose levels. CB was given orally twice daily continuously and C was given orally twice daily on days 14/21 of a 21 day treatment cycle. DLT period was 21 days. Restaging CT scans were obtained every 9 weeks with response assessment per RECIST. Adverse events were assessed per CTCv4. **Results:** 16 patients were enrolled: 38% male, 94% white, 6% African American, median age 69.5 years (43-80), mean number of cycles 7.3 (1-11). Seven patients were treated at the final dose level (CB 800 mg and C 1000 mg/m^2) and no DLTs were observed. Grade 3 adverse events included elevated ALT (n = 1), elevated AST (n = 1), anorexia (n = 1), decreased lymphocytes (n = 1), palmar-plantar erythrodysesthesia (n = 3), diarrhea (n = 1) and vomiting (n = 1). Grade 4 AEs included decreased lymphocytes (n = 1). Ten patients achieved stable disease as their best response, 9 being FP resistant. Associated median progression free survival (PFS) was 16.5 weeks among all patients (n = 16) and 29.5 weeks in PIK3CA mutant CRC patients (n = 6). At this time 2 patients remain on treatment at 31 and 3 weeks. **Conclusions:** CB 800 mg may be safely administered with C 1000 mg/m^2 with minimal toxicity. While no RECIST response was observed, several patients with prior FP resistance experienced prolonged PFS, particularly patients with PIK3CA mutant CRC. The phase II portion of this study in patients with PIK3CA mutant CRC is pending. NCT02861300, 2P50CA150964-06A1 Clinical trial information: NCT02861300.

2563 Poster Session (Board #389), Mon, 8:00 AM-11:30 AM

The utility of genomics and functional imaging to predict Sunitinib PK and PD: The Predict SU study. *First Author: Michael Michael, Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Current dosing of Sunitinib (Su) is associated with marked variability in pharmacokinetics (PK) & pharmacodynamics (PD). Despite its hepatic metabolism, genotyping & phenotyping of ABCB1 & CYP3A4 have inconsistently accounted for this variability. This study has evaluated the utility of extensive excretory/metabolic/PD pharmacogenomics (PG) combined with ^{99m}Tc-MIBI hepatic nuclear imaging (HNI, to phenotype ABCB1 biliary excretory function), to predict Su PK/PD. **Methods:** Patients (pts) had advanced renal cell carcinoma (RCC) or GIST, treated with Su, 50mg daily for 4 weeks, q6 weekly. Pts had blood analyzed by Affymetrix DMET™ Plus Array and additional PD SNPs were genotyped. For HNI, pts were given IV 800MBq ^{99m}Tc-MIBI, the imaging data was analysed for hepatic extraction/excretion parameters (Clearance [CL], Deconvolutional excretion half-life [$DeT_{1/2}$], hepatic extraction fraction [HEF]). Pts were restaged after 2 cycles (12 weeks). Blood were taken for Su parent (SuP) and metabolite (SU12662-SuM) analysis in cycles 1 & 2, days 1, 14 and 28. PK parameters derived by non-compartmental analysis. Statistical associations were evaluated between (i) HNI parameters and (2) PGs, with Su PK, toxicity, response and progression-free survival (PFS). **Results:** 15 pts analysed (10 RCC, 5 GIST). (1) PK predictors: HEF with SuP and SuM cycle 1 $logAUC_{0\text{-}14days}$ ($P < 0.05$) and $DeT_{1/2}$ with SuP cycle 1 $logAUC_{0\text{-}28days}$ ($P < 0.02$) (2) Diarrhea ≥Grade 1 (N = 4): HEF ($P = 0.03$), and gene variants VEGFR3 ($P < 0.0004$) and SCL7A8, ABCC3 ($P < 0.05$), (3) ≥Grade 3 Adverse events (N = 2): variants in ABCC4, SLC7A7 ($P < 0.05$). (4) Disease control rate: N = 7 (54%): HNF1A (79A > C) ($P = 0.4$), variants in SCLO5A1, SLC7A5, ABCG1, ABCC4, ABCB4, ($P < 0.05$). (4) PFS: SuP cycle 1 $logAUC_{0\text{-}14days}$ ($P < 0.03$), HNF1A (79A > C) ($P < 0.03$), PDGFRα (-1171C > G) ($P < 0.04$), ABCC4, ABCC1, SULT1C2, SLC01A2, CYP2D6, ($P < 0.02$). Multiparameter models were generated for the prediction of (i) SuP $logAUC_{0\text{-}14days}$ incorporating HEF + TNFα (-857C > T) ($P = 0.02$) and (ii) SuM $AUC_{0\text{-}14days}$ with VEGFR3 (150A > G) + $DeT_{1/2}$ ($P = 0.009$). **Conclusions:** Hepatic functional imaging with extensive pharmacogenomics were associated with Su PK and PD, potentially enabling individualized dosing Clinical trial information: ACTRN12610000897066.

2564 Poster Session (Board #390), Mon, 8:00 AM-11:30 AM

Pharmacokinetic (PK) and exposure-response (ER) analysis of pertuzumab (P) in patients (pts) with HER2-positive metastatic gastroesophageal junction and gastric cancer (mGEJC/GC). *First Author: Whitney Paige Kirschbrown, Genentech Inc., South San Francisco, CA*

Background: The phase 2a, dose-finding JOSHUA study reported increased P clearance (CL; 37% lower P steady-state C_{min} [$C_{min,ss}$]) in pts with HER2+ mGEJC/GC vs metastatic breast cancer (MBC). Based on these data, 840 mg q3w was selected for testing in the phase 3 JACOB study (NCT01774786) to achieve similar P concentrations (conc) to BC studies with the 840 mg then 420 mg q3w P dose. In JACOB, while there was evidence of treatment activity, addition of P to trastuzumab (H) and chemotherapy (CT) in 1st-line therapy did not significantly improve overall survival (OS) vs placebo (Pla)+H+CT (hazard ratio: 0.84 [95% CI 0.71–1.00], median OS 17.5 vs 14.2 months), in pts with HER2+ mGEJC/GC. Here we report the PK and ER analysis of P in JACOB. **Methods:** PK samples were collected at Cycles 1–4, 6, and 8 (predose); Cycles 1, 2, 4 and 8 (postdose); and at follow-up. P+H peak and trough conc were summarized by descriptive statistics and % pts with a $C_{min,ss} \geq 20$ μg/mL (target conc) tabulated. PK exposure was compared across geographic regions. The Kaplan-Meier method and a log-rank test were used to assess OS across C_{min} quartiles. PK drug-drug interactions (DDIs) were assessed using serum C_{min} geometric mean ratios. **Results:** Pts with ≥1 dose of P or H and ≥1 PK sample were included (P: n = 374 [P+H+CT]; H: n = 372 [P+H+CT] and 375 [Pla+H+CT]). Mean $C_{min,ss}$ Cycle 6 for P was 114±51.8 μg/mL, 99.3% of pts had $C_{min,ss}$ for P ≥20 μg/mL. There were no differences in OS across Cycle 1 and Cycle 6 (s-s) P C_{min} quartiles (Q1: 0.075–30.6, Q2: 30.6–39.8, Q3: 39.8–51.9, Q4: 51.9–318; n = 349, P = 0.52 and Q1: 0.075–77.1, Q2: 77.1–110, Q3: 110–145, Q4: 145–450; n = 274, P = 0.78, respectively). Mean $C_{min,ss}$ was comparable across geographic regions. No apparent DDIs were observed for CT on P $C_{min,ss}$, or P on H. Two of 349 (0.6%) evaluable pts tested positive for anti-drug antibodies to P; there was no impact on P PK. **Conclusions:** In JACOB, the 840 mg q3w P dose achieved target $C_{min,ss}$ in > 99% pts with HER2+ mGEJC/GC. ER analysis showed no correlation between P trough conc and OS. PK data were consistent with prior GC (P: 840 mg) and BC (P: 840 mg/420 mg) studies and higher P CL in HER2+ mGEJC/GC vs other tumor types. Clinical trial information: NCT01774786.

2565 Poster Session (Board #391), Mon, 8:00 AM-11:30 AM

Validation of a new model for estimating glomerular filtration rate in patients with cancer. *First Author: Edward Williams, Cancer Research UK Cambridge Institute, Cambridge, United Kingdom*

Background: Estimation of glomerular filtration rate (GFR) is essential for carboplatin chemotherapy dosing. However, the most accurate method to estimate GFR in patients with cancer is unknown. Using data from 2471 patients with cancer, we developed a new model that improves estimation of GFR (eGFR) and carboplatin dose calculations when compared to BSA adjusted CKD-EPI, the next most accurate model for determination of eGFR in patients with cancer. [1] Here we present a multi-centre validation study of this work. **Methods:** Data on age, sex, height, weight, serum creatinine, and results for GFR from ^{51}Cr-EDTA excretion measurements (^{51}Cr-EDTA GFR) were obtained from Caucasian patients aged 18 years or older with histologically confirmed cancer diagnoses from one Swedish and six UK centres. We validated the new multivariate linear model for GFR using statistical analysis. ^{51}Cr-EDTA GFR was compared with the estimated GFR (eGFR) from seven published models and the new model using root-mean-squared-error (RMSE) and median residuals. A comparison of carboplatin dosing accuracy based on an absolute percentage error more than 20% (APE > 20%) was undertaken. **Results:** Data from 3869 patients were obtained. In a pooled analysis, the new model improved the eGFR accuracy (RMSE 16.58ml/min (95% CI 16.21 to 16.95)) compared with all other published models. Body surface area (BSA) adjusted CKD-EPI remained the second most accurate model for eGFR (RMSE 17.58ml/min (95% CI 17.20 to17.99)). The new model was also the least biased model (Residual Median 0.33 (95% CI -9.56 to 10.69)). Importantly, the new model reduced the fraction of patients with a carboplatin dose APE > 20% (16.93% compared with 19.07% for the next best model). The new model was the most accurate model for patients with seminoma (n = 642), ovarian cancer (n = 553), and bladder cancer (n = 253). A further 2000-2500 patients will be included before completion of the study. **Conclusions:** In a very large multicentre data set of patients with cancer, we confirm that our new model improves eGFR and carboplatin dose calculations when compared with commonly used, published models. [1] Janowitz T and Williams EH *et al.*, J Clin Oncol. 2017 Aug 20;35(24):2798-2805. doi: 10.1200/JCO.2017.72.7578

2566 Poster Session (Board #392), Mon, 8:00 AM-11:30 AM

Selection of the recommended phase 2 dose (RP2D) for M7824 (MSB0011359C), a bifunctional fusion protein targeting TGF-β and PD-L1. *First Author: Yulia Vugmeyster, EMD Serono, Inc., Billerica, MA*

Background: The transforming growth factor β (TGF-β) pathway plays an important role in tumor immune escape and may enhance the response to PD-L1 monoclonal antibodies (mAb). M7824 is an innovative first-in-class bifunctional fusion protein composed of a human IgG1 mAb against PD-L1 fused with 2 extracellular domains of TGF-β receptor II (a TGF-β "trap") and has shown promising antitumor activity and manageable safety in phase 1 trials, including as 2L treatment for NSCLC. **Methods:** A population PK model for M7824 was developed based on serum concentration data from 350 pts from 2 clinical trials of M7824 in multiple solid tumor types. Simulations were performed using the model to explore exposure variability for various dosing regimens. Exposure-response analysis was performed for 500 and 1200 mg biweekly (q2w) 2L NSCLC cohorts (combined) using logistic regression for the investigator-assessed overall response rate (ORR) and Kaplan-Meier analyses for progression-free survival (PFS). **Results:** Simulations of AUC and C_{min} showed that variability in exposure was slightly higher for weight-based dosing compared with flat dosing, supporting the use of a flat-dose approach for M7824. Preliminary univariate analyses relating M7824 exposure (AUC and C_{min} after a single dose) to ORR in 500 and 1200 mg 2L NSCLC cohorts did not show a conclusive relationship. However, there was a trend for pts in the lowest exposure quartile (Q1, comprised of pts in 500 mg cohort only) to have a lower ORR (10% for AUC Q1; 5% for C_{min} Q1) than those in the higher exposure quartiles (25-30% and 20-40% ORR for AUC and C_{min} Q2-Q4, respectively). Results of Kaplan-Meier analysis of PFS by exposure quartiles were in line with the exposure-ORR analyses, supporting 1200 mg q2w as the RP2D. At the C_{min} associated with the RP2D, nearly complete target occupancy for PD-L1 (PBMC) and TGF-β trapping (plasma) was achieved. Moreover, these C_{min} values were associated with 95% tumor-growth inhibition in mouse models. **Conclusions:** Based on the integrated analysis and modeling data available to date, a flat dose of 1200 mg q2w is the RP2D for M7824.

2567 Poster Session (Board #393), Mon, 8:00 AM-11:30 AM

TAK-659 in combination with NKTR-214 and anti-PD-1 therapy leads to complete and sustained tumor regression and immune memory in pre-clinical syngeneic models. *First Author: Jie Yu, Takeda Pharmaceuticals, Cambridge, MA*

Background: TAK-659 is a highly potent, reversible inhibitor of spleen tyrosine kinase (SYK) and fms related tyrosine kinase 3 (FLT3) that is being tested in combination with nivolumab in patients with advanced solid tumors (NCT02834247). NKTR-214, a CD-122-biased agonist that targets the IL-2 pathway, provides sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand NK and effector CD8+ T cells over T-regulatory cells in the tumor microenvironment, and is currently in multiple Phase I and II clinical trials in combination with checkpoint inhibitors (NCT02983045, NCT03138889). Treatment with TAK-659 in pre-clinical models resulted in a decrease in MDSCs and B220+ B-cells suggesting an immunomodulatory response, and the combination with anti-PD-1 therapy in pre-clinical *in vivo* models resulted in increased anti-tumor activity and durable complete responses. NKTR-214 monotherapy increases newly proliferative CD8+ T cells in tumors, increases cell surface PD-1 on immune cells and PD-L1 on tumor cells, and the combination with anti-PD-1 therapy shows marked efficacy in mouse syngeneic models. **Methods:** Here we explored the pre-clinical combination of TAK-659 with NKTR-214 in the presence or absence of anti-PD-1 therapy in multiple syngeneic tumor models. **Results:** TAK-659 in combination with NKTR-214 with or without anti-PD-1 therapy resulted in significant anti-tumor activity and durable complete tumor regressions. In the CT-26 murine colon cancer model, the TAK-659 + NKTR-214 or the triple combination with anti-PD-1 therapy resulted in 9 out of 10 mice having a maintained complete response (CR) 55 days post the end of treatment, versus 1 CR for TAK-659 or anti-PD-1 single agents, and none for NKTR-214 single agent. Complete responders, left untreated and re-challenged with another inoculation of tumor cells, did not form tumors, suggesting a potential immune memory. **Conclusions:** NKTR-214, TAK-659 and anti-PD-1 therapy bring together complementary non-overlapping mechanisms that create a promising potential therapy, supporting the rationale for examining the clinical combination.

2568 Poster Session (Board #394), Mon, 8:00 AM-11:30 AM

Unexpected pharmacokinetics of evofosfamide observed in phase III MAESTRO study. *First Author: Jack P. Higgins, Molecular Templates, Inc., Austin, TX*

Background: Evofosfamide (Evo) is a prodrug of Br-IPM that is preferentially activated under hypoxic conditions. Hypoxia in locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC) is associated with disease progression and poor prognosis. **Methods:** Gemcitabine (Gem) was evaluated with or without Evo in a randomized phase II (Ph 2) trial (N = 214) in US patients with advanced PDAC (NCT01144455). Two doses of Evo (240 mg/m2 or 340 mg/m2) were tested with 340 mg/m2 showing a significant improvement in ORR and PFS.MAESTRO was an international, randomized, double-blind, placebo-controlled phase III (Ph 3) trial (N = 693) of Evo + Gem versus Placebo (Pbo) + Gem in patients with locally advanced unresectable or metastatic PDAC (NCT01746979) using the same Ph2 schedule and 340 mg/m2 Evo dose. **Results:** Median OS in the Ph 3 study was 8.7 mo with Evo + Gem vs 7.6 mo with Pbo + Gem; HR = 0.84 (p = 0.059). Median PFS was 5.5 mo with Evo + Gem vs 3.7 mo with Pbo + Gem; HR = 0.77 (p = 0.004). The outcomes observed in the Ph 3 study (340 mg/m2 dose) were similar to the 240 mg/m2 dose Ph 2 outcomes (median OS = 8.7 mo; median PFS = 5.6 mo). Notably, a new ethanol-based formulation to improve drug product solubility was introduced after the Ph 2 study and before the start of the Ph 3 study. **Conclusions:** : Comparison of the Evo PK profile from the Ph 3 and Ph 2 studies suggest the formulation change may have substantially reduced Evo serum exposure (Table 1). This reduction in Evo exposure could explain why the efficacy seen in the Ph 2 study at the 340 mg/m2 dose were not replicated in the Ph 3 study. Evo is currently being tested at higher doses with the new formulation (ethanol-based) in an attempt to replicate the PK seen with the previous formulation at 340 mg/m2. Clinical trial information: NCT01746979.

Evo PK Comparison: Ph 2 (old formulation) and Ph 3 (new formulation).

	Ph 2 Evo + Gem						Ph 3 Evo + Gem		
	Evo 240 mg/m2 + Gem			Evo 340 mg/m2 + Gem			Evo 340 mg/m2 + Gem		
PK Parameters	N	Geometric Mean	Mean (SD)	N	Geometric Mean	Mean	N	Geometric Mean	Mean (SD)
C_{max} (μg/mL)	47	5.32	6.09 (3.11)	51	9.27	10.17 (4.92)	317	6.34	7.54 (5.49)
AUC (μg-h/mL)	44	5.33	5.90 (2.81)	47	8.94	9.76 (4.54)	302	6.02	6.61 (3.03)

AUC (AUCINF) = Area under the concentration-time curve from 0 to infinity; C_{max} = maximum peak observed concentration;SD = standard deviation

2569 Poster Session (Board #395), Mon, 8:00 AM-11:30 AM

An open-label, randomized cross-over bioavailability and extension study of oral paclitaxel and HM30181 compared with weekly intravenous (IV) paclitaxel in patients with advanced solid tumours. *First Author: Christopher G. C. A. Jackson, Southern District Health Board, Dunedin, New Zealand*

Background: Paclitaxel has poor oral bioavailability due to active excretion by p-glycoprotein (Pgp) on intestinal epithelial cells. An oral formulation would reduce IV access, avoid allergic reaction to cremophor, forego steroid premedication, reduce day stay, and improve convenience. With a lower Cmax, oral therapy may have toxicity advantages. Oraxol (Athenex, USA) is a combination of HM30181, a novel, orally active, potent and specific inhibitor of Pgp with low systemic exposure and oral paclitaxel. We report the results of the first scheduled interim analysis of a bio-equivalence study of Oraxol compared to IV paclitaxel, and the results of an extension study with repeat PK sampling after 4 weeks administration. **Methods:** We conducted a randomized crossover study at 3 sites in New Zealand. HM30181 15mg plus paclitaxel 205mg/m^2 was given PO on days 1-3 and compared to a single dose of IV paclitaxel (80 mg/m^2) in patients (pts) with advanced solid tumours. PK blood samples were taken d1-9 for PO paclitaxel and d1-5 for IV paclitaxel. Pts who completed were permitted to enroll on an extension study of Oraxol 205mg/m^2 d1-3 q1w with repeat PK sampling at week 4. **Results:** Paclitaxel PK was compared from the first 6 pts in the bioequivalence study, to 10 pts that were enrolled in the extension study. There was one treatment related SAE (tachycardia) which resolved. Treatment related toxicities were mostly GI and haematological, and manageable. One pt remains on study > 1 year without neuropathy. Clinical trial information: ACTRN12615000894594. **Conclusions:** Oraxol 615mg/m^2 PO d1-3 achieved paclitaxel AUC comparable to IV paclitaxel 80mg/m^2. This schedule of Oraxol is within predicted range needed to demonstrate bioequivalence. 4-week PK results show PK profile is not altered with repeated dosing. A phase 3 study in patients with metastatic breast cancer is ongoing.

	Paclitaxel 80mg/m^2 IV (n = 6) Mean (SD)	Oraxol, Baseline (n = 6) Mean (SD)	Oraxol Week 4 (n = 10) Mean (SD)
$AUC_{0-\infty}$, (hr*ng/mL)	5652 (1013)	5078 (1723)	
Cmax (ng/mL)	2269.44 (227.11)	230.99 (133.84)	238.8 (86.11)
AUC_{0-56}		2493.4 (731.96)	2615.04 (707.14)
GMR (%, 90% CI)		87.09 (74.61-101.66)	
Intra-subject CV (%)		12.62	

2570 Poster Session (Board #396), Mon, 8:00 AM-11:30 AM

Gene expression and cytokine modulation in a first in human (FIH) study of a pan BET inhibitor ABBV-075 in solid tumors. *First Author: Bert H. O'Neil, Indiana University School of Medicine, Indianapolis, IN*

Background: ABBV-075 is an oral small molecule inhibitor of the BET family of bromodomain-containing proteins that function as regulators controlling many transcriptional programs required for cancer pathogenesis. ABBV-075 is currently being evaluated in a FIH study in advanced solid tumors (M14-546). Using a 3+3 dose escalation design, a total of 72 solid tumor patients were treated across 3 dosing schedules. Dose-limiting toxicities were thrombocytopenia, fatigue, aspartate aminotransferase elevation, gastrointestinal bleed, and hypertension in the dose escalation phase. **Methods:** In this report, pharmacokinetic (PK) and pharmacodynamic (PD) data are presented for 40 subjects. PD effect was measured in surrogate tissue (whole blood and serum), which was collected prior to therapy and at various time points post-dosing. Gene expression was evaluated by branched DNA assay. Soluble cytokines were analyzed by immunoassay (Myriad RBM's InflammationMAP®). **Results:** The observed T_{max} occurred at 2-4 hours post dosing, C_{max} and AUC_{inf} increased dose-proportionally within the dose-range studies, mean $t_{1/2}$: 13 - 32 hours. Exposure (C_{max}) at day 8 correlated with decrease in platelet count on day 15 compared to baseline counts (Pearson correlation: -0.46, p = 0.032). HEXIM1 and DCXR gene expression increased, CD93 gene expression decreased at 6 hours post treatment. CD93 and DCXR demonstrated dose-dependent modulation. Statistically significant correlation was observed between gene modulation at 6 hours and drug exposure at day 8 (Pearson correlation: HEXIM1 = 0.435, CD93 = 0.375, DCXR = 0.541). Soluble BDNF expression demonstrated a dose and time-dependent decrease at cycle 2 and 3 compared to baseline ($p < 0.0001$). **Conclusions:** We demonstrated target engagement in surrogate tissue via modulation of gene and soluble cytokine expression, both of which were dose dependent. Strong correlation was observed between drug exposure and gene expression modulation as well as thrombocytopenia, after ABBV-075 treatment. Correlation of these PD effects with adverse events and clinical response, are currently under investigation. Clinical trial information: NCT02391480.

2571 Poster Session (Board #397), Mon, 8:00 AM-11:30 AM

Therapeutic drug monitoring (TDM) of tyrosine kinase inhibitors (TKI) in routine practice in an oncology service. preliminary results. *First Author: Manuel Sureda, Plataforma de Oncologia, Hospital Quironsalud Torrevieja. Catedra Oncologia Multidisciplinar-UCAM, Torrevieja, Spain*

Background: TKIs show a high pharmacokinetic variability. So, fixed dosing could result in inadequate exposure with decreased efficacy or increased toxicity. TDM allows individualized posology to improve efficacy and avoid adverse events. We report the preliminary experience with TDM of TKIs in routine clinical practice, the observed variability in exposure and subsequent dose changes. **Methods:** Patients treated with erlotinib, imatinib, lapatinib, sorafenib or pazopanib between 2010 and 2017 were included. Initial dose administered was as described in the data sheet for each drug. TDM was performed in basis of the Cmin described in the literature. Individual data were obtained from medical records and analyzed with the statistical package SPSS v.20. The study was approved by the Clinical Research Ethics Committee. Informed consent was obtained. **Results:** 61 patients were evaluable. TDM shown that 51% of patients had an initial inadequate exposure with standard doses and given the possibility of a tailored subsequent correction. Table 1 shows the average doses in first and last cycle of TDM. **Conclusions:** TDM significantly improved exposure levels of TKIs, increasing its effectiveness and safety in routine clinical practice. Further studies are warranted.

	Erlotinib		Imatinib		Lapatinib		Pazopanib		Sorafenib	
no patients	First (22)	Last (13)	First (6)	Last (4)	First (15)	Last (7)	First (8)	Last (6)	First (10)	Last (4)
Mean dose mg/day	138.6	167.3	300	450	808	678.6	636	933	440	850

2572 Poster Session (Board #398), Mon, 8:00 AM-11:30 AM

Impact of curcumin with and without (+/-) piperine on tamoxifen exposure. *First Author: Gerardus Hussaarts, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Tamoxifen is extensively used as endocrine therapy for breast cancer. It is a prodrug that is primarily metabolized by CYP2D6 and CYP3A4, particular into endoxifen. In daily practice, the herb curcumin is widely used among patients (pts) because of its presumed anti-tumor effects. Preclinical studies show effects of curcumin on phase I and II drug metabolism, leading to altered plasma levels. We hypothesized that curcumin increases endoxifen exposure by affecting phase II metabolism. Therefore, we performed a randomized, 3-phase, cross-over study to compare tamoxifen exposure in breast cancer pts +/- curcumin, and with the addition of the bioenhancer piperine. **Methods:** Pharmacokinetic sampling (PK) was performed in 15 pts at the 28^{th}, 56^{th} and 84^{th} day of the trial. In the 28 days prior to PK, tamoxifen (20 mg qd) was either given alone, or combined with curcumin (1,200 mg TID), or with curcumin + piperine (10mg TID) in this order or *vice versa*. Genotyping was performed to determine CYP2D6 and CYP3A4 phenotypes. Primary endpoint was difference in geometric means for $AUC_{0\text{-}24h}$. A linear mixed model was used to analyze log-transformed area under the curve (AUC). For multiple testing a Bonferroni correction was applied. **Results:** Tamoxifen $AUC_{0\text{-}24h}$ decreased with 7.3 % (95% CI: -0.5,-13.6%; p = .04) with curcumin and 13.0% (95% CI: -5.6,-19.9%; p = .002) with curcumin and piperine, compared to tamoxifen alone. Endoxifen $AUC_{0\text{-}24h}$ decreased with 8.9% (95% CI: -0.9,-16.3%; p = .029) and 13.5% (95% CI: -2.8,-23.0%; p = .015), respectively. *CYP2D6*-screening resulted in 6 intermediate metabolizers (IM), and 6 extensive metabolizers (EM). Interestingly, for pts with a EM phenotype, effects of curcumin with piperine on drug exposure ($AUC_{0\text{-}24h}$) seem to be higher than for IM phenotype pts (a decrease of 21.8% *vs* 4.8% for tamoxifen, and 22.6% *vs* 10.2% for endoxifen, respectively). No severe toxicity resulting from co-treatment was observed. **Conclusions:** In contrast to our hypothesis, the exposure of tamoxifen and endoxifen significantly decreased by concomitant use of curcumin +/- piperine. Although limited effects in most pts, co-treatment with these herbs could drop endoxifen levels below the threshold for efficacy, especially for EM phenotype pts. Clinical trial information: NTR6149.

2573 Poster Session (Board #399), Mon, 8:00 AM-11:30 AM

The clinical relevance of multiple DPYD polymorphisms on patients candidate for fluoropyrimidine based-chemotherapy: A case-control study in a Northern Italy Cancer Centre. *First Author: Francesco Iachetta, Medical Oncology Unit, Clinical Cancer Center, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy*

Background: Deleterious polymorphisms in gene-encoding DPD (DPYD) may result in the severe reduction of DPD enzymatic activity that causes life-threatening toxicities when the standard dose of fluorouracil is used. DPYD*2A (IVS14+1G > A) is the most common single-nucleotide polymorphism (SNP) associated with critical DPD deficiency. To enhance prevention of fluoropyrimidine toxicity, we assessed the potential clinical impact of additional DPYD polymorphisms. **Methods:** In 2011, we began screening DPYD*2A in patients candidate for fluoropyrimidine based-chemotherapy. We planned a case-control study with all cases of DPYD*2A wild type who developed CTC-NCI-V.3 toxicity ≥ G3 and with a cohort of patients who did not present severe toxicities (ratio 1:1.5). The two groups were matched for tumour site, staging (I-III vs IV) and patient's age. Then we tested the additional SNPs (c.2846A > T, c.1679T > G, c.2194G > A) using Real Time PCR. **Results:** From 2011 to 2016 we screened 1,827 patients for DPD deficiency, of those 31 subjects (1.7%) showed DPYD*2A SNP. Complete clinical information was available only for 668 patients and of those, 146 (21.9%) developed severe toxicities (Case group). A control group was instead established with 220 patients who experienced no or mild toxicities. Fifty-three patients carried a variant in one of the additional SNPs: 35 subjects (66%) fell into the Case group and 18 (34%) into the Control group (OR 3.53, 95% IC 1.91-6.53. p < 0.0001). c.2194G > A was the most frequent SNP (12.5%, 46 of 366 pts) and showed a correlation with hematologic toxicity. In particular, neutropenia was observed in 50% of the patients carrying c.2194G > A (23 out of 46) vs 21% of patients c.2194 WT (67 out of 320) (OR = 3.75 95%IC 1.98-7.10; p < 0001). We confirmed that c.2826A > T (1.37%, 5 of 366 pts) was related to various toxicity (p = 0.0097) and c.1679T > G (0.55%, 2 of 366 pts) showed only gastrointestinal toxicity (p = 0.0027). **Conclusions:** Our data suggested that additional DPYD polymorphisms could enhance prevention of fluoropyrimidine toxicity. c.2194G > A is the most frequent polymorphism and it resulted associated with neutropenia.

2574 Poster Session (Board #400), Mon, 8:00 AM-11:30 AM

Clinical pharmacology assessment of PF-06647020 (PF-7020), an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in adult patients (pts) with advanced solid tumors. *First Author: Dawei Xuan, Pfizer Early Oncology Development & Clinical Research, La Jolla, CA*

Background: PF-7020, an ADC composed of humanized monoclonal antibody (Ab) against PTK7, auristatin payload, and valine-citrulline linker, is being investigated in the ongoing first in human Phase 1 study in pts with advanced solid tumors resistant to standard therapy. We present preliminary results of clinical pharmacology assessments of PF-7020, including pharmacokinetic (PK) analyses, and exploratory exposure-response analyses for efficacy and safety endpoints. **Methods:** Non-compartmental PK analyses were conducted on data from dose escalation and expansion studies of once every 3 weeks dosing (Q3W). A semi-mechanistic model that integrates ADC, total Ab (TAb), and unconjugated payload (PL) was built to characterize PK. We explored the relationship between objective response rate (ORR, current 27%) in ovarian cancer pts (OVCA) and PF-7020 exposure ($C_{min,C1D21}$) with logistic regression modeling. A semi-mechanistic PK-pharmacodynamic (PD) model was built to explore the relationship between PL concentrations and absolute neutrophil counts (ANC). **Results:** As of Oct 24, 2017, 112 pts were treated with PF-7020 at doses of 0.2 – 3.7 mg/kg Q3W. PK exposure increased in a dose related manner, with a terminal half-life for PF-7020 of approximately 3 days at 2.8 mg/kg. Integrated PK model suggests that deconjugation and proteolytic degradation of ADC played major roles in elimination of PF-7020, and PL formation. A significant correlation was identified between ADC $C_{min,C1D21}$ and OVCA ORR based on univariate analysis ($P < 0.05$); ORR increased with higher $C_{min,C1D21}$, suggesting pts with lower exposures may benefit from increase in dose/dosing intensity. PK/PD analysis suggests higher PL concentrations were associated with lower ANC. **Conclusions:** The PK exposure increased in a dose related manner, with a terminal half-life for PF-7020 of approximately 3 days at 2.8 mg/kg. Increase in PK exposure correlated with better clinical response in OVCA pts. The PL exposure appeared to correlate with ANC profiles. The preliminary PK/PD analyses support evaluating PF-07020 under once every 2 weeks dosing (Q2W) in the ongoing study.

2575 Poster Session (Board #401), Mon, 8:00 AM-11:30 AM

The NantOmics Pharmacogenomics Test: An integrative panomic approach to pharmacogenomics screening. *First Author: Camille Schwartz, NantOmics, Santa Cruz, CA*

Background: Numerous oncology drugs have pharmacogenomics warnings on their FDA labels, yet pharmacogenomics screening is not routinely applied in clinical practice. Pharmacogenomics testing is used to reduce the chance of drug-induced toxicities, improve patient outcomes, and reduce treatment costs by tailoring therapies to the patient's genotype. Here we present the NantOmics Pharmacogenomics test, which screens for pharmacogenomics variants related to 19 gene-drug pairs with CPIC guidelines and FDA label indications. **Methods:** Pharmacogenomics screening was performed on whole genome and whole exome sequencing data of FFPE tumors and matched normals from 1,879 oncology patients. Patients were screened using a panel of 31 germline markers in 11 genes linked to toxicities from 14 cancer therapies. The test has been validated on 10 cell lines from the CDC GeT-RM, on a set of synthetic data, as well as on a cohort of patients previously genotyped by an independent CLIA-validated PCR-based panel. **Results:** Of the 1879 patients screened, 96.4% contained a variant with a pharmacogenomics recommendation. Furthermore, 6.8% of patients had genomic variants associated with severe or life-threatening drug toxicities. For all alleles in our clinical panel, we observed similar allele frequencies to those reported in the ExAC database. In all validation studies, we were able to demonstrate that the test detects each variant in our panel, and correctly determines patient genotype in all studied cases. **Conclusions:** The NantOmics pharmacogenomics test is able to accurately detect pharmacogenomic variants in oncology patients. Observed allele frequencies correspond well to known population frequencies, and validation studies demonstrated that the test detects each variant in our panel, and correctly determines patient genotype in all studied cases. Given the high percentage of patients with potentially treatment-altering genomic variants, these results underscore the need for more routine pharmacogenomics screening in the oncological setting.

2576 Poster Session (Board #402), Mon, 8:00 AM-11:30 AM

Dihydropyrimidine dehydrogenase gene (*DPYD*) polymorphism among pts with 5-FU/capecitabine (CAP)-related adverse events (AEs): Experience of 2 decades. *First Author: Nauman S Siddiqui, Tufts Medical Center, Boston, MA*

Background: *DPYD* gene encodes *DPD*, the rate-limiting enzyme responsible for catabolism of 5-FU and is responsible for > 85% of 5-FU elimination. Deficiency of *DPD* due to *DPYD* polymorphism gives rise to severe 5-FU AEs from reduced catabolism. This pharmacogenetic '*DPD syndrome*' manifests typically as severe or fatal diarrhea, mucositis/stomatitis, myelosuppression and even rare toxicities, such as hepatitis, encephalopathy and acute cardiac ischemia following first or second dose of 5-FU. The most compelling reason to introduce routine *DPD* testing is to avoid severe AEs in pts who receive 5-FU/CAP. *DPYD* mutations are found in 50% of severe 5-FU toxicity cases. **Methods:** We analyzed all pts who were tested for *DPD* deficiency after excessive toxicities from 5-FU/CAP, treated for GI cancers. *DPD* activity was evaluated by PBMC radioassay, genotyping of *DPYD*, or 2-^{13}C uracil breath test after an informed consent. Demographics of pts, grades of toxicity, chemotherapy (dose, route) and outcomes were analyzed. **Results:** A total of 52 pts with *DPD* deficiency were identified [age range: 35 - 79 yrs; M:F = 1.3:1; Ethnicities: Caucasian (≥ 60%), African-American, unknown, Asian]. Most commonly used regimens in decreasing order were infusion 5-FU, CAP and bolus. Excessive AEs included mucositis (70%), diarrhea (40%), cytopenias (40%), nausea/vomiting (30%), HFS or skin rashes (20%), neurotoxicity (12%) and cardiotoxicity (5%). 11/12 pts had low *DPD* activity (range:0.064 – 0.18nmol/min/mg). *DPYD* genotyping showed: IVS14 + 1 G > A (c.1905+1 G > A, rs3918290) 38%, D949V (c.2846A > T, rs67376798) 21%, C29R (rs1801265) 4%, and Y186C (rs115232898, c.557 A > G) 2%. UraBT confirmed *DPD* deficiency in 2 pts: DOB_{50} of 49.4% and 52.5%. Re-challenge with CAP in 5 pts resulted in atypical or similar AE. 6 pts received vistogard; 5 recovered. 3 pts died due to AEs. **Conclusions:** *DPYD genotyping* (+ *TYMS*) may identify ≥ 50% of pts, who are at greatest risk of AEs. At present, no formal recommendations regarding testing for *DPYD* exist except warning on FDA website and prescription inserts. Our data mandates the need for prospective studies to develop guidelines in pts receiving 5-FU/CAP.

2577 Poster Session (Board #403), Mon, 8:00 AM-11:30 AM

Pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced solid tumors from a phase 1 study. *First Author: Bin Fan, Agios Pharmaceuticals, Inc., Cambridge, MA*

Background: Mutant isocitrate dehydrogenase 1 (mIDH1) produces the oncometabolite D-2-hydroxyglutarate (2-HG). Ivosidenib (IVO; AG-120) is a targeted mIDH1 inhibitor under evaluation in an ongoing phase 1 study (NCT02073994) in mIDH1 advanced solid tumors including cholangiocarcinoma (CC), chondrosarcoma (CS), and glioma. We explored the PK profile of IVO, the relationship between IVO exposure and 2-HG inhibition, and the effect of intrinsic/extrinsic patient factors on IVO exposure. **Methods:** IVO was administered orally once (QD) or twice (BID) daily in continuous 28-day cycles. As of May 12, 2017, 168 patients (pts) had received IVO 100 mg BID to 1200 mg QD in dose escalation (8 dose levels, n = 60) and 500 mg QD in expansion (n = 108). IVO was assessed in plasma and 2-HG in plasma and tumor biopsies using LC-MS/MS assays. **Results:** After single and multiple doses, IVO showed good oral exposure, was rapidly absorbed, and plasma levels declined bi-exponentially after peaking, with a mean terminal half-life of 40–102 h after a single dose. IVO exposure and half-life were lower in pts with glioma than with CC/CS. IVO exposure increased less than dose proportionally. Steady state (SS) was reached within 14 days, with moderate accumulation (1.5- to 1.7-fold for AUC at 500 mg QD) across all tumors. No intrinsic patient factors were identified that affected IVO exposure. Mild/moderate renal impairment, mild hepatic impairment, and concomitant administration of weak CYP3A4 inhibitors/inducers had no effect on IVO clearance at SS. After multiple doses in pts with CC/CS, plasma 2-HG was reduced by up to 98% to levels seen in healthy subjects. Maximal plasma 2-HG reduction occurred at 500 mg QD in most pts, with no additional inhibition at higher doses. Tumor 2-HG showed a substantial reduction and positive correlation with plasma 2-HG. There was no significant pretreatment elevation of plasma 2-HG in glioma pts. **Conclusions:** IVO demonstrated good oral exposure and a long half-life, enabling oral QD dosing, and robust, persistent 2-HG inhibition in pts with mIDH1 CC/CS. IVO 500 mg QD is appropriate for these pts irrespective of intrinsic patient factors or concomitant weak CYP3A4 inhibitors/inducers. Clinical trial information: NCT02073994.

2578 Poster Session (Board #404), Mon, 8:00 AM-11:30 AM

A multicenter study of the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib plus durvalumab in patients with relapsed/refractory (R/R) solid tumors. *First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ibrutinib (ibr), a first-in-class, once-daily inhibitor of BTK, is approved in the US for the treatment of various B-cell malignancies. In solid tumors, ibr may inhibit EGFR, HER2, mast cell function, and alter Th1/Th2 polarity. Preclinical data suggest benefit with PD-L1 inhibitors for pancreatic adenocarcinoma (PC), non–small cell lung cancer (NSCLC), HER2+ breast cancer (BC), and triple neg BC (TNBC). These mechanisms may act synergistically. This study assessed the safety and efficacy of ibr plus durvalumab, a PD-L1–targeting antibody, in patients (pts) with R/R solid tumors. **Methods:** This open-label, multicenter, ph 1b/2 trial enrolled pts with R/R stage III/IV PC, BC (HER2+, TNBC), or NSCLC (adenocarcinoma, squamous). Pts must have failed ≥1 (PC, NSCLC) or ≥2 (BC) prior systemic therapy lines. Ph 1b (6+3 dose de-escalation design) determined the recommended ph 2 dose (RP2D). PD-L1 expression was assessed retrospectively. **Results:** In ph 1b, 560 mg ibr PO daily and 10 mg/kg durvalumab IV every 2 wk was identified as the RP2D. Of 124 pts enrolled, 122 pts were treated at the RP2D (PC n = 49; BC n = 45; NSCLC n = 28). Median age was 60.5 y; 94% had stage IV disease; median prior radiation/cancer therapies was 4 (range: 1–20); 5 NSCLC pts, but no PC or BC pts, had tumors with high PD-L1 expression. Response rates in evaluable pts were 3% for BC (1 complete response in a TNBC pt; duration of response [DOR]: 23 mo), 2% for PC (1 partial response; DOR: 10 mo), and 0% for NSCLC. Median progression-free survival was 2 mo in each cohort; median overall survival was 4, 4, and 8 mo in the PC, BC, and NSCLC cohorts, respectively. No clinically meaningful differences in the safety profile were observed across tumor types, except differences due to tumor type, location, and prior therapies. Gr ≥3 treatment-emergent adverse events in ≥5% of pts were hyponatremia (10%), dyspnea (7%), maculopapular rash (7%), pneumonia (7%), anemia (6%), and diarrhea (6%). **Conclusions:** The combination of 560 mg ibr daily and 10 mg/kg durvalumab every 2 wk had an acceptable safety profile, but limited activity in the solid tumors studied, which may be due in part to heavy pretreatment and low PD-L1 expression. Clinical trial information: NCT02401048.

2579 Poster Session (Board #405), Mon, 8:00 AM-11:30 AM

A phase 1b dose-escalation study of prexasertib, a checkpoint kinase 1 (CHK1) inhibitor, in combination with cisplatin in patients with advanced cancer. *First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL*

Background: CHK1 is a key kinase for DNA replication and repair. Prexasertib, a CHK1 inhibitor, enhanced the nonclinical activity of cisplatin and is predicted to potentiate the clinical activity of DNA-damaging agents like cisplatin. **Methods:** This Phase 1b study in patients (pts) with advanced cancer assessed escalating doses of prexasertib with 75 mg/m^2 cisplatin by IV infusion every 21 days, and had 3 parts: Part A, prexasertib (20 - 70 mg/m^2)/cisplatin given on Day 1; Part A2, prexasertib (40 - 105 mg/m^2)/cisplatin on Day 1 with prophylactic G-CSF starting on Day 2; Part A3, cisplatin on Day 1 and prexasertib (40 - 90 mg/m^2) on Day 2. Safety, dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), preliminary efficacy, and prexasertib pharmacokinetics (PK) are reported. **Results:** 57 pts were enrolled (Part A: n = 14; A2: n = 24; A3: n = 19). Study treatment-related common adverse events (AEs) were leukopenia/neutropenia (68%; G4 49%), thrombocytopenia (63%; G4 33%), anemia (46%), nausea (44%), fatigue (32%), and vomiting (23%). 4 pts (7%) experienced febrile neutropenia (2 each in Parts A and A2). The nature of AEs was comparable between Parts. All DLTs were either febrile neutropenia or neutropenia > 5 days. The MTD for Parts A, A2, and A3 were 40, 90, and 80 mg/m^2, respectively. The prexasertib PK profile was consistent with the prexasertib monotherapy PK profile across all doses/schedules. In Part A, 3 pts (21%) achieved a partial response (PR: anal squamous cell carcinoma [SCC]; HNSCC; small cell lung cancer [SCLC]), and 2 pts (14%) had stable disease (SD). In Part A2, 12 pts (50%) had SD but no PR/CR. In Part A3, 1 pt (5%) achieved a CR (cholangiocarcinoma) and 2 pts (11%) achieved a PR (SCLC; follicular dendritic cell sarcoma) for a CR/PR rate of 16%; 7 pts (37%) had SD. Of the 6 pts with a CR/PR, 3 pts (at prexasertib doses: 45-90 mg/m^2) had previously received prior platinum. None had an objective response to the prior platinum. **Conclusions:** Prexasertib and cisplatin demonstrated acceptable safety and PK and preliminary evidence of anticancer activity. A dose of 80 mg/m^2 prexasertib given 24 h after cisplatin was selected for further study in the ongoing dose expansion. Clinical trial information: NCT02124148.

2580 Poster Session (Board #406), Mon, 8:00 AM-11:30 AM

Vorolanib (CM082) in Chinese patients with advanced solid tumor: A phase 1, open-label, dose escalation study. *First Author: Yan Song, National Cancer Center/Cancer Hospital,Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Vorolanib (CM082) is a potent and selective inhibitor of VEGFR and PDGFR, which is well tolerated from 20 to 400 mg without G3/4 treatment-related AEs (TRAEs) in patients in US. Here we present a phase I dose escalation study that assessed vorolanib in Chinese patients with advanced solid tumor. **Methods:** Patients with advanced solid tumors were enrolled to receive escalating dose of vorolanib once daily from 50 mg to 300 mg following the 3+3 design. Primary endpoints included evaluation of safety, pharmacokinetics, and maximum-tolerated dose (MTD) determination. **Results:** 19 patients were enrolled and treated, including 12 RCC. Most patients (n = 18) have received at least one prior systemic treatments, in which 10 have been treated with VEGFR TKIs. No DLT was seen, the MTD was not achieved. The most common TRAEs were leukopenia (9/19), fatigue (9/19), diarrhea (8/19), neutropenia (8/19), and hypertension (8/19). G3 or higher events were seen in 7 patients across 100 to 250 mg dose cohort. PK analysis was shown in table 1. Partial response was seen in 1 RCC patients in the 200 mg cohort, and 11 stable disease were seen in all dose cohorts. **Conclusions:** Vorolanib has an acceptable safety profile and showed preliminary activities in RCC. An expansion of RCC-enriched cohort is ongoing. Clinical trial information: NCT01863485.

PK parameters.

		50 mg (n = 4)	100 mg (n = 3)	150 mg (n = 3)	200 mg (n = 3)	250 mg (n = 4)
Single dose						
t1/2	hr	3.95 ± 0.56	8.01 ± 1.67	5.78 ± 0.53	5.25 ± 0.40	6.20 ± 1.82
Tmax	hr	4.00	2.33 ± 0.58	2.67 ± 0.58	3.67 ± 0.58	2.75 ± 0.96
Cmax	ng/mL	239.82 ± 39.24	566.86 ± 253.54	727.75 ± 133.36	857.22 ± 94.49	1003.79 ± 92.73
AUC(0-48 h)	hr*ng/mL	1973.24 ± 435.85	5501.26 ± 2972.74	6327.04 ± 654.03	7689.95 ± 1684.58	8435.56 ± 1515.97
AUC (0-inf)	hr*ng/mL	1981.85 ± 437.81	5586.84 ± 3011.58	6352.55 ± 669.81	7706.55 ± 1688.32	8481.12 ± 1539.81
Multiple doses						
t1/2	hr	4.28 ± 0.75	5.03 ± 1.69	6.25 ± 0.81	4.83 ± 0.14	4.46 ± 0.78
Tmax	hr	4.00 ± 1.63	2.33 ± 0.58	3.00 ± 1.00	3.00 ± 1.00	2.75 ± 0.05
Cmax	ng/mL	254.19 ± 94.23	649.98 ± 147.51	923.83 ± 208.44	811.55 ± 266.45	959.62 ± 431.12
AUC (0-24 h)	hr*ng/mL	2168.81 ± 874.37	5910.91 ± 1909.47	9224.53 ± 3153.11	6579.73 ± 2264.7	6968.75 ± 3265.82
AUC (0-inf)	hr*ng/mL	2235.38 ± 883.95	6283.97 ± 2337.41	10068.74 ± 3487.21	6823.74 ± 2345.54	7221.1 ± 3439.7

2581 Poster Session (Board #407), Mon, 8:00 AM-11:30 AM

Clinical pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced hematologic malignancies from a phase 1 study. *First Author: David Dai, Agios Pharmaceuticals, Inc., Cambridge, MA*

Background: Mutant isocitrate dehydrogenase 1 (mIDH1) produces the oncometabolite D-2-hydroxyglutarate (2-HG). Ivosidenib (IVO) is a selective mIDH1 inhibitor under evaluation in patients with mIDH1 hematologic malignancies. This translational analysis explored the PK profile of IVO, the relationship between IVO exposure and 2-HG suppression, and the impact of intrinsic/extrinsic patient factors on IVO exposure from the phase 1 monotherapy study (NCT02074839). **Methods:** IVO was administered orally once (QD) or twice (BID) daily in continuous 28-day cycles. As of May 12, 2017, 258 patients had received IVO at doses ranging from 100 mg BID to 1200 mg QD in dose escalation (n = 78) and at 500 mg QD (n = 180) in dose expansion. IVO levels were assessed in plasma and 2-HG levels in plasma/bone marrow using LC-MS/MS methods. **Results:** After single and multiple doses, IVO was readily absorbed (median T_{max} 3 h). After peaking, IVO concentrations declined in a bi-exponential manner, with a mean terminal half-life of 72–138 h after a single dose. Dose-exposure nonlinearity of IVO from 300 to 1200 mg QD suggests doubling of the dose would result in a ~30% increase in AUC. Steady state (SS) was reached within 14 days. Moderate accumulation was observed after 500 mg QD, with mean AUC and C_{max} accumulation ratios of 1.9- and 1.46-fold. IVO clearance was not altered by intrinsic patient factors. Concomitant administration of weak CYP3A4 inhibitors/inducers did not affect IVO clearance, though moderate/strong CYP3A4 inhibitors decreased IVO clearance and increased IVO SS exposure ($AUC_{0\text{-}24hr}$ by ~56%; C_{max} by ~47%). Plasma 2-HG reduction reached a plateau within 14 days of dosing after multiple doses of 500 mg QD, and was reduced by ≥90% over the range of IVO SS AUC in patients with newly diagnosed and relapsed/refractory AML, regardless of IDH1-R132 mutation type. **Conclusions:** IVO demonstrated a long half-life suitable for QD dosing, moderate accumulation, and robust 2-HG inhibition in patients with mIDH1 myeloid malignancies. Intrinsic/extrinsic patient factors, including concomitant moderate/strong CYP3A4 inhibitors, did not significantly alter IVO exposure. Clinical trial information: NCT02074839.

2582 Poster Session (Board #408), Mon, 8:00 AM-11:30 AM

BAX-BAK heterodimer as a pharmacodynamic biomarker of on-target drug action of Mcl-1 inhibitors to evaluate in-vivo effectiveness. *First Author: Apurva K. Srivastava, Clinical Pharmacodynamics Biomarker Program, Frederick National Laboratories for Cancer Research, Frederick, MD*

Background: Clinical development of promising small molecule Mcl-1 inhibitors is underway. The Mcl-1 inhibitors act by disrupting complexes of Mcl-1 with pro-apoptotic proteins such as BAK/BIM/Noxa, leading to formation of oligomers of BAK and BAX at the mitochondrial membrane and activation of an apoptosis cascade. Therefore, measurement of BAX-BAK heterodimers on the mitochondrial membrane is considered an on-target pharmacodynamic (PD) biomarker for this class of drugs. We describe use of the BAX-BAK assay to screen and prioritize small molecule Mcl-1 inhibitors (Taekyu et al, FEBS Let 2017) for on-target activity and in vivo potency in relevant cancer models. **Methods:** The BAX-BAK heterodimer immunoassay was developed on the Luminex platform using monoclonal antibodies specific to active BAX and BAK proteins. Single-dose PD and PK of each Mcl-1 inhibitor was evaluated at 100-mg/kg (IP) in nude mice bearing AMO-1 (myeloma) or NCI-H929 xenografts. Tumors quadrants were collected at 4, 8, 12, 18 and 24 hours after dosing, mitochondrial (mito.) fractions prepared, and biomarkers measured as described previously (Srivastava et al, Clin Can Res 2016). **Results:** The sandwich oassay provided a reliable, quantitative measurement of BAX-BAK levels in mito. fractions from both in-vitro (AMO-1, MOLP-8, MOLT-4, NCI-H929) and in-vivo xenograft (AMO-1, NCI-H929) models. The PD study showed a wide range of BAX-BAK activation, with the most potent compounds causing a 10-20 fold increase in peak BAX-BAK levels between 4-18 hours after dosing. Compounds that produced the highest levels of BAX-BAK also produced the highest cleaved caspase-3 levels and were associated with the highest tumor drug concentrations. The PD biomarker strategy, in conjunction with PK, prioritized select compounds for further development. **Conclusions:** We describe the application of a BAX-BAK heterodimer assay to effectively identify potent Mcl-1 inhibitors with early proof of on-target activity in tumor tissue. The PD biomarker could provide a benchmark assay to compare and contrast potency and mechanism-of-action of Mcl-1 inhibitors in clinical studies. Funded by NCI Contract No HHSN261200800001E.

2583 Poster Session (Board #409), Mon, 8:00 AM-11:30 AM

Phase 1/2 precision medicine study of the next-generation BRAF inhibitor PLX8394. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: First-generation BRAF inhibitors (BRAFi) show high response rates and prolonged survival in some *$BRAF^{V600}$*-mutant cancers; however, paradoxical activation of the RAF/MEK/ERK pathway promotes resistance and development of skin malignancies. PLX8394 is a next-generation, orally available small-molecule BRAFi that does not induce the RAF/MEK/ERK paradoxical activation and blocks signaling from both monomeric $BRAF^{V600}$ and dimeric $BRAF^{non\text{-}V600}$ protein. **Methods:** This is a phase 1/2 study of PLX8394 and cobicistat (cstat,150mg), a CYP3A4 inhibitor used to enhance PLX8394 exposure, to determine the safety, tolerability in subjects with refractory solid tumors (phase 1) and RECIST response rate in $BRAF^{V600}$ and dimer-dependent, RAS-independent $BRAF^{non\text{-}V600}$ mutant patients (phase 2). A hot-melt extrusion (HME) formulation of PLX8394 was used for this study. Results are reported as of January 8, 2018. Results: Phase 1: The RP2D was 900mg BID + cstat (Proc AACR-NCI-EORTC 2017, abst B176). A single DLT of reversible grade (G) 3 transaminitis occurred in a subject treated with PLX8394 900mg BID + cstat. Cstat co-administration resulted in a 2-3-fold increase in PLX8394 systemic exposure. Of 13 evaluable $BRAF^{V600}$-mutated subjects, 3 (23%) achieved partial responses [colorectal cancer (42%), glioma (65%); both BRAFi naïve, and ovarian cancer (62%) previously treated with 3 lines of BRAF/MEKi]. Phase 2: Of 18 patients enrolled, 13 had $BRAF^{V600}$ mutation [melanoma (n = 5), colorectal (n = 4), glioblastoma (n = 2), thyroid (n = 2)] and 5 $BRAF^{non\text{-}V600}$ mutation [pancreatic (n = 2), and prostate, thyroid, and colorectal (each n = 1)]. No prior MAPK pathway inhibitors were permitted for non-melanoma subjects. G≥3 AEs included G3 transaminitis and hyperbilirubinemia in one patient. Of 10 evaluable patients, 3 (30%, all with $BRAF^{V600}$ mutations) had stable disease (+7%, -10%, -14%, respectively). Efficacy and exploratory biomarker analysis including transcriptome and ctDNA analysis is on-going. **Conclusions:** PLX8394 + cstat has been well tolerated and shows promising activity in refractory solid tumors with BRAF mutations. This work was sponsored by Plexxikon Inc. Clinical trial information: NCT02428712.

2584 Poster Session (Board #410), Mon, 8:00 AM-11:30 AM

Precision oncology: Results of a phase I study of M2698, a p70S6K/AKT targeted agent in patients with advanced cancer and tumor PI3K/AKT/mTOR (PAM) pathway abnormalities. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: M2698 is a potent and selective dual inhibitor of p70S6K and AKT1/3 in the PAM pathway. M2698 has the advantages of being an oral, brain penetrant, PAM pathway inhibitor, which can mitigate the effects of the AKT feedback loop, a potential escape mechanism in tumors resistant to standard therapies. **Methods:** Patients (pts) with advanced cancer received once-daily oral M2698 (15–380 mg; 9 dose levels) in 21-day cycles. The 3+3 dose escalation [DE] design was followed by an expansion phase (240 mg/day) in a pt population enriched with tumors that have PAM molecular alterations (PAM+). PAM+ profiles, potential resistance markers (RM), including *EGFR*, *KRAS* and *Akt2*, safety and efficacy were investigated (cut-off Nov 2017). **Results:** From 12/2013 to 3/2017, of 66 pts screened, 50 received M2698 (DE [n = 40] and expansion [n = 10]); 18 men, 32 women, 78% were < 65 years old. Of these 50 pts, 44 were PAM+ (37 without RM, 7 with RM). M2698 was well tolerated. Adverse events were transient. The maximum tolerated dose was not reached at the maximum dose tested. Efficacy outcomes are shown in the table. In addition, 5 pts in the PAM+ without RM subgroup had tumor control > 6 months (mo; range, 6.9–15.2 mo), whereas no pts in the PAM+ with RM subgroup had such prolonged tumor control. Clinical trial information: NCT01971515. PFS, progression free survival; SD, stable disease. **Conclusions:** M2698 was well tolerated. PAM+ pts without RM were more likely to have sustained tumor control. Molecular characterization of tumor resistance signals may help identify patients who are likely to benefit from M2698.

	All pts (n = 50)	PAM+ pts (n = 44)	PAM+ pts with RM (n = 7)	PAM+ pts without RM (n = 37)
Best overall response, SD, n (%)	20 (40)	18 (41)	1 (14)	17 (46)
SD at week 12, n (%)	16 (32)	14 (32)	1 (14)	13 (35)
Median PFS, mo [95% CI]	2.4 [1.4, 3.7]	2.8 [1.4, 4.1]	1.4 [1.3, -]	2.8 [1.8, 4.1]
Median time on treatment, mo (range)	1.9 (0.2, 16.6)	2.1 (0.2, 16.6)	1.4 (0.8, 3.0)	2.3 (0.2, 16.6)

2585 Poster Session (Board #411), Mon, 8:00 AM-11:30 AM

A phase 1 study of NOX66 in combination with carboplatin in patients with end stage solid tumours. *First Author: Paul L. de Souza, University of Western Sydney School of Medicine, Liverpool, Australia*

Background: NOX66 is under development as an enhancer of chemotherapy and radiotherapy across multiple tumour types. The primary mechanism of action of idronoxil (the active ingredient of NOX66) stems from its selective binding to ENOX2 - a tumour-specific NADH oxidase - inhibiting Sphingosine kinase activity within tumour cells and leading to inhibition of the PI3K/Akt pathway and induction of apoptosis. Here we report the results of the first-in-human study of NOX66 as monotherapy and in combination with carboplatin (carbo). **Methods:** 19 patients with metastatic end stage solid tumours were recruited to one of two dose cohorts, NOX66 400mg, and 800mg respectively. Following a monotherapy run in period (NOX66 administered PR, Day 1-14 followed by a 7 day break) patients received 6 cycles of combination therapy - NOX66 administered on Day 1-7 and intravenous carbo on Day 2 of a 28-day schedule. Carbo was administered at AUC4 for 3 cycles, followed by AUC6 for 3 cycles. Recruitment is complete, with last patient last visit scheduled for May 2018. **Results:** 16 patients have completed study treatment. Radiologic assessment of disease state is shown in the table below (Progressive Disease – PD; Stable Disease – SD; Partial Response – PR). 4 SAEs (including 3 deaths) were reported, none were considered related to NOX66. One Adverse Event (Grade 2 anaemia, NOX66 800mg + carbo AUC4) considered possibly related to NOX66 has been reported. **Conclusions:** NOX66 is well tolerated as a monotherapy and in combination with carboplatin at AUC = 4 or AUC = 6. Efficacy signals from this study warrant further investigation of NOX66 as a chemo-sensitizing agent. Clinical trial information: NCT02941523.

NOX66 Dose	400mg	800mg
Enrolled	8	11
Completed 3 cycles carbo (AUC4)	8	10
Evaluable	4 (All SD)	9 (1PR; 7SD; 1PD)
Completed 6 cycles carbo (AUC4; AUC6)	6	5
Evaluable	2 (1SD; 1PD)	3 (2SD; 1PD)
Ongoing	0	3

2586 Poster Session (Board #412), Mon, 8:00 AM-11:30 AM

A phase I study of LXH254 in patients (pts) with advanced solid tumors harboring MAPK pathway alterations. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: CRAF is a key mediator of oncogenic mitogen-activated protein kinase (MAPK) pathway reactivation following MEK or BRAF inhibition. LXH254 is a BRAF and CRAF inhibitor with antitumor activity in MAPK-driven tumor models. This Phase I dose-finding study of LXH254 in pts with advanced solid tumors harboring MAPK pathway alterations is evaluating safety/tolerability and preliminary antitumor activity (NCT02607813). **Methods:** Primary objective: characterize the safety/tolerability of single-agent LXH254 and identify a recommended dose (RD)/schedule for future study. Secondary objectives: characterize antitumor activity (per RECIST 1.1) and PK. Dose escalation was guided by a Bayesian model-based approach. Eligible pts had advanced, pretreated solid tumors with MAPK pathway alterations. **Results:** At data cut-off 4 Dec 2017, 75 pts were enrolled in 9 dose cohorts: 100 (n = 4), 200 (n = 4), 300 (n = 5), 400 (n = 6), 800 (n = 12), 1200 mg QD (n = 12), and 200 (n = 7), 400 (n = 12), 600 mg BID (n = 13). Pts (ECOG PS 0/1, 41% male, median age 57 yrs) had lung (n = 16), colorectal (n = 14), ovarian (n = 12), melanoma (n = 12), or other (n = 21) cancers. Median duration of exposure was 7.7 wks; 59/75 (79%) pts discontinued treatment, due to disease progression (49 pts [65%]), physician/pt decision (5 pts [7%]), death (3 pts [4%]), or AE (2 pts [3%]). Three DLTs were reported: platelet count decrease (Gr 4, 1 pt 1200 mg QD), pruritus and maculopapular rash (both Gr 3, 1 pt 600 mg BID). The most common (> 15%) drug-related, any-Gr AEs were rash (dermatitis acneiform/rash/maculopapular rash, 53%), fatigue (20%), and nausea (20%). Gr ≥3 drug-related AEs occurred in 16% of pts, most frequently rash, myalgia, and increased lipase (2 [3%] pts each). Plasma peak drug concentration (C_{max}) and exposure (AUC) after QD/BID oral doses increased approximately dose-proportionally. There were two confirmed partial responses (with > 50% tumor size reduction) in pts with *KRAS*-mut and *BRAF*-mut cancers; stable disease was reported in 25/75 (33%) pts. **Conclusions:** Oral LXH254 was well tolerated, all AEs were manageable, and preliminary antitumor activity was observed. The study is ongoing to establish a RD/schedule, and further establish antitumor activity. Clinical trial information: NCT02607813.

2587 Poster Session (Board #413), Mon, 8:00 AM-11:30 AM

Safety, tolerability, and antitumor activity of once-daily Wee-1 inhibitor AZD1775. *First Author: Naoko Takebe, NCI/ NIH, Elkridge, MD*

Background: Wee1 tyrosine kinase promotes G2 cell cycle arrest following DNA damage via inactivating phosphorylation of cyclin-dependent kinase 1. We are conducting a phase I study of the oral Wee1 inhibitor AZD1775 in patients (pts) with advanced solid tumors, examining twice daily (Arm A) and once daily (Arm B) schedules. Results for Arm A have been reported previously, and partial responses (PR) were observed in 2 pts with *BRCA* mutations. Here, we present results for Arm B. **Methods:** AZD1775 was given orally once daily (QD) for 5 days during weeks 1 and 2 of a 21-day cycle (Arm B) or twice daily (BID) for 5 doses during weeks 1 and 2 (Arm A). Primary objectives were to determine safety, tolerability, and pharmacokinetics (PK). Secondary objectives were to assess pharmacodynamic (PD) biomarkers of DNA damage in tumor tissue and circulating tumor cells and evaluation of antitumor activity. Dose-limiting toxicity was evaluated during cycle 1, and response was defined by CT using RECIST 1.1. **Results:** Thirty-four pts have enrolled on Arm B; of the 28 assessable for response, 4 (14%) had a PR (3 ovarian, 1 endometrial) and 18 (64%) experienced stable disease (mean: 7.22 cycles). Of the 9 Arm B pts with confirmed *BRCA* mutations, 2 had a PR (22%; ovarian) and 6 had SD (67%; mean: 7.17 cycles). The maximum tolerated dose (MTD) for Arm B was 300 mg; dose-limiting toxicities were grade (gr.) 4 myelosuppression and gr. 3 fatigue. The type, rate, and severity of commonly observed gr. 3/4 toxicities were similar between Arms A and B, including (Arm A [%]; Arm B [%]): anemia (28%; 24%), lymphopenia (20%; 35%), neutropenia (16%; 15%), and thrombocytopenia (12%; 12%), and fatigue (0%, 12%). Preliminary PK data indicate improved AZD1775 exposure (AUC and C_{max}) for Arm B vs. Arm A MTD cohorts. **Conclusions:** Once-daily AZD1775 is well tolerated, with toxicities comparable to twice-daily AZD1775. Plasma drug exposure was higher for the QD vs. BID MTD cohort. AZD1775 antitumor activity was observed in pts with and without known *BRCA* mutations. Accrual to Arm B is ongoing, as is PD analysis. Future whole-exome sequencing analyses may uncover additional predictive biomarkers. Clinical trial NCT01748825. Supported in part by NCI Contract HHSN261200800001E. Clinical trial information: 01748825.

2588 Poster Session (Board #414), Mon, 8:00 AM-11:30 AM

Dose finding study of varlitinib ± trastuzumab with carboplatin/paclitaxel in advanced solid tumors. *First Author: Matilda Lee, National University Health System, Singapore, Singapore*

Background: Varlitinib (V) is a reversible inhibitor of HER1/HER2/HER4. This is a phase 1b dose confirmation study to determine safety and early efficacy signals of V ± T combined with weekly P 80mg/m^2 and C AUC = 2 (NCT02396108). **Methods:** Eligible patients had metastatic solid tumors. A 3+3 dose de-escalation study design was used and pharmacokinetic (PK) analyses of V and P were done. **Results:** 37 patients (median age 56.8 years [31.8 – 73.8]) were enrolled into 8 cohorts with median 3 (0-14) prior lines of palliative therapies. PC + V 500mg BD continuously (cont) was deescalated to 300mg BD intermittently (int) (4 days on, 3 days off) due to DLTs, most commonly febrile neutropenia (FN) and electrolyte disturbances, and was deemed intolerable. Recommended dose (RD) was V 300mg BD int with P alone; addition of T to RD of P+V was safe with no DLTs (Table). 20/37 had HER2+ metastatic breast cancer (MBC) with median 4 (0-14) prior treatment lines. 7 achieved partial response (PR) and 3 stable disease (SD); 6 had disease control with single agent V for a median 7.0 more months (4.3 – 13.3) after chemotherapy ceased. 2/17 with other tumor types achieved PR (HER2- MBC = 1, NSCLC = 1). 3/10 patients (HER2+ MBC = 2) in the V 300mg BD int cohorts achieved PR. No correlation was seen between V and P mean AUC (ng.h/mL) in those with and without DLTs (V 10336.5 vs 20758.8, p = 0.21; P 4882.1 vs 5197.6, p = 0.77). No interaction was seen between V dose/schedule with P PK. **Conclusions:** The RD of V combined with P is 300mg BD int, and is active in HER2+ MBC; T can be added safely. The triple combination will be evaluated as neoadjuvant therapy in HER2+ breast cancer. Clinical trial information: NCT02396108.

Cohorts	DLT in cycle 1	No. with PR/SD
N = 3 V 500mg BD cont CP	3/3 (G3 hyperbilirubinemia = 1, received < 75% intended V dose due to toxicities = 2)	1/0
N = 5 V 400mg BD cont CP	3/5 (FN = 3)	2/3
N = 4 V 400mg BD int CP	2/4 (G3 hypophosphatemia = 1, G3 hyponatremia, G3 hypokalemia, intolerable G2 fatigue = 1)	2/2
N = 6 V 300mg BD int CP	2/6 (FN = 1 , G3 hypophosphatemia, G3 vomiting = 1)	1/2
N = 6 V 300mg BD int P	0/6	2/2
N = 4 V 400mg BD int P	2/4 (FN = 1, G3 transaminitis = 1)	1/1
N = 6 V 300mg BD cont P	4/6 (G3 diarrhea = 1, G4 neutropenia > 7days = 1, received < 75% intended V dose due to toxicities = 2)	1/1
N = 3 V 300mg int P SC T 600mg	0/3	Ongoing

2589 Poster Session (Board #415), Mon, 8:00 AM-11:30 AM

Phase 1 study of pegargiminase combined with cisplatin and pemetrexed in patients with ASS1-deficient uveal melanoma. *First Author: Pui Ying Chan, Barts Health NHS Trust, London, United Kingdom*

Background: Argininosuccinate synthetase (ASS1) loss is a biomarker to select for tumors sensitive to arginine deprivation therapy. In a phase 1 dose-escalation study of ASS1-deficient thoracic cancers, we demonstrated tolerability and a high disease control rate using weekly pegargiminase (ADI-PEG 20) combined with first-line pemetrexed (PEM) and cisplatin (CIS) chemotherapy (Beddowes *et al.*, JCO 2017; ADIPEMCIS). Here, we report the safety and early activity of ADIPEMCIS in an expansion cohort of patients (pts) with metastatic uveal melanoma (UM). **Methods:** Chemotherapy naïve pts aged 18 years or older with ASS1-deficient, histologically proven metastatic UM were eligible. ADI-PEG 20 (36 mg/m^2 i.m.) was administered weekly together with PEM (500mg/m^2) and CIS (75 mg/m^2) every 3 weeks for a maximum of 18 weeks. Pts with stable disease or better were eligible to continue on ADI-PEG 20 until disease progression. Adverse events (AEs) were graded using CTCAE v4.03. Radiological response was assessed by CT or MRI every 6-8 weeks according to RECIST 1.1, alongside pharmacodynamic and immunogenicity analyses, median progression-free and overall survival (PFS and OS) estimates. **Results:** 10 of 14 screened pts with ASS1-ve metastatic UM received ADIPEMCIS with a median of 1 line of prior therapy (i.e. ipilimumab monotherapy; range 0 to 5). Treatment was well tolerated; neutropenic sepsis was the only grade 3 AE (n = 1 pt). The best response was stable disease with a median PFS of 3.0 months (range, 1.3 to 8.1 months) and a median OS of 11.5 months (range, 3.2 to 24.0+ months). Despite the emergence of anti-ADI-PEG 20 antibodies, plasma arginine concentrations remained low by 18 weeks with a reciprocal increase in plasma citrulline. Tumor rebiopsies at progression revealed ASS1 re-expression (n = 2/2 pts). **Conclusions:** ADIPEMCIS is well tolerated and has activity in metastatic UM, for which there is no established therapy. Based on recent preclinical data showing synthetic lethality of combining ADI-PEG 20 with PD-1/PD-L1 inhibition, a phase 1 study of ADI-PEG 20 with immune checkpoint blockade is planned in advanced UM. ClinicalTrials.gov identifier: NCT02029690. Clinical trial information: NCT02029690.

2590 Poster Session (Board #416), Mon, 8:00 AM-11:30 AM

Outcomes of patients with gene fusion driven cancers treated on early phase clinical trials. *First Author: Roman Groisberg, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Gene fusions result in a constitutively activated tyrosine kinase that causes uncontrolled cell proliferation. Some fusions are actionable with multi-kinase inhibitors that are FDA approved or in development. We reviewed patients with gene fusions treated with a targeted agent in a large Phase 1 program. **Methods:** We reviewed charts of patients treated on trials with targeted therapies in our phase 1 clinic between 2009 and 2017. Targeted was defined as affecting either the fusion gene itself or a downstream pathway. Demographic information including diagnosis, age, sex, date of first dose on trial, date of progression, best response by RECIST, and date of death. Information on fusions was obtained from next generation sequencing or FISH performed as part of oncologic management. **Results:** A total 85 patients (M:F, 46:39) with gene fusions were identified and 59 (68.6%) were treated with a targeted agent. Tumors included sarcomas (N = 49, 57.6%), NSCLC (N = 17, 20%), cholangiocarcinoma (N = 7, 8.2%), salivary gland (N = 4, 4.7%), thyroid (N = 3, 3.5%), GBM (N = 2, 2.3%), HG neuroendocrine tumors (N = 2, 2.3%), colon and lymphoma (N = 1 each, 1.1%). Most common fusions were RET (KIF5B = 15, CCDC6 = 2, Other: 1) and EWS-FLI1 (N = 12, 20%). Other fusion partners in our dataset included FGFR2/3 (N = 9, 15.3%), NTRK1/3 (N = 7, 11.9%), ALK (N = 3, 5.1%), ROS1 (N = 2, 3.4%), and BRAF (N = 1, 1.7%). Most therapies targeted the fusion itself except in sarcomas where downstream pathways (c-MET, IGF1R, nuclear redistribution) were targeted. Best response was CR in three patients (5%), PR in 12 patients (20%), and SD in 21 patients (35.6%) for a clinical benefit rate of 61%. Median PFS was 7.1 months, 95% CI [4.8,15.4] and OS was 19.6 months, 95% CI [10.8, 29.4]. This compares favorably with historical unmatched (PFS = 2.2, OS = 9 mo) and matched therapy for mutations (PFS = 5.2, OS = 13.4 mo) in phase 1 trials (PMID: 22966018). **Conclusions:** Gene fusion driven cancers are actionable. Patients with fusions have comparable response rates to historical molecularly matched targeted therapy data in our phase 1 group, but have longer PFS and OS. Further study is needed for molecular mechanisms of response and resistance to fusion targeted therapies.

2591 Poster Session (Board #417), Mon, 8:00 AM-11:30 AM

Phase 1b trial of nintedanib in combination with bevacizumab in patients with advanced solid tumors. *First Author: Ravi Kumar Paluri, University of Alabama at Birmingham, Birmingham, AL*

Background: Vascular endothelial growth factor (VEGF) inhibitors have produced demonstrable but limited clinical benefit for various cancers. One mechanism of resistance includes revascularization secondary to up-regulation of alternative pro-angiogenic signals such as platelet derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) pathway. Nintedanib (Nin) is an oral triple kinase inhibitor that blocks the VEGFR, PDGFR and FGFR pathways and may improve antitumor activity by overcoming resistance to anti-VEGF therapies. This study evaluated the safety & tolerability (primary objective) of Nin in combination with bevacizumab (Bev). **Methods:** Patients (pts) were treated with escalating doses of Nin (150mg or 200mg oral twice daily) and Bev (15 mg/kg once intravenously every 3 weeks) until disease progression or unacceptable toxicity using standard 3 + 3 phase1 design. The plasma levels of angiogenic biomarkers were correlated with clinical outcomes. **Results:** Eighteen pts with advanced tumors [lung (9), colon (8) and cervical (1)] pretreated with at least two lines of chemo were enrolled. Fifty percent (9 patients) were pretreated with bev. The final dose of Nin is 200mg twice a day with no observed dose limiting toxicities (DLT). The common adverse events were fatigue (grade 1-3); nausea & diarrhea (grade 1-2). Two pts came off study due to grade 3 fatigue. The disease control rate (DCR) was 72% (1 CR,1 PR & 11 SD).The median progression free survival (PFS) was 4 months (m), and median overall survival (OS) was 14m. The PFS rate at 6, 12, and 18m was 22%, 11%, and 11% and the OS rate at 6, 12, and 18 m was 83%, 70% and 28% respectively. Durable clinical response was observed in pre-Bev treated pts (1CR, 4 SD). The median OS for colon (n = 8) not reachable with 57% alive at 18m; median OS for lung (n = 9) was 13m with 13% alive at 18m. Better DCR was correlated with lower baseline PIGF levels as well as increased level from baseline. Longer PFS was associated with higher than the median baseline values for VEFGR2, E-selectin and lower SDF-1α. **Conclusions:** Nin was well tolerated with Bev with no DLT's. Significant clinical activity was observed in Bev pretreated patients suggesting Nin can overcome Bev resistance. Clinical trial information: NCT02835833.

2592 Poster Session (Board #418), Mon, 8:00 AM-11:30 AM

A phase I, open-label, multicenter dose escalation study to assess the safety, tolerability, and pharmacokinetics of AZD2811 nanoparticle in patients with advanced solid tumors. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Aurora kinases represent potential targets for anticancer therapy in solid tumors and hematological malignancies. The aurora B kinase inhibitor AZD1152 (barasertib) has shown benefit in patients (pts) with untreated AML versus low-dose AraC when given as a 7-day continuous infusion. AZD2811 nanoparticle is a novel, encapsulated slow release inhibitor of aurora kinase B which offers several advantages compared to AZD1152 (Ashton S et al., Sci Transl Med 2016). AZD2811 nanoparticle mimics the AZD1152 7-day continuous infusion as a 2-hr infusion on Day 1 and 4, and resulted in increased efficacy preclinically. We report the first-in-man dose-escalation of AZD2811 in pts with advanced solid tumors (NCT02579226). The objectives were to determine the MTD, safety profile, dosing schedule and preliminary efficacy of AZD2811. **Methods:** Adult pts with advanced solid tumors were given AZD2811 nanoparticle IV on Day 1 and 4 every 28 days. Pts were enrolled according to a standard 3+3 design. Pharmacokinetics (PK) were assessed in cycle 1. **Results:** 24 pts were treated in 6 cohorts: 15 mg (3 pts), 25 mg (3 pts), 38 mg (3 pts), 51 mg (3 pts), 100 mg (3 pts) and 200 mg (9 pts). Of those 24 pts, 20 pts discontinued due to disease progression, (1 pt) due to death, (1 pt) withdrew consent (1 pt), physician's decision. Preliminary efficacy indicated one confirmed ongoing partial remission in cohort 6 at 16 months. In Cohorts 1-5, common treatment-related AEs (any grade) were diarrhea, nausea, and fatigue; in Cohort 6 (200 mg per infusion) common treatment-related AEs (any grade) were fatigue, decreased appetite, and neutropenia (5 pts, all grade 4 including 1 DLT of $>$ 7 days without G-CSF), an expected pharmacodynamics marker of target engagement. There were no infections, fever of unknown origin or treatment-related deaths. AZD2811 total blood PK appear dose proportional with a $t_{1/2}$ of 30-50 hours. **Conclusions:** AZD2811 nanoparticle is safe and well tolerated at a dose of 200 mg Day 1 and 4 every 28-days. A single day 1 infusion once every 21 days with G-CSF is also being investigated. Further safety and updated efficacy data will be reported at the annual meeting. Clinical trial information: NCT02579226.

2593 Poster Session (Board #419), Mon, 8:00 AM-11:30 AM

A phase I study of a novel IAP inhibitor APG-1387 in patients with advanced solid tumors. *First Author: Ruihua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: APG-1387 is a bivalent small molecule Smac mimetic that antagonizes the IAPs. Preclinical studies have shown its dose- and schedule-dependent, strong antitumor activities in multiple human cancer xenograft models. In addition, the preclinical results strongly support the notion that APG-1387 in combination with anti-PD1 antibody would be a very attractive approach for cancer therapy. **Methods:** Phase I dose-escalation study enrolled 28 patients with advanced solid tumors in China (#CTR20150161). During dose escalation, the patients received APG-1387 (0.3–45 mg) intravenous infusion for 30 minutes once every week for 3 out of 4 weeks in a 28-day cycle until disease progression. Endpoints included safety (primary), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity assessed every 8 weeks per RECIST v1.1. **Results:** Till Jan 15, 2018, 28 patients had been treated in 8 cohorts of APG-1387(0.3mg, 0.6mg, 4mg, 7mg, 12mg, 20mg, 30mg, 45mg). Twenty-eight patients received at least 1 cycle of treatment. The MTD was not reached yet. No DLT was observed during Cycle 1 across dose levels. Twenty-five of 28 patients experienced at least 1 TEAE. The most common TEAEs were vomiting, abdominal pain, anemia, cough, headache, AST increased and ventricular arrhythmia. Of these, 4 grade 3/4 clinical TEAEs including blood bilirubin increased, ALT increased, hypokalemia , pain and soft tissue infection were documented across dose levels. A total of 12 definitively or possibly drug-related AE occurred to date. Human PK data of APG-1387 showed a dose proportionality in exposure, elimination appeared to be linear, no significant accumulation was observed in plasma. Preliminary results from the Human Cytokine 30-Ple analyses indicated that IL-12, IP-10 and MCP-1 were significantly increased in the patient plasma after treatment with APG-1387, indicating potential effects of APG-1387 on the host immune responses. **Conclusions:** APG-1387 was well tolerated and had manageable adverse events.Further evaluation of APG-1387 in combination with immunotherapy agents in patients with advanced solid tumors or hematologic malignancies is recruiting. Clinical trial information: NCT03386526. Clinical trial information: 20150161.

2594 Poster Session (Board #420), Mon, 8:00 AM-11:30 AM

A phase I study of novel dual Bcl-2/Bcl-xL inhibitor APG-1252 in patients with advanced small cell lung cancer (SCLC) or other solid tumor. *First Author: Nehal J. Lakhani, START Midwest, Grand Rapids, MI*

Background: We have developed a unique strategy to tactically reduce on-target platelet toxicity with APG-1252, a novel dual Bcl-2/Bcl-xL inhibitor, while maintaining strong *in vivo* antitumor activity. APG-1252 potently inhibits tumor growth in human cancer xenograft models including SCLC models while trigged significantly less platelet killing APG-1252 demonstrated a higher therapeutic index than ABT-263 in preclinical studies. **Methods:** This Phase I study (NCT03080311) enrolled patients with advanced SCLC or other solid tumors. In dose escalation, the patients received APG-1252 (10–400 mg) intravenously twice weekly for 3 weeks in a 28-day-cycle, until disease progression. Study objectives include safety (primary endpoint), pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity assessed every 8 weeks per RECIST v1.1. **Results:** As of Jan 31, 2018, 13 patients (including 6 pts with SCLC) have been treated in 5 cohorts of APG-1252. Current dose level being explored is 160 mg. The median number of prior systemic anticancer therapies was 2 (range 1-6). The pts received a median of 2 cycles of APG-1252 (range 1-6). MTD has not been identified yet. TRAEs were reported in 10 pts (77%). The most common AE's (reported in $\geq$10% of pts) included: arthralgia, AST/ALT increased, vomiting, and fatigue. All TRAEs were grade $\leq$ 2 in severity. There were no AEs leading to treatment discontinuation. No thrombocytopenia or other cytopenias have been observed six pts had $\geq$1 on-treatment tumor assessment. One confirmed partial response was observed in 1 patient with metastatic SCLC at the 40 mg dose, and the duration of response lasted for more than 6 cycles. PK analyses indicate that AUC and Cmax increase dose proportionally over 10-40 mg range on day 1, while AUC increases more than dose proportionally on Day 22. AUC at 40 mg on Day 22 is close to *in vivo* efficacious exposure. **Conclusions:** APG-1252 was well-tolerated across all dose levels tested. No hematologic toxicity has been reported so far. Dose escalation and further evaluation of APG-1252 in patients with SCLC and other advanced solid tumors is ongoing. Clinical trial information: 03080311.

2595 Poster Session (Board #421), Mon, 8:00 AM-11:30 AM

Safety and pharmacodynamics of the DRD2 antagonist ONC201 in advanced solid tumor patients with weekly oral administration. *First Author: Mark N. Stein, Columbia University Medical Center, New York, NY*

Background: ONC201 is a small molecule antagonist of DRD2, a G protein-coupled receptor overexpressed in several malignancies, that has prolonged antitumor efficacy in preclinical cancer models via induction of the CHOP/DR5-mediated integrated stress response pathway and caspase-dependent apoptosis. In addition to cytotoxic effects in tumor cells, DRD2 antagonism can induce the activation of NK and other immune cells. The first-in-human trial of ONC201 previously established a recommended Phase II dose (RP2D) of 625 mg once every three weeks. Here, we report the results of a Phase I study that evaluated the safety, pharmacokinetics (PK), and pharmacodynamics with weekly oral administration of ONC201. **Methods:** Patients $\geq$18 years old with an advanced solid tumor refractory to standard treatment were enrolled. Dose escalation proceeded with a 3 + 3 design from 375 mg to 625 mg of ONC201. One cycle, also the dose-limiting toxicity (DLT) window, was 21 days. The primary endpoint was to determine the RP2D of ONC201 with weekly oral administration, which was subsequently confirmed in an 11-patient dose expansion cohort. **Results:** A total of 20 patients were enrolled: 3 at 375 mg and 17 at 625 mg of ONC201. The RP2D was defined as 625 mg with no DLT, treatment discontinuation, or dose modifications due to drug-related toxicity. Pharmacokinetic profiles were consistent with every three week dosing and similar between the first and fourth dose. Serum prolactin and caspase-cleaved cytokeratin-18 were detected, along with intratumoral induction of integrated stress response (CHOP/DR5), apoptosis (TUNEL) and infiltration of granzyme B+ Natural Killer cells. Induction of immune cytokines and effector molecules was higher in patients who received ONC201 once every week versus once every three weeks. Stable disease of $>$ 6 months was observed in several prostate and endometrial cancer patients. **Conclusions:** Weekly, oral ONC201 is well-tolerated and results in prolonged stable disease, intratumoral apoptotic signaling and enhanced immunostimulatory activity that warrants further investigation. Clinical trial information: NCT02250781; NCT02324621.

TPS2596 Poster Session (Board #422a), Mon, 8:00 AM-11:30 AM

The GATTO study: A phase I of the anti-MUC1 Gatipotuzumab (GAT) in combination with the anti-EGFR Tomuzotuximab (TO) in patients with EGFR positive solid tumors. *First Author: Sebastian Ochsenreither, Charité Comprehensive Cancer Center, Berlin, Germany*

Background: TO (CetuGEX) is a second-generation anti-EGFR antibody that specifically binds to EGFR and acts as a competitive antagonist at the ligand binding site. GAT (PankoMab-GEX) is a novel humanized monoclonal antibody, which recognizes the tumor-specific epitope of mucin-1 (TA-MUC1) expressed on tumor cells. Both antibodies are glyco-engineered to potentiate antibody-dependent cellular cytotoxicity (ADCC). Compelling preclinical evidence suggests a complex interaction between EGFR and cell surface expressed TA-MUC1 in driving cancerogenesis processes as well as shows a synergistic ADCC activity with the dual targeting of these molecules. Based on this evidence, this study aims to assess the tolerability, safety and preliminary activity of a combination with anti-EGFR and anti-TA-MUC1 glyco-engineered antibodies. **Methods:** The GATTO is an open label phase Ib dose evaluation study in patients with EGFR positive metastatic solid tumors, for whom no standard treatment is available. The proposed doses and schedule are 1400 mg Q2W for GAT and 1200 mg Q2W for TO. A staggered approach will be utilized in order to minimize the number of patients exposed and to evaluate the safety of the combination treatment. The first 6 patients will be enrolled into a safety run-in phase where the number of dose-limiting toxicities (DLTs) will be evaluated. Assuming that the safety criteria are met (ie. observation of 0 or 1 DLT), the dose will remain unchanged and further patients will be recruited at this dose level. If this is not the case, a step-wise dose reduction approach will be applied. The antitumor activity of the combined treatment will be evaluated as secondary endpoints including best overall response rate (ORR), duration of objective response, progression-free (PFS) and overall (OS) survival. Extensive pharmacokinetics (PK) and pharmacodynamics (PD) (cellular immune status, serum and tissue biomarkers) will be also analyzed. As of January 2018, the study is ongoing and 2 patients have been treated. (ClinicalTrials.gov Identifier: NCT03360734). Clinical trial information: NCT03360734.

TPS2597 Poster Session (Board #422b), Mon, 8:00 AM-11:30 AM

AMC 095 (AIDS Malignancy Consortium): A phase I study of ipilimumab (IPI) and nivolumab (NIVO) in advanced HIV associated solid tumors (ST) with expansion cohorts in HIV associated solid tumors and classical Hodgkin lymphoma (cHL). *First Author: Lakshmi Rajdev, Montefiore Medical Center, Bronx, NY*

Background: Immune checkpoint blockade (ICB) using agents that target the priming phase (i.e. CTLA-4) and effector phase (e.g. PD-1) of host immunity, used individually or in combination, has emerged as a therapeutic strategy for cancers. Little is known about the safety, tolerability and efficacy of ICB in patients (pts) with HIV infection and cancer. **Methods:** AMC 095 (NCT02408861) is a multicenter, international phase I study of the PD-1 inhibitor, nivo alone or in combination with a CTLA-4 inhibitor, ipi, in 2 cohorts stratified by CD4 counts (Stratum 1: CD4 counts≥200/uL and Stratum 2: CD4 count 100-200/uL) with additional expansion cohorts at the recommended phase II dose in pts with ST and cHL. The primary study objective is to determine the safety and feasibility of nivo alone and the nivo +ipi combination. Secondary objectives are to evaluate the effects of single agent nivo, and ipi+ nivo, on HIV replication and immune function (HIV viral load in plasma using conventional assay, CD4+, and CD8+ cells), and to obtain preliminary information regarding response. Clinical trial information: NCT02408861. The trial was initiated in 8/15, as of 2/2/18, the study is ongoing, and 29 pts have been enrolled. Updated information on the safety and responses will be presented. Funded by the NCI Grant #UM1CA121947.

Agent/dose	Stratum 1-CD4 ≥ 200/uL 2-CD4 < 200 /uL	No. Treated
Nivo 3 mg/kg q 2 wk	1	6
Nivo 3 mg/kg q 2 wk	2	6
Nivo 240 mg q 2 wk + Ipi 1 mg/kg q 6 wk	1	6
Expansion cohort in Solid Tumors Nivo 240 mg q 2 wk	1/2	9
Expansion cohort in cHL Nivo 240 mg q 2 wk	1/2	2
Total		29

TPS2598 Poster Session (Board #423a), Mon, 8:00 AM-11:30 AM

MASTER KEY project: A basket/umbrella trial for rare cancers in Japan. *First Author: Hitomi Sumiyoshi Okuma, National Cancer Center Hospital, Tokyo, Japan*

Background: Establishment of standard therapies for patients with rare cancers have been poor compared to those of major cancers, due to lack of basis for clinical studies and investigations. The MASTER KEY Project is a biomarker driven basket/umbrella trial using a "master protocol", aiming to find more efficient ways to evaluate treatments for rare cancers and to build a treatment development infrastructure by collaborating with industries. Similar studies including NCI–MATCH trial are ongoing; however, MASTER KEY Project is the first to be reported for such large scale trials that proceeds concurrently with a quality assured registry study focused only on rare cancers. **Methods:** The project is a two–stage structured study: the prospective registry study part and the multiple clinical trials (sub–study) part. Patients with advanced rare cancers/cancers of unknown primary/rare pathological subtypes of major cancers, who have priorly been evaluated by a molecular diagnostic testing, such as a validated next generation sequencing assay, are enrolled into the registry study. Rare cancer is defined as "annual incidence less than 6 cases per 100,000 population". The primary objective of the registry study part is to collect consecutive data on biomarker, clinicopathological background, and prognosis of rare cancers to build a large–scale database that is highly reliable as historical control data for future use in clinical trials of rare cancers. In the sub–studies, drugs are provided by various industries, who are collaborators, and could be approved or investigational agents. Sub–studies are placed under a "master protocol", allowing new sub–studies to be added at any time. Each sub–study is ordinarily a single arm study and will enroll 5–20 patients with the appropriate biomarker of interest, regardless of histopathologic tumor type. Typically, the primary endpoint is response rate (set according to each sub–study), and Bayesian method will be used. A biomarker–negative sub–study will also be available so that all patients have a chance to be enrolled in a sub–study. The project opened in May 2017. As of Jan 2018, 154 of a planned 100 patients/year have been enrolled. There is one ongoing sub–study and three sub–studies will open in April 2018. Clinical trial information: UMIN000027552.

TPS2599 Poster Session (Board #423b), Mon, 8:00 AM-11:30 AM

A phase 1 dose escalation (DE) and cohort expansion (CE) study of ERY974, an anti-Glypican 3 (GPC3)/CD3 bispecific antibody, in patients with advanced solid tumors. *First Author: Yoshitaka Ogita, Chugai Pharma USA, Berkeley Heights, NJ*

Background: ERY974 is a bispecific T cell–redirecting antibody immunotherapy that redirects T cells to tumor cells by engaging CD3 on T cells and the glypican 3 (GPC3) antigen (which is selectively expressed on tumor cells). ERY974 T cell–dependent cellular cytotoxicity has been demonstrated in vitro and transient cytokine elevations have been observed in toxicology studies (Takahiro Ishiguro et al., Sci Transl Med 2017;9:eaal4291). The primary objective of DE is to determine the maximum tolerated dose (MTD) of ERY974 in patients with locally advanced or metastatic solid tumors expressing GPC3. The primary objective of CE is to assess ERY974's preliminary anti-tumor activity. **Methods:** The study includes adult subjects with a life expectancy ≥ 3 months, histologically confirmed, measurable malignant solid tumors and/or metastatic disease not amenable to standard therapy, including patients with ≤ 1cm and ≤ 1 brain metastasis. Patients with interstitial lung disease, or acute/active chronic infection are excluded. ERY974 is administered IV and dosed weekly. DE occurs per an accelerated titration design (ATD), followed by a one-parameter logistic mode modified continual reassessment method (mCRM) to determine MTD (where the DLT occurrence rate is ≤ 0.25). The ATD and mCRM permit rapid dose escalation and determination of MTD while minimizing the number of subjects exposed to sub-therapeutic doses. Within DE, a flexible study design has been implemented to include a stepped increase in steroid administration and an ERY974 Fixed Day 1, Day 8 and Day 15 dosing regimen. Seven cohorts have completed without DLT and Cohort 8 began in December 2017. Additional measures will be implemented to help induce CRS tolerance. The CE will utilize a 2-stage design with futility analysis and will include the following 3 arms: GPC3+ gastric/gastroesophageal junction adenocarcinoma; GPC3+ squamous esophageal cancer; and other GPC3+ tumors. Clinical trial information: NCT02748837.

TPS2600 Poster Session (Board #424a), Mon, 8:00 AM-11:30 AM

Trial design of a first-in-human phase 1 evaluation of SY-1365, a first-in-class selective CDK7 inhibitor, with initial expansions in ovarian and breast cancer. *First Author: Geoffrey Shapiro, Dana-Farber Cancer Institute, Boston, MA*

Background: SY-1365 is a selective and potent covalent CDK7 inhibitor. CDK7 activity has been implicated in various solid tumors with transcriptional dependencies. Recent preclinical studies have shown robust antitumor activity of SY-1365 in ovarian and breast cancer. In ovarian cancer, SY-1365 induced apoptosis in vitro and complete regressions in PDX models derived from heavily pre-treated patients (pts). In breast cancer, SY-1365 induced cell death in vitro across subtypes and displayed synergy when combined with fulvestrant in HR-positive models. These observations led to a change in the design of the expansion phase of this first-in-human study of SY-1365 to include a new focus on these tumors. The primary objectives of this study are to assess the safety and tolerability of SY-1365, and to determine dose-limiting toxicities, the MTD and the recommended Phase 2 dose. Secondary objectives include evaluation of pharmacokinetics and pharmacodynamic (PD) effects of SY-1365 in tumor and surrogate tissues, and assessment of preliminary antitumor activity. **Methods:** This is a multicenter, open-label Phase 1 trial expected to enroll approximately 117 pts. The dose escalation phase of the trial is open to solid tumor pts for whom standard curative or palliative measures do not exist or are no longer effective. SY-1365 is administered intravenously in two dose schedules, weekly and twice weekly for 3 weeks of each 4-week cycle. The expansion phase will evaluate preliminary antitumor activity in 3 ovarian cancer cohorts, either as a single agent or in combination with carboplatin, an HR+ breast cancer cohort in combination with fulvestrant in pts who failed treatment with a CDK4/6 inhibitor in combination with an AI, and a cohort in pts with tumors of any histology to evaluate PD endpoints in paired tumor biopsies. SY-1365 target engagement in PBMCs and available tumor biopsies will be assessed by measuring CDK7 occupancy over the course of treatment. Biological impact of SY-1365 will be assessed by quantifying gene expression and induction of tumor cell apoptosis when feasible. This trial opened in May 2017. Clinical trial information: NCT03134638.

TPS2601 Poster Session (Board #424b), Mon, 8:00 AM-11:30 AM

A phase 1, open label, dose escalation study of MGD009, a humanized B7-H3 x CD3 DART protein, in combination with MGA012, an anti-PD-1 antibody, in patients with relapsed or refractory B7-H3-expressing tumors. *First Author: Sadhna Shankar, MacroGenics, Inc., Rockville, MD*

Background: T cells naturally undergo activation-induced upregulation of co-inhibitory pathways, which may limit the antitumor immune response. Blocking these inhibitory pathways may enhance the antitumor activity of CD3 bispecifics. MGD009 is a clinical stage B7-H3 x CD3 DART protein designed to redirect T cells to kill B7-H3 expressing tumor cells. B7-H3, a member of B7 family of immune regulators, is overexpressed in a variety of solid tumors and has limited expression in normal tissues. In preclinical studies, MGD009 causes T-cell infiltration, activation and expansion in the tumors. It upregulates PD-1 on T cells and PD-L1 on tumor cells and immune cells in vitro. Preliminary observations in patients enrolled in the ongoing phase 1 dose escalation trial with MGD009 alone indicate evidence of PD-1 up-regulation on both peripheral CD4 and CD8 T-cells. MGA012 is an anti-PD-1 antibody under investigation in an ongoing Phase 1 clinical trial and has shown clinical responses. In vitro and in vivo studies have shown enhanced antitumor activity with the combination of MGD009 and MGA012 beyond that achieved with MGD009 alone. A combination approach that blocks checkpoint inhibition of T cells with MGA012, while recruiting cytotoxic and helper T cells to B7-H3-expressing tumors with MGD009, may show anti-tumor activity in a variety of tumors. **Methods:** This is a Phase 1, open-label, dose escalation, and cohort expansion study designed to characterize the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary antitumor activity of MGD009 in combination with MGA012, both administered by IV infusion. Patients with B7-H3-expressing unresectable, locally advanced or metastatic solid tumors of any histology will be enrolled in the Dose Escalation Phase. Prior checkpoint inhibitor therapy is allowed. Dose escalation uses a 3+3+3 design, with patients treated every 2 weeks with escalating doses of IV MGD009 (starting dose 3μg/kg) and MGA012 at a dose of 3mg/kg in all cohorts. Cohort expansions will be limited to 6 tumor types (N = 20/cohort) treated at the maximum tolerated dose of the combination. Clinical trial information: NCT03406949.

TPS2602 Poster Session (Board #425a), Mon, 8:00 AM-11:30 AM

A phase 1 study of MSC-1, a humanized anti-LIF monoclonal antibody, in patients with advanced solid tumors. *First Author: David Michael Hyman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Leukemia Inhibitory Factor (LIF) is a pleiotropic cytokine involved in many physiological and pathological processes. LIF is highly expressed in a subset of tumors across multiple tumor types and shown to correlate with poor prognosis. LIF is hypothesized to contribute to tumor growth and progression by acting on multiple aspects of cancer biology, including immunosuppression of the tumor microenvironment (TME), and is a key regulator of cancer initiating cells (CICs), which are thought to underpin tumor growth, metastasis, and resistance to therapy. MSC-1, a first-in-class humanized IgG1 monoclonal antibody, is a potent and selective inhibitor of LIF. MSC-1 leads to robust STAT3 inhibition by disrupting the LIF signaling through the LIF receptor (LIFR). Blocking LIF with MSC-1 decreased tumor growth in multiple mouse tumor models and drove reprogramming of the TME through differentiation of immunosuppressive macrophages and modulation of several immune cell types. These findings form the basis of a robust therapeutic hypothesis, whereby MSC-1 treatment may lead to clinical activity in multiple cancer indications. **Methods:** The Phase 1 study of MSC-1 will enroll patients with advanced relapsed/refractory solid tumors. The study will employ an accelerated 3+3 escalation design to explore the safety, PK, immuno-regulatory activity and preliminary anti-tumor activity of MSC-1. Patients will receive treatment with MSC-1 intravenously once every three-weeks until confirmed disease progression or intolerable toxicity. Four tumor specific expansion cohorts will be initiated once dose and schedule are established from dose escalation and include NSCLC, ovarian cancer, pancreatic cancer and a basket of advanced solid tumors; enrollment will be restricted to patients with LIF-High expression in their tumors using a diagnostic selection assay. Response will be assessed every 6 weeks per RECIST v1.1.

TPS2603 Poster Session (Board #425b), Mon, 8:00 AM-11:30 AM

A phase 1 multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity, and antitumor activity of MEDI7247 in patients with select relapsed/refractory hematologic malignancies. *First Author: Amir Tahmasb Fathi, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Survival outcomes in patients with relapsed/refractory multiple myeloma (MM), acute myeloid leukemia (AML), or diffuse large B-cell lymphoma (DLBCL) remains poor, and there is a high unmet need for new therapeutic options in these patient populations. MEDI7247 is a first-in-class antibody-drug conjugate consisting of an anti–Na^+-dependent alanine-serine-cysteine transporter 2 (ASCT2) monoclonal antibody, site-specifically conjugated to highly cytotoxic DNA cross-linking pyrrolobenzodiazepine (PBD) dimers (drug-to-antibody ratio of close to 2) via a protease-cleavable linker. ASCT2 is overexpressed in a broad range of solid tumors and hematologic malignancies (e.g. MM, AML, and DLBCL), and has low expression in normal tissues. MEDI7247 has demonstrated potent and specific in vitro and in vivo antitumor activity in a variety of preclinical models with varying levels of ASCT2 expression. **Methods:** This is a first-in-human, phase 1, multicenter, open-label, dose-escalation and dose-expansion study in patients with selected hematologic malignancies (MM, AML, and DLBCL) who have relapsed after, or are refractory to prior standard therapy, and for whom there is no standard salvage regimen available (NCT03106428). The primary objectives are to assess safety and tolerability, describe dose-limiting toxicities, and determine the maximum tolerated dose or a recommended dose of MEDI7247. The secondary objectives are to evaluate the antitumor activity (best overall response, objective response rate, time to response, duration of response, progression-free survival, and overall survival as defined in the relevant response criteria), pharmacokinetics, and immunogenicity of MEDI7247. Recruitment is ongoing for this study; as of February 6, 2018, 19 patients have been enrolled (AML, n = 11; DLBCL, n = 6; MM, n = 2) with a target enrollment of up to 228 patients. Clinical trial information: NCT03106428.

TPS2604 Poster Session (Board #426a), Mon, 8:00 AM-11:30 AM

A phase 1 study evaluating the safety, pharmacology and preliminary activity of MM-310 in patients with solid tumors. *First Author: Marc S. Ernstoff, Cleveland Clinic, Cleveland, OH*

Background: Ephrin receptor A2 (EphA2) is expressed in cancer and stroma cells in a wide range of solid tumors. MM-310 is an EphA2-targeting liposomal form of a docetaxel prodrug. Preclinical investigation revealed a high correlation between EphA2 expression on cancer cells and MM-310 uptake. *In vivo* studies in multiple xenograft models demonstrated superior antitumor activity compared with standard of care agents, whereas toxicology analysis in rodents and non-rodent animal models revealed a favorable toxicity profile. The overexpression of EphA2 in a wide range of tumors, the high tumor specificity of MM-310 through the enhanced permeability and retention effect, and the EphA2 targeting support the investigation of MM-310 for potential clinical utility. **Methods:** This is a first-in-human, non-randomized, open-label Phase 1 study of MM-310 in patients with relapsed or refractory solid tumors. The clinical trial is divided into 3 parts. In the ongoing first part, MM-310 is assessed as a monotherapy, administered every 3 weeks at increasing dose levels (dose escalation), in patients with metastatic solid tumors, including urothelial carcinoma, gastric carcinoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic ductal adenocarcinoma, prostate adenocarcinoma, non-small cell lung cancer, small cell lung cancer, triple negative breast cancer, endometrial carcinoma and soft tissue sarcoma. The primary objective is to determine the maximum tolerated dose (MTD) of MM-310 monotherapy. Secondary endpoints include: characterization of adverse event profile, determination of pharmacokinetics and immunogenicity parameters, and assessment of preliminary activity of MM-310 monotherapy. In the dose-finding phase, the study uses a modified toxicity probability interval approach (mTPI) to determine the MTD of MM-310. After an MTD of monotherapy is established, an expansion cohort, and tolerability of MM-310 in combination with other therapies will be assessed. Enrollment was initiated in March 2017. Five sites in the United States are open for enrollment. Clinical trial information: NCT03076372.

TPS2605 Poster Session (Board #426b), Mon, 8:00 AM-11:30 AM

First-in-human phase 1 study of DS-1062a in patients (pts) with advanced solid tumors (AST). *First Author: Jacob M. Sands, Dana-Farber Cancer Institute, Boston, MA*

Background: DS-1062a is a trophoblast cell-surface antigen 2 (TROP2)-targeting antibody drug conjugate. TROP2 is overexpressed in epithelial cancers, including non-small cell lung cancer (NSCLC), and its overexpression is associated with poor survival in solid tumors. In preclinical studies, DS-1062a showed promising antitumor activity and an acceptable safety profile in TROP2-positive tumors with a long half-life, allowing for every-3-week (Q3W) dosing. This dose escalation (ESC) and dose expansion (EXP) study will investigate DS-1062a in pts with ASTs (NCT03401385). Primary objectives are to determine the maximum tolerated dose and recommended dose for expansion (RDE) based on the dose limiting toxicity (DLT) rate (ESC) and assess safety and tolerability (ESC + EXP). Secondary objectives include pharmacokinetics (PK), antitumor activity and anti-drug antibody (ADA) incidence. **Methods:** In this multicenter, open-label study in the US and Japan, pts aged ≥18 (US) or ≥20 (Japan) years with unresectable relapsed or refractory advanced NSCLC are eligible regardless of TROP2 expression; other ASTs may be included if safety and efficacy in NSCLC is demonstrated. In ESC, initial intravenous DS-1062a infusion will start at 0.27 mg/kg, followed by 21-day observation. Subsequent doses will be given Q3W. In EXP, pts will receive RDE Q3W. Pts will be treated until unacceptable toxicity, progressive disease, consent withdrawal or death. Endpoints include DLTs, adverse events (safety) and tumor response evaluated using RECIST v1.1 (efficacy). Pre-, on- and post-treatment tumor samples will be evaluated for TROP2 expression and other biomarker analyses. Immunogenicity will be assessed via ADA incidence and titer. Population PK and exposure-response analysis will be conducted. Pts will be enrolled in ESC using a modified continuous reassessment method and dose escalation with overdose control, with at least 3 DLT-evaluable pts per dose level. For EXP, 40 pts with NSCLC and up to 40 pts with other solid tumors will be enrolled. Enrollment is open. Clinical trial information: NCT03401385.

TPS2606 Poster Session (Board #427a), Mon, 8:00 AM-11:30 AM

CD205-Shuttle study: A first-in-human trial of MEN1309/OBT076 an ADC targeting CD205 in solid tumor and NHL. *First Author: Elena Garralda, Medical Oncology Department, Vall d'Hebron University Hospital; Molecular Therapeutics Research Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: MEN1309/OBT076 is a DM4-loaded Antibody Drug Conjugate (ADC), directed against CD205/Ly75, a type I transmembrane surface protein belonging to the macrophage mannose receptor family. CD205 is therapeutically relevant, because of its broad expression in multiple cancer types, its emerging role at facilitating metastatic invasion and its effective internalization upon antibody binding. Extensive preclinical evidence demonstrated MEN1309 antitumor activity in vitro, in xenograft and patient-derived xenograft (PDX) models. **Methods:** The CD205-Shuttle study is a two-step, open-label, multicenter, dose-escalation FIH study. Step 1 involves patients affected by different solid tumors, following an Accelerated Titration Design (ATD) whereby 1 patient per dose cohort is enrolled and the dose doubled at each cohort. If grade ≥2 toxicity is observed the trial design is expected to revert to a 3+3 scheme with a Fibonacci ascending dose scheme. Step 2 is designed to test MEN1309/OBT076 at minus 2 levels of the tolerated doses during Step 1 in patients with Non-Hodgkin-Lymphoma (NHL). Each dose level escalation will be subject to the assessment of the Cohort Review Committee (CRC). CD205-positive patients are selected by IHC staining of archived tumor material. Patient with locally advanced or metastatic solid tumor in progression can be included if failed on ≥2 previous cancer treatments and if no standard therapy is available. The primary endpoint is to identify dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of MEN1309/OBT076 administered by i.v. infusion once every 21-days. The secondary endpoints includes assessment of pharmacokinetics (PK), immunogenicity, preliminary clinical efficacy of MEN1309/OBT076 and correlation with CD205 expression. Adverse Events (AE) will be graded according to NCI CTCAE v. 4.03. Responses will be evaluated according to RECIST v1.1 and Cheson criteria (2014). Study variables will be presented by dose-cohort and overall using appropriate descriptive statistics. The enrollment began in October 2017 in European sites; up to date 3 cohort levels have been achieved. NCT03403725. NOTE: First and Second author equally contributed to this work Clinical trial information: NCT03403725.

TPS2607 Poster Session (Board #427b), Mon, 8:00 AM-11:30 AM

Phase 1b multi-indication study of the antibody drug conjugate anetumab ravtansine in patients with mesothelin-expressing advanced or recurrent malignancies. *First Author: Alex A. Adjei, Mayo Clinic, Rochester, MN*

Background: Mesothelin expression is associated with poor prognosis in patients with a wide variety of tumors, including mesothelioma, pancreatic, gastric/gastroesophageal juncture, NSCLC, ovarian, triple-negative breast cancer, and thymic carcinomas. Anetumab ravtansine is a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4. We are conducting a signal-generating study with anetumab ravtansine in five tumor types with high unmet medical need in patients prescreened for mesothelin expression (NCT03102320). **Methods:** Eligibility criteria include: ≥18 years, unresectable locally advanced or metastatic recurrent or relapsing disease, no prior (pancreatic adenocarcinoma) or one or more prior lines of therapy for their advanced stage of disease, and availability of tumor tissue for mesothelin expression testing as determined by the Ventana MSLN (SP74) immunohistochemistry assay. Mesothelin-positive patients with selected adenocarcinomas (gastric including gastro-esophageal junction, NSCLC, and triple negative breast) and thymic carcinoma will receive anetumab ravtansine as monotherapy at 6.5 mg/kg IV on a 21-day cycle. Following a safety run-in phase (18-24 patients each), patients with pancreatic adenocarcinoma will receive anetumab ravtansine in combination with gemcitabine (1000 mg/m2 IV day 1 and 8 on a 21-day cycle). The primary objective is objective response rate (ORR) of anetumab ravtansine as monotherapy or combination therapy in patients with either of two mesothelin expression levels: high (≥30% positive tumor cells with moderate and stronger membrane staining intensity) and low-mid (≥5% all intensities and < 30% positive tumor cells with moderate and stronger membrane staining intensity). Secondary objectives include safety, disease control rate, duration of response, durable response rate, and progression-free survival. Approximately 350 patients will be enrolled. Clinical trial information: NCT03102320.

TPS2608 Poster Session (Board #428a), Mon, 8:00 AM-11:30 AM

A phase II trial of the DNA methyl transferase inhibitor, SGI-110 (guadecitabine), in children and adults with wild type GIST, pheochromocytoma and paraganglioma associated with succinate dehydrogenase deficiency and HLRCC-associated kidney cancer. *First Author: Jaydira Del Rivero, Center for Cancer Research, NCI, NIH, Bethesda, MD*

Background: Loss of activity of Krebs cycle components succinate dehydrogenase (SDH) complex or fumarate hydratase (FH) has been identified as a mechanism of tumorigenesis in SDH-deficient gastrointestinal stromal tumor, pheochromocytoma and paraganglioma (PHEO/PGL), and hereditary leiomyomatosis and renal cell cancer (HLRCC). Accumulation of the metabolites succinate or fumarate inhibits α-ketoglutarate-dependent dioxygenases leading to DNA hypermethylation in these tumors. Guadecitabine is a small molecule derivative of decitabine that acts as a DNA methyltransferase inhibitor. We hypothesize that guadecitabine will impact tumor growth by reversing DNA hypermethylation in tumors with Krebs cycle abnormalities (NCT03165721). **Methods:** This single site, open label, phase II study uses a small optimal two-stage design to evaluate response in three groups of patients: SDH-deficient GIST, SDH-deficient PHEO/PGL and HLRCC-associated renal cell carcinoma. The primary objective is to assess the clinical activity (CR or PR) of guadecitabine in these patients. Adults and children (≥12 years of age) receive guadecitabine subcutaneously at a dose of 45mg/m^2/day for 5 consecutive days on a 28-day cycle. Activity is assessed by imaging response of measurable disease using RECISTv1.1 using CT, MRI and/or PET. Toxicity is graded using version 4.0 of the NCI Common Toxicity Criteria. Guadecitabine related toxicities ≥grade 3 will be considered treatment limiting, unless they are reversible within 72 hours with supportive care. Following recovery from toxicity up to 2 dose reductions will be allowed. Initially 7 evaluable patients in each group will be enrolled and if 1 or more (14.3%) have a response, accrual will continue until a total of 21 patients have enrolled. If at least 3 responses (14.3%) are observed among the 21 evaluable patients the agent will be considered worthy of further testing in this disease. Clinical trial information: NCT03165721.

TPS2609 Poster Session (Board #428b), Mon, 8:00 AM-11:30 AM

Phase 1/2 trial evaluating intratumoral administration of INT230-6 alone and in combination with an anti-PD1 antibody for advanced malignancies. *First Author: Yada Kanjanapan, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: INT230-6 is a supermolecular complex of cisplatin, vinblastine, and an amphiphilic penetration enhancer, formulated for intratumoral injection. This agent utilizes technology that facilitates drug dispersion throughout the tumor and enhances receptor independent transport into cancer cells. INT230-6 preferentially saturates cancer cells, due to their greater membrane fluidity over normal cells. In Colon26 mouse models, intratumoral injections of INT230-6 resulted in up to 80% complete responses(CRs) with generation of antigen specific CD8 T-cells. Responses were seen in both injected tumors as well as bystander lesions. Animals maintained lifelong protection from tumor rechallenge, and partial protection from 4T1 (a different tumor type) which was dependent on CD4 and CD8 T-cells. Clear benefit with anti-PD1 was shown preclinically (increased CR and OS). **Methods:** This adaptive Phase 1/2 trial evaluates intratumoral INT230-6 in advanced malignancies (NCT03058289). The first cohort examines injection into superficially palpable tumors, dosed at 1ml:4cc drug:tumor concentration and administered monthly for 5 cycles. Intrapatient dose escalation is allowed. Additional cohorts include deep tumor injection, more frequent administration every 2 weeks, increased proportion of drug to tumor (1ml:2cc), and combination with an anti-PD1 antibody. Eligible patients (pts) have metastatic cancer and progressed on or are not candidates for approved therapies, or non-resectable locally advanced disease recurring within 6 months post radiation, with tumors suitable for injection. The primary objective is assessment of safety, with secondary objectives of PK and preliminary analysis of response in injected and bystander tumors. Correlative endpoints include tumor infiltrating lymphocytes in pre and on-study biopsies of injected and bystander lesions, peripheral blood for flow cytometry and circulating cytokine analyses. The superficial cohort has been completed with no DLTs in 6 treated pts. The deep tumor and every 2 week dosing cohorts are ongoing with tumor type specific expansion cohorts as guided by the Study Steering Committee. Clinical trial information: NCT03058289.

TPS2610 Poster Session (Board #429a), Mon, 8:00 AM-11:30 AM

A Cancer Research UK phase I/IIa trial of BT1718 (a first in class Bicycle Drug Conjugate) given intravenously in patients with advanced solid tumours. *First Author: Udai Banerji, The Institute of Cancer Research and The Royal Marsden, London, United Kingdom*

Background: Membrane type I matrix metalloproteinase (MT1-MMP) is a member of the matrix metalloproteinase (MMP) family which are involved in tissue remodelling through proteolysis of extracellular matrix components. Overexpression of MT1-MMP is seen in multiple tumour types including non-small cell lung cancer (NSCLC), triple negative breast cancer (TNBC) and sarcoma. BT1718 is a novel first in class bicyclic targeting peptide that binds MT1-MMP and is linked to the maytansinoid tubulin inhibitor DM1 by a cleavable disulfide linker. Bicyclic peptides have a low molecular weight in comparison to other conjugated toxin approaches enabling rapid penetration and a short systemic half-life, potentially reducing toxicity. **Methods:** This is an open label first in human phase I/IIa study. The primary objective is to propose a recommended phase 2 dose (RP2D) and schedule of BT1718. Secondary objectives include pharmacokinetic (PK) parameters and preliminary clinical responses in biomarker pre-defined cohorts of patients. Tertiary objectives include correlative studies related to predictive biomarkers of response. Dose escalation (phase I) Stage 1: In keeping with preclinical PK and safety studies, initial cohorts of patients will be dosed twice a week. There will be single patient cohorts until either Grade 2 drug related toxicity occurs or the dose exceeds 6 mg/m^2 twice a week. A 3+3 design will then be followed until the RP2D has been established. Stage 2: Once a RP2D is established in Stage 1, Stage 2 will commence in a once weekly schedule using a 3+3 design until the RP2D has been established for this schedule. Dose expansion (phase IIa) Part A: 14 patients with MT1-MMP expressing NSCLC or TNBC will be treated with BT1718 in the twice a week schedule at the RP2D. At least 6 patients will have pre & post treatment biopsies. Part B: 14 patients with MT1-MMP expressing NSCLC or TNBC will be treated with BT1718 at the RP2D in the once weekly schedule. At least 6 patients will have pre & post treatment biopsies. Part C/D: following parts A & B a decision will be made to explore the selected schedule in tumour-specific cohort(s) of around 15 patients, with refined MT1-MMP biomarker selection. Clinical trial information: 2016-004633-24.

TPS2611 Poster Session (Board #429b), Mon, 8:00 AM-11:30 AM

Phase I study of the pan-HER inhibitor neratinib given in combination with everolimus, palbociclib or trametinib in advanced cancer subjects with *EGFR* mutation/amplification, *HER2* mutation/amplification or *HER3/4* mutation. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Over expression and aberrant function of ErbB receptor tyrosine kinases (EGFR, HER2, HER3 and HER4) contributes to tumorigenesis. Multiple drugs targeting EGFR or HER2 are already approved for various cancers. In spite of clinical successes with EGFR or HER2 inhibitors, single-agents are prone to drug resistance due to aberrant or compensatory activation of additional downstream signaling pathways. We sought to determine whether neratinib, a potent irreversible pan-HER tyrosine kinase inhibitor, would be safe and efficacious in combination with approved inhibitors of mTOR, CDK4/6, or MEK. **Methods:** This is an investigator-initiated, single-center, non-randomized, multi-arm phase I trial of subjects ≥18 years old with measurable advanced solid tumors with no curative therapeutic options and whose tumors harbor somatic mutations or amplifications in ErbB genes. Prior HER2 or EGFR directed therapy are allowed. The study will have 3-arms: Arm 1: neratinib + everolimus, Arm 2: neratinib + palbociclib, Arm 3: neratinib + trametinib. Patients are selected for each arm at investigator's discretion based on tumor type and molecular aberrations present. A standard 3 + 3 dose-escalation design will be utilized and patients will be recruited into five dose levels for each arm of the study. Additional subjects will be treated in dose-expansion cohort(s) once the MTD has been established. A treatment cycle is 28 days. Primary endpoint is determination of the maximum tolerated dose and dose limiting toxicities for each treatment arm. Secondary endpoints include pharmacokinetic and pharmacodynamic analysis along with preliminary anti-tumor efficacy. Prophylactic use of antidiarrheal medication is mandatory during first cycle. Imaging will be performed at 8 week intervals and response will assessed by RECIST v1.1. Enrollment to the study has already commenced. Clinical trial information: NCT03065387.

TPS2612 Poster Session (Board #430a), Mon, 8:00 AM-11:30 AM

A phase 1a / 1b first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study of oral TP-0903, a potent inhibitor of AXL kinase, administered daily for 21 days to patients with advanced solid tumors. *First Author: John Sarantopoulos, Institute for Drug Development, Mays Cancer Center at University of Texas Health San Antonio, San Antonio, TX*

Background: AXL kinase has emerged as a key regulator of the epithelial to mesenchymal transition (EMT), a process that enables cancer cells to develop migratory and invasive properties and acquire resistance to chemotherapeutics and targeted agents. AXL kinase is also known to serve to dampen the immune response to dying tumor cells. By activating EMT, AXL signaling allows cancer cells to engulf neighboring cancer cells undergoing apoptosis, reducing presentation of pro-inflammatory stimuli to the immune system. Consequently, the inhibition of AXL by TP-0903 may potentially reduce cancer cell metastasis, target cancer cells that demonstrate immunity to chemotherapeutics and activate the anti-cancer immune response. **Methods:** Patients with advanced solid tumors that are refractory or intolerant to established therapy have been enrolled in a standard 3+3 dose escalation trial of TP-0903 given orally once daily for 21 days of a 28-day cycle. Cohort dose levels 1 through 5 have been completed without DLT, enrollment into cohort 6 began January 2018. The primary objective is to determine the MTD and DLTs; secondary objectives are PK, radiographic response, PD activity (e.g. GAS6/AXL and other EMT markers), biological activity and RP2D. Key eligibility criteria include age $\geq$ 18 years, ECOG $\leq$1, adequate organ function, life expectancy of $>$ 3 mos. Once the MTD has been reached, the study will be expanded into 5 cohorts of 20 patients each: 1) Patients on immunotherapy who demonstrate progression but are clinically stable, 2) EGFR + NSCLC having progressed on $\leq$ 2 lines of TKIs, 3) BRAF, KRAS or NRAS mutated CRC with no standard therapy remaining, 4) Platinum refractory/resistant ovarian, 5) BRAF mutated melanoma that hasn't responded to immunotherapy or combination BFAF/MEK inhibitor. Patients will be biopsied in each cohort to explore changes to the EMT phenotype. Clinical trial information: NCT02729298.

TPS2613 Poster Session (Board #430b), Mon, 8:00 AM-11:30 AM

Toca 6: A phase 1b study of Toca 511 and Toca FC in patients with advanced solid tumors or lymphoma. *First Author: Jaime R. Merchan, University of Miami, Miami, FL*

Background: Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector that selectively infects cancer cells. Toca 511 spreads through tumors, stably delivering an optimized cytosine deaminase (CD) gene that converts the prodrug, Toca FC (investigational, extended-release 5-FC), into 5-FU within the tumor microenvironment. Preclinical studies show 5-FU kills infected dividing cancer cells and diffuses and kills surrounding cancer cells, myeloid derived suppressor cells, and tumor associated macrophages, thus reestablishing tumor immunity. A prior clinical study showed CD protein expression in resected high grade glioma tumors after intravenous (IV) Toca 511 ([1]Cloughesy T, Walbert T, Bota D, et al. Neuro Oncol 2016; 18(suppl 6):vi17). In animal models of metastatic colorectal cancer, IV Toca 511 infected metastases; subsequent 5-FC treatment resulted in decreased tumor size, improved survival, and durable antitumor immunity ([2]Yagiz K, Rodriguez-Aguirre ME, Espinoza FL, et al. Molecular Therapy: Oncolytics. 2018; 8:14-26). **Methods:** Toca 6 is a Phase 1b, multicenter, open-label study (NCT02576665) investigating changes in immune activity after treatment with Toca 511 & Toca FC in patients with advanced solid tumors or lymphoma. Toca 511 is injected IV daily for 3 days, then intratumorally following biopsy or, for patients with brain metastases, into resection cavity walls following resection. Oral Toca FC is started ~4 weeks later and repeated every 4-6 weeks. Changes from baseline in intratumoral immune activity (infiltrating T-cell subpopulations, B cells, monocytes) at 4 weeks after start of Toca FC are assessed. Peripheral blood is analyzed for effector, memory, Treg, and myeloid lineage cells. Viral RNA, DNA, and CD protein expression in tumor after IV Toca 511 are measured. Safety and efficacy are assessed. Approximately 30 patients will be enrolled at 4 sites in the United States. Enrollment progress by tumor type will be provided at the time of the meeting. Clinical trial information: NCT02576665.

TPS2614 Poster Session (Board #431a), Mon, 8:00 AM-11:30 AM

A modular, multi-arm, multi-part, first time in patient study to evaluate the safety and tolerability of the dual MET kinase/OCT2 inhibitor, OMO-1, alone and in combination with anti-cancer treatments, in patients with locally advanced, unresectable or metastatic solid malignancies. *First Author: Elizabeth Ruth Plummer, Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, United Kingdom*

Background: OMO-1, a highly selective, oral, small molecule MET kinase/OCT2 inhibitor, demonstrated single agent cellular and in vivo anti-tumour activity, including regression in MET driven xenograft models. Preclinical studies to identify optimal drug combinations Predicted efficacious exposures of OMO-1 were reached without clinically relevant adverse events in healthy volunteers, data from this study expedited the ongoing patient study. **Methods:** This novel study design consists of distinct study modules, each investigating a different hypothesis. Module 1, investigating OMO-1 monotherapy, commenced in Aug 2017. It consists of Part A (dose finding) and an optional Part B (cohort expansions in relevant clinical indications eg MET amplification or exon 14 skipping mutation). Part A is a traditional 3 + 3 dose escalation design. Part B expansions are powered to compare response rates to historical data. The option to start Part B and add further modules will be based on emerging data, a substantial protocol amendment being put in place before starting a new module. The dosing schedule/sequence of OMO-1 in each module may be adapted in response to emerging data. The maximum tolerated dose of OMO-1 for individual modules may differ based on the emerging safety profile for each combination. For all modules, Part A cohorts may be expanded by up to 12 additional patients, mandatory serial tumour biopsies will be taken and assessed for relevant PD biomarkers. This design allows one protocol to respond to emerging data, supporting studies in both monotherapy and multiple combinations, reducing the time to 'first subject in study' compared with multiple individual studies. It also allows investigators to pre-empt emerging data and changes to the treatment landscape. These challenges emphasize the need for flexible designs as the landscape of drug development continues to quickly evolve. Clinical trial information: NCT03138083.

TPS2615 Poster Session (Board #431b), Mon, 8:00 AM-11:30 AM

An explorative phase 2 study of afatinib for advanced cancers carrying an EGFR, a HER2 or a HER3 mutation: A Precision trial of the Belgian Society of Medical Oncology. *First Author: Lore Decoster, UZ Brussel, Brussels, Belgium*

Background: Next generation sequencing of solid tumors will increasingly reveal mutations in cancer genes, including EGFR, HER2 and HER3 mutations. Afatinib is a small molecule, which selectively and irreversibly inhibits EGFR, HER2 and HER4 and which blocks transphosphorylation of HER3. Afatinib monotherapy has shown activity in EGFR and HER2 mutated lung cancer and preclinical activity in rare HER3 mutated lung cancer. In addition, synergy has been reported between afatinib and paclitaxel. The aim of this Belgian multicentre multicohort basket trial is to study the activity of afatinib in cancers of any type with an EGFR, a HER2 or a HER3 mutation and to study the efficacy of adding paclitaxel to afatinib at disease progression, regardless of tumor type. **Methods:** Methods: This is a multicenter, open-label, phase 2 study of afatinib in three cohorts of patients with advanced cancer harbouring an EGFR mutation, a HER2 mutation or a HER3 mutation. For each cohort an optimal Simon's two-stage design is used (p0 = 0.10; p1 = 0.30; alpha = 0.05; power 80%). The primary endpoint for each cohort is objective response as determined according to RECIST 1.1. Secondary endpoints are progression free survival, overall survival and toxicity. At progression, paclitaxel weekly will be added to afatinib and response rate, progression free survival and toxicity will be evaluated. In addition to genotype specific response determination, the activity of afatinib in each cancer type will also be evaluated. Rebiopsy will be performed at progression. Major eligibility criteria are: Patients with locally advanced or metastatic cancers harbouring an EGFR, HER2 or a HER3 mutation, excluding EGFR mutated lung cancer. Failure of at least one line of standard systemic therapy. ECOG performance status $\leq$2. Adequate organ function. This study is in progress and has currently recruited 4 patients (2 lung cancers, 2 breast cancers) in the HER2 mutated cohort. No patients have yet been recruited in the EGFR or HER3 mutated cohorts. EudraCT No.: 2016-003411-34 Clinical trial information: 2016-003411-34.

TPS2616 Poster Session (Board #432a), Mon, 8:00 AM-11:30 AM

A phase 2, open-label study of the combination of spartalizumab (PDR001) and LAG525 for patients with advanced solid tumors and hematologic malignancies. *First Author: Sarina Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Spartalizumab is an immunoglobulin G4 humanized monoclonal antibody that binds with subnanomolar affinity to PD-1. LAG525 is an immunoglobulin G4 humanized monoclonal antibody that binds LAG-3 with low nanomolar affinity, inhibiting the LAG-3 interaction with MHC class II and potentially restoring the activity of antitumor effector cells and enhancing anti–PD-1 antitumor activity. Preclinical studies demonstrated that simultaneous inhibition of PD-1 and LAG-3 resulted in synergistic antitumor activity (Woo SR. *Cancer Res.* 2012). PDR001XUS01 will evaluate the clinical benefit of combination checkpoint blockade (CPB) with LAG525 plus spartalizumab across multiple tumor types that are associated with low response rates (overall response rate [ORR] $< 30\%$) to monotherapy CPB. **Methods:** This phase 2, open-label, parallel-cohort study will enroll patients aged $\geq$18 years with documented progression of small cell lung cancer, gastric/esophageal adenocarcinoma, castration-resistant prostate adenocarcinoma, soft tissue sarcoma, ovarian adenocarcinoma, advanced well-differentiated neuroendocrine tumors, or diffuse large B-cell lymphoma who received 1-5 prior lines of therapy, including $\geq$1 line of CPB monotherapy. A minimum of 5 patients and a maximum of 30 patients will be enrolled in each of the 7 tumor-type cohorts for a total planned enrollment between 35 to 210 patients. Patients will receive spartalizumab in combination with LAG525, administered intravenously every 3 weeks. The primary endpoint is the clinical benefit rate (CBR) at 24 weeks of treatment. CBR will be assessed by RECIST 1.1 for solid tumors and the Revised Response Criteria for Malignant Lymphoma for lymphoma (Cheson BD. *J Clin Oncol*. 2007). Secondary endpoints include ORR, time to response, duration of response, time to progression, and safety/tolerability. Accrual is ongoing. Clinical trial information: NCT03365791.

TPS2617 Poster Session (Board #432b), Mon, 8:00 AM-11:30 AM

A phase 2A open-label, multicenter trial of the safety and efficacy of LYC-55716, a first-in-class oral, small-molecule RORγ agonist to treat select solid tumors. *First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: LYC-55716 is a first-in-class, oral, small-molecule agonist of the retinoic acid receptor–related orphan receptor γ (RORγ) under development as a novel immuno-oncology agent for solid tumors. Preclinical evidence suggests that LYC-55716 alters immune cell anti-tumor effector functions and immunosuppressive mechanisms, leading to reduced tumor growth and enhanced survival. In the Phase 1 portion of an ongoing Phase 1/2A trial, LYC-55716 was well tolerated with no dose-limiting toxicities. Evidence of pharmacodynamic target engagement was demonstrated and disease stabilization with tumor reduction was noted in patients after failure of PD-1 therapy. The Phase 2A trial (NCT02929862) is underway in patients with advanced non–small cell lung, head and neck, gastroesophageal, renal cell, urothelial, and ovarian cancers. **Methods:** The Phase 2A portion of the trial will enroll ~70 adult patients who will receive 28-day treatment cycles of LYC-55716 administered twice daily. The primary endpoint is to determine the objective response rate (ORR). Secondary endpoints will include duration of response, progression-free survival, overall survival, safety, and pharmacokinetics. As an exploratory endpoint, immune-related biomarkers will be assessed in blood samples from all patients, taken at screening and every 2-4 weeks through treatment cycle 4, and in tissue biopsy samples of selected patients, taken at screening and 4-12 weeks after beginning cycle 1. Immune markers of interest will be evaluated using a NanoString platform and immunohistochemistry. Results will be analyzed using descriptive and summary statistics. Clinical trial information: NCT02929862.

TPS2618 Poster Session (Board #433a), Mon, 8:00 AM-11:30 AM

Safety, dose tolerance, pharmacokinetics and pharmacodynamics study of CPX-POM in patients with advanced solid tumors. *First Author: Scott James Weir, University of Kansas Cancer Center, Westwood, KS*

Background: Ciclopirox (CPX) is an antifungal agent contained in a number of FDA-approved topical drug products. CPX possesses anticancer activity in a number of *in vitro* and *in vivo* preclinical models, however, it's clinical utility is limited due to low oral bioavailabilty, gastrointestinal toxicity, and poor water solubility. Ciclopirox Prodrug (CPX-POM) selectively delivers its active metabolite, CPX, to the entire urinary tract following systemic administration. In a chemical carcinogen mouse model of bladder cancer, CPX-POM treatment resulted in significant decreases in bladder weight, a clear migration to lower stage tumors, dose-dependent reductions in Ki67 and PCNA staining, and inhibition of Notch 1 and Wnt signaling pathways. **Methods:** Study CPX-POM-001 (NCT03348514) is an ongoing US multicenter, Phase I, open-label, dose escalation study to evaluate dose-limiting toxicities (DLTs), define the maximum tolerated dose (MTD), and to determine the recommended Phase II dose of IV CPX-POM. Approximately 24 patients with any histologically- or cytologically-confirmed solid tumor type refractory to standard therapy, and also meet other standard Phase I eligibility criteria, will be enrolled in dose escalation cohorts. The MTD will be defined as the dose BELOW that dose which causes DLTs in $\geq$33% of patients. Safety and tolerability will be based on an assessment of adverse events, physical examinations, vital signs, electrocardiogram, clinical laboratory tests, ophthalmologic assessments, and concomitant medications. Single dose and steady-state pharmacokinetics of CPX-POM, CPX and ciclopirox glucuronide are being characterized in both plasma and urine. Urine ß-glucuronidase activity is also being determined. Single and multiple dose pharmacodynamics of CPX-POM are being characterized by measuring circulating biomarkers of Wnt and Notch cell signaling pathways. Enrollment began in January 2018 at a starting IV CPX-POM dose of 30 mg/m^2. Doses are currently being escalated in 100% increments until a $\geq$Grade 2 is encountered, at which point that cohort and all subsequent cohorts will follow a classical "3 + 3" dose escalation design. Clinical trial information: NCT03348514.

TPS2619 Poster Session (Board #433b), Mon, 8:00 AM-11:30 AM

First-in-human phase 1-2A study of CB-103, an oral Protein-Protein Interaction Inhibitor targeting pan-NOTCH signalling in advanced solid tumors and blood malignancies. *First Author: Jose Manuel Perez Garcia, Medical Oncology Department (IOB), Quiron Hospital, Barcelona, Spain*

Background: NOTCH signalling is a key development pathway whose aberrant activation is recognised to play an oncogenic role in human cancers. When NOTCH signalling is inappropriately activated by genetic alterations, it becomes an oncogenic driver for NOTCH-dependent cancers, while upregulation of NOTCH receptors is linked to resistance to standard of care. CB-103 is a new small molecule protein-protein interaction (PPI) inhibitor able to target assembly of the NOTCH transcription complex in the cell nucleus leading to downregulation of NOTCH target genes (c-MYC, CCND1, HES1) and inhibition of NOTCH signalling independently of NOTCH mechanisms of activation. CB-103 has demonstrated efficacy and tolerability in different preclinical tumor models derived from various NOTCH-driven cancer indications and in blood from NOTCH-activated leukemia pts. **Methods:** This study is a multi-centre, open label, non-randomised, phase 1-2A dose escalation study in adult patients (pts), with expansion arms of oral CB-103. Aim of phase 1 is to find the MTD/RP2D. The starting dose is targeting a plasma exposure (daily AUC) that has reasonable safety margin and allows reliable determination of pharmacokinetics (PK). An adaptive Bayesian logistic regression model for dose escalation is implemented in phase 1 to guide determination of MTD/RP2D. Full PK sampling profiles will be taken on days 1 & 8 of cycle one (28 days) and day 1 of cycle two. NOTCH-related PD and Biomarker exploratory analyses are planned on tumour biopsies, hair follicles and blood samples (liquid biopsy). Administration schedule (once-daily) may be adapted depending on PK and safety. 3-6 eligible pts regardless of NOTCH pathway activation status are enrolled per dose group in phase 1, while pts in phase 2A will be selected for NOTCH pathway genetic alterations. Phase 2A will assess preliminary efficacy of CB-103 in expansion arms across different indications using Bayesian design. Enrolment into 1st dose group (15mg) started with first pt treated on 20Dec17: 7 pts registered with 2 screen failures, 1 discontinued due to early cancer progression and 4 in treatment in their first treatment cycle. Clinical trial information: NCT03422679.

TPS2620 Poster Session (Board #434a), Mon, 8:00 AM-11:30 AM

Phase 1 study of an oxidative phosphorylation inhibitor IM156 in patients with advanced solid tumors. *First Author: Sun Young Rha, Severance Hospital, Seoul, Republic of Korea*

Background: IM156 is a novel oral agent with a biguanide structure, which has anticancer activity through AMPK activation and reduction of oxidative phosphorylation. Inhibition of oxidative phosphorylation (OXPHOS) is detrimental to OXPHOS dependent drug resistant cancer cells which adapt metabolic shift upon cancer treatment or are intrinsically OXPHOS dependent cancer cells. OXPHOS dependent cancer cells are prone to energy stress such as OXPHOS inhibition that ultimately cause cancer cell death. Preclinical in vitro and in vivo experiments demonstrated that IM156 can be effective in glioblastoma, and other solid tumors. Therefore, a phase I dose-escalation study to determine safety and preliminary signals of activity of IM156 has been designed and activated (NCT03272256). **Methods:** This is an open label, single center, dose-escalation study using the 3+3 design to determine the maximum tolerated dose and/or recommended phase 2 dose, dose limiting toxicities (DLT), safety, pharmacokinetics, pharmacodynamics and preliminary signals of anticancer efficacy of IM156 in patients with advanced solid tumors refractory to standard therapies. Eligible patients are adults with advanced solid tumors refractory to standard therapies with adequate performance status (ECOG $\leq$2) and organ function with measurable disease per RECIST 1.1 (or RANO for gliomas). IM156 is administered orally every other day starting on day 1 of each 28 days cycle. The study has total of 6 dose levels ranging from 100 mg to 1,800 mg and the dose escalation continues per 3+3 design as long as the proportion of DLTs $<$ 33% ($<$ 2/6). DLTs are evaluated during the first 28 days of therapy (cycle 1). Efficacy per RECIST 1.1 (RANO for gliomas) is evaluated every two cycles. Pharmacokinetics studies have been designed to determine Cmax, AUC, T1/2 and other parameters. Pharmacodynamics studies include PET scans with FDG and acetate probes, tissue and blood biomarkers including lactate levels. As of 2/8/18 the study enrolled 6 patients into two dose levels (100mg and 200mg respectively) and enrollment continues. Clinical trial information: NCT03272256.

TPS2621 Poster Session (Board #434b), Mon, 8:00 AM-11:30 AM

Phase I study of procaspase activating compound-1 (PAC-1) for treatment of advanced malignancies. *First Author: Oana C. Danciu, University of Illinois at Chicago, Chicago, IL*

Background: Dysregulation in apoptotic pathways is a hallmark feature of cancer, offering opportunities for pharmacologic intervention in its treatment. Caspases, a family of proteases, play several roles in apoptosis. Caspase-3 catalyzes the intra-cellular proteolysis that characterizes part of the apoptotic process. Caspase-3 levels are low in many tumors including: glioblastoma; breast, colon, lung, and liver cancers: lymphoma: neuroblastoma; and melanoma. In contrast, procaspase-3, the precursor of caspase-3 is elevated in these tumors. We describe a phase I study of PAC-1, a drug that catalyzes the conversion of procaspase -3 to caspase-3. It induces apoptosis in tumor cell lines *in vitro*. *In vivo* activity has also been shown, when combined with alkylating chemotherapy, in rodent glioma models and in canines diagnosed with malignant glioma. **Methods:** This Phase I dose escalation study has two components: the first (C1) to determine the maximum tolerated dose (MTD) of PAC-1 in advanced malignancies; the second (C2) to determine the MTD of PAC-1 when combined with temozolomide (TMZ) in patients with recurrent anaplastic astrocytoma (AA) or glioblastoma (GBM). A modified Fibonacci 3 + 3 design is used, expanding to nine subjects at the MTD level in each component. PAC-1 pharmacokinetics is assessed in all subjects during the first cycle. Secondary objectives include pharmacodynamics and correlations of PAC-1 activity with procaspase-3 expression in tumor tissue. Neurologic toxicity is closely monitored throughout the study. Inclusion criteria: diagnoses of advanced malignancies (C1) and recurrent AA or GBM (C2), ECOG PS 0-2, adequate organ function. Exclusion criteria: prior cytotoxic therapy in the last 3-6 weeks (varying with drug class) or uncontrolled chronic illness. Administration and design: For C1, PAC-1 (orally administered) is dosed at 75-1,000 mg daily on days 1-21 of each 28 day cycle. For C 2, the first PAC-1 dose is 375 mg daily with potential for escalation to 1,000 mg daily. TMZ, PO, is dosed at 150 mg/m2 daily, days 8-12, of each cycle. Enrollment to date for C1 is 27, (dose level 6); and for C2 is 4 (dose level 1). The study is open to accrual. Clinical trial information: NCT02355535.

3000 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

ICONIC: Biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in patients (pts) with advanced cancers. *First Author: Timothy Anthony Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ICOS is a costimulatory molecule expressed on the surface of activated T cells. JTX-2011 is an ICOS agonist designed to stimulate CD4 T effector (T eff) cells and deplete intratumoral T regulatory (Treg) cells. Preclinical efficacy was seen with mouse JTX-2011 monotherapy (mono) and combination (combo) with anti-PD-1 in ICOS+ tumors. **Methods:** Relapsed/refractory cancer pts received escalating doses of JTX-2011 mono or combo with nivo in Phase 1 (P1), and the recommended P2 dose (RP2D) in P2, based on safety, target engagement (TE), immunophenotyping and cytokines. P2 gastric (GC) and triple negative breast (TNBC) combo cohorts completed enrollment. ICOS was assessed by IHC in archival (arch) and fresh pre-treatment tumor biopsies (bx) or by flow in peripheral blood. **Results:** 164 pts had ≥1 dose of JTX-2011; 71 P1 (40 mono, 31 combo); 93 P2 (25 mono, 68 combo) including 7 GC mono, 24 GC and 16 TNBC combo. Pts ≥3 prior therapies: 57% GC mono, 48% GC combo, 56% TNBC combo. JTX-2011 RP2D: 0.3mg/kg q3w mono and combo with nivo 240 mg q3w. DLTs: raised AST/ALT and pleural effusion at 1 mg/kg mono. At 0.3mg/kg: TE > 70% sustained through 3wks; no substantial change in # of peripheral T eff or Tregs; dose dependent increase in IFN-γ at 1-6 hrs. P2 adverse events (AEs): drug-related G3-4 8% mono, 13% combo; immune-related 4% mono, 21% combo; infusion related 12% mono, 19% combo. Of 13 GC combo pts with paired arch and fresh bx, 6 were ICOS hi on both, 5 changed from low to hi. Of 7 TNBC combo pts with paired bx, 5/7 archival were ICOS hi, 4/7 fresh were ICOS hi. RECIST antitumor activity: JTX-2011 mono: 1/7 partial response (PR) in GC; 2/5 stable disease (SD) in P1 TNBC. JTX-2011 combo: 2 PRs (0.1, 0.3mg/kg) and 2 ongoing SD in 19 P1/2 GC; 1 PR in 15 P2 TNBC. Of 17 evaluable pts, 4 had emergence of peripheral CD4 T cell ICOS hi subsets during JTX-2011 therapy, including 1 PR mono, 2 PR combo and 1 SD; none were seen in pts with progressive disease. **Conclusions:** JTX-2011 mono and combo with nivo were well tolerated with antitumor responses in heavily pre-treated GC and TNBC pts. Emergence of peripheral blood CD4 ICOS hi T cell subsets may be a surrogate biomarker of response. Further trials of JTX-2011 are planned. Clinical trial information: NCT02904226.

3001 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Anti-CD27 agonist antibody varlilumab (varli) with nivolumab (nivo) for colorectal (CRC) and ovarian (OVA) cancer: Phase (Ph) 1/2 clinical trial results. *First Author: Rachel E. Sanborn, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR*

Background: Preclinical studies demonstrate synergistic antitumor activity of PD-1 blockade and varli, a CD27 agonist antibody. Ph1 results were previously presented from a Ph1/2 study assessing the safety of nivo with varli; we now report Ph1/2 results for CRC and OVA. **Methods:** Pts with advanced, treatment refractory (anti-PD-1/L1 naïve) solid tumors received nivo (Ph1: 3 mg/kg; Ph2: 240 mg) every two weeks (Q2W). Ph1 cohorts also received varli at 0.1, 1, or 10 mg/kg Q2W. Ph2 cohorts received varli at 3 mg/kg Q2W (CRC and OVA), 0.3 mg/kg Q4W (OVA), or 3 mg/kg Q12W (OVA). Primary study objectives: safety (Ph1) and overall response rate (Ph2). **Results:** 42 CRC and 66 OVA pts received nivo and varli. Toxicity was consistent with the safety profile of each agent; treatment-related serious events occurred for 3 pts with CRC (mixed motor sensory neuropathy, pneumonitis, elevated ALT) and 2 pts with OVA (acute kidney injury, hepatitis, small bowel obstruction). Of 49 (8 Ph1, 41 Ph2) evaluable OVA pts, 5 (10%; all Ph2) had RECIST 1.1 Partial Response (PR) and 19 (39%; 6 Ph1, 13 Ph2) had Stable Disease (SD). On-treatment biopsies revealed an increase in PD-L1 expression ($p < 0.006$), and CD8+ T cells ($p < 0.005$), which was more prevalent among pts with better outcome (PR or ≥ 16 weeks of SD), $p < 0.017$ and $p < 0.002$. Of 41 (21 Ph1, 20 Ph2) evaluable CRC pts, 2 (5%; 1 Ph1, 1 Ph2) had PR (Ph1 pt MSI-low, Ph2 pt MSI-high; both PD-L1 neg) and 7 (17%; 3 Ph1, 4 Ph2) had SD. 89% of CRC pts had PD-L1 neg tumors at baseline. In contrast to OVA, increase in tumor PD-L1 expression or CD8+ T cells during treatment in CRC patients was infrequent, correlating with less overall clinical impact. **Conclusions:** Varli with nivo was well tolerated without evidence of additive toxicity. In OVA pts, treatment induced significant tumoral changes that correlate with better outcome. Remaining analyses of OVA pts will examine the impact of varli dosing schedule on clinical outcome and biomarkers. The mechanisms that mediate the lack of T cell and PD-L1 increase in some pts are being explored by further tumor molecular profiling. Clinical trial information: NCT02335918.

3002 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

A first-in-class, first-in-human phase 1 pharmacokinetic (PK) and pharmacodynamic (PD) study of Hu5F9-G4, an anti-CD47 monoclonal antibody (mAb), in patients with advanced solid tumors. *First Author: Branimir I. Sikic, Stanford University School of Medicine, Stanford, CA*

Background: Hu5F9-G4 (5F9) is a humanized mAb that inhibits CD47, a "don't eat me" signal for macrophages, and can enhance tumor cell phagocytosis and T-cell priming. Preclinically, 5F9 is active against a wide range of tumors. **Methods:** Patients (pts) were enrolled in 3 dose escalation groups using a 3+3 design (NCT02216409). Part A (11 pts) defined 1 mg/kg of 5F9 as the optimal week (wk) 1 priming dose that was used subsequently in Parts B & C. Part B (14 pts) evaluated higher weekly (wkly) maintenance doses starting wk 2 and Part C (18 pts) evaluated an additional loading dose in wk 2. Safety, PK, PD and efficacy data are presented here. **Results:** In 58 pts (median age 60 y; median prior treatments 5) the common tumor types were colorectal (CRC), ovarian, adenoid cystic, breast, pancreatic, and squamous cell head & neck cancers. Using a priming + load/maintenance dose, no maximum tolerated dose (MTD) was reached in Part B where 14 pts received ≥20 mg/kg of 5F9 wkly, nor in Part C where doses of 20 (7 pts), 30 (8 pts) and 45 mg/kg (3 pts) were well tolerated. Common Part C drug-related adverse events were fatigue 50%, chills 50%, pyrexia 45%, anemia 39%, headache 34%, lymphopenia 28%, hemagglutination 17%, transient hyperbilirubinemia 17%, and myalgias 11%. Most AEs were Grade (Gr) 1 or 2 occurring in cycle 1 (28 days) with Gr 3+ being uncommon and no cumulative effects. Transient Grade 1/2 acute anemia due to CD47 blockade on older RBCs was common but was mitigated by the priming dose strategy. Saturation of nonlinear PK occurred at ≥10 mg/kg resulting in a prolonged $t_{1/2}$ ~14 days, 5F9 levels exceeding preclinical antitumor activity thresholds (200 ug/mL) and resulting in > 99% WBC CD47 receptor occupancy. The recommended Phase 2 dose is 1 mg/kg priming dose wk 1 followed by 30 mg/kg wkly x 3 and then 30 mg/kg Q2 wks thereafter. Two pts (ovarian and fallopian tube cancers) had confirmed partial responses and were treated for 23 and 41+ weeks, respectively. In 13 CRC pts treated at doses ≥20 mg/kg, 6 had stable disease with a median treatment duration of 18 wks. **Conclusions:** 5F9 prime + maintenance doses are well tolerated and demonstrate monotherapy antitumor activity. Clinical trial information: NCT02216409.

3003 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Durability of response in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B-cell lymphoma. *First Author: Frederick Lundry Locke, Moffitt Cancer Center, Tampa, FL*

Background: Axi-cel, an anti-CD19 CAR T cell therapy, demonstrated significant clinical benefit and a manageable safety profile for pts with refractory large B cell lymphoma in ZUMA-1 (Neelapu & Locke et al. *NEJM*. 2017). These results led to its approval by the US FDA for the treatment of adult pts with relapsed or refractory large B cell lymphoma after ≥ 2 prior lines of therapy. Here, we examined responses over time in phase 2 of ZUMA-1. **Methods:** Pts with refractory large B cell lymphoma received 2×10^6 CAR T cells/kg after low-dose conditioning (Neelapu & Locke et al. *NEJM*. 2017). Best objective response rates (BOR) were analyzed locally by investigators (local) and centrally by independent review committee (IRC; Cheson et al. *J Clin Oncol*. 2007); concordance was measured as the percentage of pts whose IRC matched local. **Results:** As of 8/11/17, median follow-up (f/u) was 15.1 mo for the 101 pts treated with axi-cel. While the BOR of 82% at primary analysis (PA; median f/u 8.7 mo) by local remained consistent (83%) at long-term f/u (LTFU; median of 15.1 mo), complete response (CR) rates increased from 54% to 58% (Table). Out of 34 pts with partial response (PR) at 1 mo, 11 (32%) converted to CR by the LTFU. High concordance (77% - 79%) was observed for objective response rates (ORR [CR + PR]) between local and IRC at all times assessed. Landmark analysis of progression-free survival (PFS) by response status (per local) revealed that most of the 60 pts with disease control (stable disease or better) at 3 mo had prolonged disease control with a 73% 12-mo PFS rate. Of the 42 pts with CR and 9 with PR at 3 mo, the 12-mo PFS rates were 79% and 78%, respectively. **Conclusions:** Treatment with axi-cel induces high response rates in pts with refractory large B cell lymphoma. CR rates increased through the LTFU, suggesting that responses deepen over time and that pts with PR can achieve CR as late as a year post-infusion. ORR at 3 mo may be prognostic for prolonged PFS. Drs Locke and Neelapu contributed equally. Clinical trial information: NCT02348216.

	BOR, n (%)				
	Local		IRC		ORR Concordance, %
Data-cut; median f/u, mos N = 101	ORR	CR	ORR	CR	
PA; 8.7	83 (82)	55 (54)	72 (71)	52 (51)	77
YESCARTA USPI; 11.6	84 (83)	55 (54)	73 (72)	52 (51)	79
LTFU; 15.1	84 (83)	59 (58)	73 (72)	52 (51)	79

3004 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Treatment of metastatic human papillomavirus-associated epithelial cancers with adoptive transfer of tumor-infiltrating T cells. *First Author: Sanja Stevanovic, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Adoptive T-cell therapy (ACT) is a promising cancer treatment modality. However, its study in epithelial cancers has been limited. Human papillomavirus (HPV)-associated cancers are difficult to treat epithelial malignancies for which better systemic treatments are needed. We conducted a clinical trial of ACT for the treatment of metastatic HPV-associated cancers. **Methods:** The clinical trial was a phase II design with two disease cohorts (cervical cancers and non-cervical cancers). Patients were treated with a single infusion of tumor-infiltrating lymphocytes (TIL), which were generated, when possible, from TIL subcultures with HPV-oncoprotein reactivity (HPV-TIL). HPV-TIL infusion was preceded by a lymphocyte-depleting conditioning regimen followed by systemic high-dose aldesleukin. **Results:** Objective tumor responses occurred in 5/18 (28%) patients in the cervical cancer cohort and 2/11 (18%) patients in the non-cervical cancer cohort. In the cervical cancer cohort, two patients experienced complete responses that are ongoing 53 and 67 months after treatment. Three patients experienced partial responses that were three months in duration. In the non-cervical cancer cohort, partial responses were observed in a patient with anal cancer (four months duration) and a patient with oropharyngeal cancer (five months duration). The latter patient had previously been treated with six systemic anti-cancer agents. Multiple thoracic metastases responded completely after HPV-TIL infusion. A brain metastasis developed five months after treatment and was surgically resected. He is without evidence of disease 51 months after treatment. **Conclusions:** HPV-TIL can mediate regression of metastatic HPV-associated cervical, oropharyngeal and anal epithelial cancers in some patients. These findings support the study of ACT for HPV-associated cancers and possibly other epithelial malignancies. Clinical trial information: NCT01585428.

3005 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Pilot study of NY-ESO-1^{c259} T cells in advanced myxoid/round cell liposarcoma. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Metastatic myxoid/round cell liposarcoma (MRCLS) has a poor prognosis. NY-ESO-1 is expressed in 80-90% of MRCLS tumors. This study evaluates affinity enhanced autologous NY-ESO-1^{c259}T cells recognizing an NY-ESO-1 derived peptide complexed with HLA-A*02 (SPEAR T-cells) in MRCLS (NCT02992743). **Methods:** This open label phase I/II single arm pilot study evaluates efficacy, safety and translational research endpoints. Eligible pts are $\geq$ 18 yr; HLA-A*02:01^{+}, *02:05^{+} or *02:06^{+}; have advanced MRCLS expressing NY-ESO-1 at 2+/3+ intensity in $\geq$30% of tumor cells by IHC; measurable disease; received anthracycline therapy; ECOG status 0 or 1; and adequate organ function. Following apheresis, T cells are isolated, expanded, transduced with a lentiviral vector containing the NY-ESO-1^{c259}TCR, and 1–8 $\times$ 10^{9} transduced T-cells are infused on day 1 after lymphodepletion with Flu 30 mg/m^{2}/d and Cy 600 mg/m^{2}/d on d -7 to -5. Response is assessed at 4, 8, 12, and 24 wk and then every 3 mo until disease progression. **Results:** 37 patients were screened; 19 had the requisite HLAs. NY-ESO-1 was present at required levels in 13/14 tumors tested. 2 patients received the TCR therapy (as of 30Jan18). The tumors of treated pt expressed NY-ESO-1 at 3+ in 100% and 2 or 3+ in 60% of tumor cells. The 1st patient received 5.00 $\times$ 10^{9} transduced T-cells and achieved an unconfirmed partial response; the target lesions showed 32% reduction from baseline at wk 12. AEs include grade (G) 4 lymphopenia, neutropenia, leukopenia, G3 thrombocytopenia and G2 anemia; all were considered related to lymphodepletion and resolved. G1 CRS with fever, G1 AST elevation, and G2 ALT elevation were also reported. The CRS resolved and was considered related to TCR therapy. Transduced cells were detected in peripheral blood 12 wk post infusion. The 2nd patient received 1.04 $\times$ 10^{9} transduced T-cells and achieved an unconfirmed partial response; target lesions showed 37% reduction from baseline at wk 4. AEs include G4 lymphopenia, G3 anemia, G2 thrombocytopenia, G2 CRS with fever and rash. Confirmatory scans are pending. **Conclusions:** The data indicate that treatment with NY-ESO-1^{c259}T cells in MRCLS is feasible with potential for anti-tumor effects. We will report updated results. Clinical trial information: NCT02992743.

3006 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

NKTR-214 (CD122-biased agonist) plus nivolumab in patients with advanced solid tumors: Preliminary phase 1/2 results of PIVOT. *First Author: Adi Diab, Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PIVOT is an ongoing, open-label, phase 1/2 study of NKTR-214 (214; CD122-biased agonist) plus PD-1 inhibitor nivolumab (N) in patients (pts) with advanced cancers (MEL, RCC, NSCLC, TNBC, and UC). 214 monotherapy increases newly proliferative CD8^{+} T cells in tumors and increases cell surface PD-1 and PD-L1 expression, demonstrating a potentially synergistic mechanism with anti-PD-1 therapy. **Methods:** In P1 dose escalation, pts received 214 (0.003, 0.006 or 0.009 mg/kg) with N (240 mg or 360 mg) administered IV as outpatient Q2W or Q3W; in P2 expansion, the RP2D of 214 (0.006 mg/kg) with N (360 mg) Q3W was administered concurrently. Response was assessed Q8W by RECIST v1.1. Matched tumor samples were evaluated for changes from baseline in immune cell populations, gene expression, and T cell receptor repertoire. Tumor baseline and on treatment PD-L1 protein expression was assessed (28-8 IHC assay). **Results:** As of 7FEB2018, 162 pts (P1, n = 38; P2, n = 124) were evaluable for safety. The most common TRAEs of all grades at the RP2D ($>$ 25%) in pts were flu-like symptoms (63%), fatigue (39%), rash (38%) and pruritus (30%). G3+ TRAEs at the RP2D were 11%. No pts discontinued treatment or died from TRAEs. A total of 60 IO-treatment naïve stage IV pts (P1, n = 30; P2, n = 30) were efficacy evaluable ($\geq$1 scan) (23 MEL, 24 RCC, 6 NSCLC, 4 UC, 3 TNBC). 22/30 P2 pts had only 1 scan. ORR (CR+PR) and DCR (CR+PR+SD) in 23 MEL (1L) pts was 52% and 78%. 18/23 MEL pts had known PD-L1 status. ORR was 5/9 (56%) for PD-L1(+) pts and 4/9 (44/%) for PD-L1(-) pts. ORR and DCR in 24 RCC (1L) pts was 54% and 79%. 20/24 RCC pts had known PD-L1 status. ORR was 4/7 (57%) for PD-L1(+) pts and 7/13 (54%) for PD-L1(-) pts. ORR and DCR in 6 NSCLC (1-2L) pts was 50% and 67%. 5/6 pts had known PD-L1 status. ORR was 3/5 (60%) in PD-L1(-) pts. ORR and DCR in 4 UC (1L) was 75% and 100%. ORR/DCR in 3 TNBC (1- 2L) pts was 33%. In 60 evaluable pts, 32/32 responses are ongoing (0.3+ to 12.0+ mos) with 45/60 pts still on treatment. **Conclusions:** 214 plus N was well-tolerated with no TRAE discontinuations. Preliminary efficacy shows encouraging ORR/DCR with responses observed in 5 of 5 tumor types in I-O treatment naïve 1-2L pts. Updated data to be presented. Clinical trial information: NCT02983045.

3007 **Oral Abstract Session, Sat, 3:00 PM-6:00 PM**

Safety and activity of M7824, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with HPV associated cancers. *First Author: Julius Strauss, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Therapies targeting PD-1/L1 have produced response rates of 15-20% in patients (pts) with HPV associated cancers (HAC) including cervical (cerv), anal or head and neck squamous cell carcinoma (HNSCC). Another potential target for these diseases is transforming growth factor-β (TGF-β) as genome wide association studies in HPV+ cancers have shown TGF-β to be significantly overexpressed. M7824 is a bifunctional fusion protein targeting PD-L1 and TGF-β comprised of a human IgG1 monoclonal antibody against PD-L1 fused to 2 extracellular domains of TGF-β receptor II, which functions as a TGF-β "trap". We report data from pts with HAC on a fully enrolled dose escalation portion of a phase 1 trial of M7824. **Methods:** NCT02517398 is a phase 1, 3+3 dose-escalation study. Pts received M7824 at 1, 3, 10, 20, or 30 mg/kg Q2W until PD or unacceptable toxicity. The primary objective was safety and maximum tolerated dose (MTD). A key secondary objective was best overall response per RECIST v1.1. **Results:** As of Feb 5 2018, 16 pts with HAC (9 cerv, 4 anal and 3 HNSCC) were enrolled. HPV was + in 11 pts and unknown (uk) in 5 pts. Grade 3 treatment related adverse events (TRAEs) occurred in 3/16 (colitis, cystitis, gastroparesis; all cerv). Notably all 3 also had disease reduction. Grade 4 hypokalemia accompanied the gastroparesis. No other grade 4-5 TRAEs were seen. The only DLT was colitis (at 20 mg/kg) and no MTD was reached. 9/16 (56%) have had disease reduction on treatment including 1 pt (cerv; HPV+) with a durable CR, 4 pts (2 HNSCC, 2 anal; all HPV+) with durable PRs, 1 pt (cerv; HPV uk) with an unconfirmed PR, 2 pts (2 cerv; both HPV uk) with near PRs (-25%, -27%) and 1 pt (anal; HPV uk) with modest reduction (-9%). In all, 6/16 (37.5%) have ongoing responses, 5/6 confirmed. Of pts with known HPV+ disease, 5/11 (45.5%) have ongoing confirmed responses. **Conclusions:** Data from a phase 1 trial of M7824 suggests a manageable safety profile and an ORR of 37.5% in pts with HAC including a confirmed ORR of 45.5% in pts with known HPV+ disease. M7824 is a promising drug for pts with HAC or HPV+ cancers and continues to be evaluated in phase I and II trials. Clinical trial information: NCT02517398.

3008 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

ALT-803, an IL-15 superagonist, in combination with nivolumab in metastatic non-small cell lung cancer: Ongoing experience and biomarker development from a non-randomized, open-label, phase Ib/II trial. *First Author: John M. Wrangle, Johns Hopkins Univ School of Medcn, Baltimore, MD*

Background: PD-1/PD-L1 blockade fails to yield a response in about 80% of unselected non-small cell lung cancer (NSCLC) patients and acquired resistance will lead to treatment failure in most responders. Cytokine therapy with IL-2/IL-15Rbg agonists has demonstrated durable responses in select solid tumors, though the response rates are low. There have been no published reports of combination trials of IL-2/IL-15Rbg agonists cytokines with anti-PD1 immunotherapy. **Methods:** In this phase Ib/II trial NSCLC patients received anti-PD1 immunotherapy in combination with ALT-803, an IL-15 super-agonist. Eligibility criteria include measurable disease, no history of auto-immune disease, and ECOG performance status of 0 or 1. Nivolumab was administered IV every 14 days and ALT-803 was administered subcutaneously weekly for six months. The primary objective of the phase Ib study was to define safety, tolerability and to define a recommended phase II dose (RP2D) of ALT-803 in combination with nivolumab. Phase II enrollment is ongoing. **Results:** As of February 13, 2018, 38 subjects have been enrolled to trial. No dose-limiting toxicities have been observed. Common adverse events are injection site reactions and flu-like symptoms. The RP2D of ALT-803 is weekly subcutaneous 20 mcg/kg in combination with intravenous nivolumab 240mg every two weeks. The most common grade 3 adverse event, occurring in two patients each, was lymphocytopenia and fatigue. A Grade 3 myocardial infarction occurred in one patient. No grade 4 or 5 toxicity was observed. Among patients in the phase Ib experience who had PD1 immunotherapy relapsed or refractory tumors, the disease control rate was 91% (10 of 11) patients, with 27% (3 patients) partial responses and 64% (7 patients) stable disease noted. Among 10 patients with PD-L1 negative tumors, the disease control rate was 70% and a 30% partial response rate. **Conclusions:** The combination of nivolumab with ALT-803 can be safely administered in an outpatient setting. There is encouraging anti-tumor activity with the combination of nivolumab with ALT-803. Phase II study of the combination is ongoing. Clinical trial information: NCT02523469.

3009 Poster Discussion Session; Displayed in Poster Session (Board #223), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Cardiovascular adverse events in immune checkpoint inhibitor clinical trials: A U.S. Food and Drug Administration pooled analysis. *First Author: Laleh Amiri-Kordestani, U.S. Food and Drug Administration, Bethesda, MD*

Background: Immune checkpoint inhibitors (ICI) have been approved for numerous cancers and have transformed patient outcomes. There is a growing recognition of immune-related adverse events (AE), including cardiovascular (CV) AE. While rare cases of fulminant myocarditis have been reported, the full extent of CV AE remains unknown. **Methods:** This exploratory observational study pooled data from prospective ICI trials submitted to FDA in initial or supplemental Biologics License Applications until 1/2018. To systematically categorize CV AE, we combined CV MedDRA Preferred terms with a focus on the underlying pathology. Descriptive statistics were used to characterize the incidence of CV AE by exposure to ICI and calculate relative risks (RR) between arms of interest. To account for bias with respect to duration of exposure, we based our analyses on the first 6-month treatment window. **Results:** Within 59 trials (N = 21,664), ICI therapy was associated with higher rates of myocarditis, vasculitis, ischemia, arrhythmia, and pericardial disease compared to non-ICI therapy. When ICIs were used in combination, CV AE increased across most categories compared to monotherapy. Five fatal cases of myocarditis were reported with ICI therapy. **Conclusions:** To our knowledge, this is the largest report of CV AE associated with ICI in clinical trials. Our results show that combination ICI therapy appears to be associated with an increase in observed incidence rates of CV AE relative to ICI monotherapy.

CV AE for patients with/without ICI.

	Incidence Rates (%)			Relative Risks		
Grouping	All ICI N = 18605	Combo N = 1533	Mono N = 17072	Non-ICI N = 3059	ICI/Non-ICI	Combo/Mono
CHF	0.53	0.65	0.52	0.78	0.67	1.27
Arrhythmia	5.56	8.41	5.31	5.03	1.11	1.59
Myocarditis	0.03	0.13	0.02	0	*	7.42
Valvular	0.03	0.2	0.02	0.13	0.25	11.14
Vasculitis	0.04	0.07	0.04	0.03	1.32	1.59
Vascular/Thromboembolic/Bleeding	8.93	11.61	8.69	10.33	0.86	1.34
HTN	3.86	5.28	3.73	9.25	0.42	1.42
Sudden Cardiac Death	0.3	0.46	0.28	0.42	0.70	1.62
Vascular/PVD	0.27	0.52	0.25	0.56	0.48	2.12
Pericardial/Pericarditis	0.7	0.26	0.74	0.62	1.13	0.35
Ischemia	0.58	1.3	0.51	0.42	1.35	2.56

*not available due to 0 events in the Non-ICI group

3010 Poster Discussion Session; Displayed in Poster Session (Board #224), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Cumulative antibiotic use and efficacy of immune checkpoint inhibitors in patients with advanced cancer. *First Author: Nadina Tinsley, Christie Hospital, Manchester, United Kingdom*

Background: Efficacy of immune checkpoint inhibitors (CKIs) for treatment of cancer may be affected by the use of antibiotics (ABX). The gut microbiome is involved in immunotherapy responses therefore ABX known to alter the gut microbiome may affect tumour inflammation and microenvironment, leading to decreased CKI efficacy. **Methods:** Retrospective data analysis was undertaken on metastatic cancer patients (pts) treated with CKIs between January 2015 and March 2017 at the Christie NHS Foundation Trust. Melanoma, renal and non-small cell lung cancer (NSCLC) pts were included. Demographics, prior systemic treatment, extent of disease, CKI agent and use of ABX (route, duration, multiple concurrent/successive courses) were collected. Progression free survival (PFS) and overall survival (OS) were compared between ABX groups (ABX^+ defined as pts treated with ABX within 2 weeks of CKI initiation or 6 weeks after, ABX^- as pts with no ABX during specified period). Statistical analyses were performed with univariate and multivariate models. **Results:** Of 303 included pts (201 (66%) melanoma, 56 (18%) NSCLC and 46 (15%) renal) 94 (31%) received ABX (commonest beta-lactam ABX and macrolides). In multivariate analysis, ABX^+ pts had shorter PFS and OS when compared to ABX^- pts: PFS 97 days (95% CI 84-122) vs 178 days (95% CI 155-304) p = 0.049; OS 317 days (95% CI 221-584) vs 651 days (95% CI 477-998) p = 0.001. Cumulative ABX ($>$ 10 days, multiple concurrent/successive courses) demonstrated particularly shortened PFS 87 days (95% CI 83-122) p = 0.0093 and OS 193 days (95% CI 96-355) p = 0.00021. Pts treated with ABX prior to CKI initiation had shorter PFS and OS than those treated after CKI initiation (HR 1.37 and HR 1.72) p = 0.29 and 0.08 respectively. **Conclusions:** To our knowledge, this is the largest multivariate analysis showing ABX use is an independent predictor of shorter PFS and OS in cancer pts treated with CKI. It is the first analysis to demonstrate cumulative ABX use is associated with even poorer outcomes across multiple tumour types independent of clinical factors. The data suggests a trend towards reduced PFS in pts who received ABX prior to CKI initiation, warranting further validation in a larger cohort.

3011 Poster Discussion Session; Displayed in Poster Session (Board #225), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Association of gut microbiome with immune status and clinical response in solid tumor patients who received on anti-PD-1 therapies. *First Author: Shota Fukuoka, Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Significant advances have been made in cancer immunotherapy with immune check point blockade (ICB). Yet, most patients with various tumor types finally experienced disease progression after ICB. Therefore, to investigate predictive biomarker(s) and resistance mechanism (s) against ICB are of importance. While modulation of the gut microbiome reportedly augments anti-tumor immune responses induced by ICB in murine models, the association between gut microbiome and immune status in tumor microenvironment remains unclear. Here, we addressed this issue with a Japanese patient cohort harboring solid cancers (non-small cell lung cancer and gastric cancer) who received anti-PD-1 therapies. **Methods:** We performed Meta-sequencing analyses of bacterial 16S ribosomal DNA amplified from stools from 38 solid tumor (lung cancer, 14: gastric cancer, 24) patients. Tumor-infiltrating lymphocytes (TIL) were analyzed from 17 patients. Patients were classified as follows: Responder (R) with an objective response (complete or partial response, or stable disease lasting at least 6 months) and Non responder (NR) with disease progression or stable disease lasting less than 6 months) based on REICIST criteria. **Results:** We observed significant differences in the diversity and composition of gut microbiome in R (n = 7) versus NR (n = 31). No significant differences were observed in patient base-line characteristics between Rs and NRs including PD-L1 expression. Rs had a significantly higher alpha diversity compared with NR using Shannon's index (p = 0.0047). Progression-free survival was significantly longer in patients with high diversity than patients with lower diversity patients (median 93 vs. 28 days, p = 0.002). Particularly, Ruminococcaceae family in Clostridiales order was enriched in R with LEfSe analysis. Immune profiling revealed a statistically significant positive correlation between $PD\text{-}1^+CD8^+$T cell in TIL and abundance of Ruminococcaceae (r = 0.57, p = 0.020). **Conclusions:** The diversity of and composition of gut microbiome could predict the effect of ICB, suggesting that gut microbiome potentially augment therapeutic responses to ICB in patients with solid tumors.

3012 Poster Discussion Session; Displayed in Poster Session (Board #226), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Phase I/II study of LAG525 ± spartalizumab (PDR001) in patients (pts) with advanced malignancies. *First Author: David S. Hong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LAG525 and spartalizumab (PDR001), humanized IgG4 mAbs, block binding of LAG-3 to MHC class II and PD-1 to PD-L1 and PD-L2, respectively. Preclinical studies show synergistic anti-tumor activity when blocking PD-1 and LAG-3. Here, we report dose escalation results from a Phase I/II study of LAG525 ± spartalizumab in advanced malignancies (NCT02460224). **Methods:** LAG525 was dosed Q2W (1–15 mg/kg, or 240/400 mg) or Q4W (3–10 mg/kg, or 400 mg); LAG525 + spartalizumab was dosed at 15 dose levels/schedules from 0.3 mg/kg LAG525 + 1 mg/kg spartalizumab Q2W to 1000 mg LAG525 + 400 mg spartalizumab Q4W. Phase I endpoints (dose-limiting toxicities [DLTs], additional safety, pharmacokinetics, efficacy, and biomarkers) were used along with an adaptive Bayesian logistic regression model guided by escalation with overdose control to support future study dosing. Baseline and on-treatment tumor samples were collected. **Results:** As of 31 Jul 2017, 115/119 pts (97%) receiving LAG525 and 99/121 pts (82%) receiving LAG525 + spartalizumab had discontinued treatment, primarily due to progressive disease (79% and 67%, respectively). DLTs occurred in 4 pts in each arm (LAG525 arm: Gr 3 intra-abdominal fluid collection, lipase increase, vomiting; Gr 4 acute kidney injury. Combination arm: Gr 3 hyperglycemia, pneumonitis, brain tumor edema, fatigue; Gr 4 autoimmune hepatitis) without clear dose relationship. Common (≥10%) related AEs were fatigue (10%) for LAG525 alone and fatigue (18%), diarrhea (15%), and nausea (12%) for the combination. Gr 3–4 related AEs were reported in 10 pts (8%) in the LAG525 arm and 10 pts (8%) in the combination arm. Approximately dose-proportional increases in LAG525 exposure were seen. No MTD was identified for either arm. LAG525 + spartalizumab led to durable RECIST responses (11 PR, 1 CR) in a variety of solid tumors, including mesothelioma (2/8 pts) and triple-negative breast cancer (TNBC; 2/5 pts). In TNBC tumor biopsies, a trend in conversion of immune-cold to immune-activated biomarker profiles was seen. **Conclusions:** Treatment was well tolerated with preliminary anti-tumor activity and immune profile modulation observed for LAG525 + spartalizumab. Phase II is ongoing in selected indications. Clinical trial information: NCT02460224.

3013 Poster Discussion Session; Displayed in Poster Session (Board #227), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Initial results from first-in-human study of IPI-549, a tumor macrophage-targeting agent, combined with nivolumab in advanced solid tumors. *First Author: Ryan J. Sullivan, Massachusetts General Hospital, Boston, MA*

Background: IPI-549 is a potential first-in-class, oral, selective PI3K-γ inhibitor that in preclinical studies reprograms macrophages from an immune-suppressive to an immune-activating phenotype and can overcome resistance to checkpoint inhibitors. **Methods:** Ph 1/1b study IPI-549-01 (NCT02637531) is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunomodulatory activity of IPI-549 to determine its recommended Ph 2 dose (RP2D) and preliminary efficacy, as monotherapy and combined with nivolumab (nivo), in advanced solid tumor pts. Pre- and on-treatment blood samples were obtained for flow cytometry, gene expression, and serum analysis. **Results:** Initial combination dose-escalation results are reported. 31 pts (30 evaluable), median age 57 yrs and median 4 prior therapies (8 with prior anti PD-(L)1 therapy), received IPI-549 20, 30, and 40 mg QD + nivo 240 mg Q2W in a 6+6 design. IPI-549 PK/PD were unaffected by nivo. The MTD was not reached. Most treatment-emergent adverse events (TEAEs) were Gr 1-2. The most common (≥ 2 pts) treatment-related TEAEs included rash (23%); pruritus (10%); and nausea, anemia, ALT increase, AST increase, and pyrexia (6% each), with no treatment-related deaths. 2 DLTs each occurred at IPI-549 30 mg (Gr 3 rash) and 40 mg QD (Gr 3 rash; Gr 3 ALT/AST increase). 2 pts demonstrated partial responses at first assessment (8 wks): 1 with adrenocortical carcinoma and 1 with microsatellite-stable gallbladder carcinoma receiving IPI-549 30 and 40 mg QD, respectively. 40% of pts (n = 12) remained on study ≥ 12 wks and 6 pts were ongoing at the 05 Feb data cutoff. Based on safety + PK/PD data, the RP2D was IPI-549 40 mg QD + nivo 240 mg Q2W. On-treatment blood samples show evidence of immune activation and reduced immune suppression, including upregulation of IFNg-responsive factors, such as PD-L1 and CXCL9/10, and dose-dependent re-invigoration/proliferation of exhausted PD1+CD8+CD45RA- T cells, evidenced by Ki67 increases. **Conclusions:** IPI-549 + nivo demonstrates favorable tolerability, early signs of clinical activity, and evidence of immune modulation. Combination expansion cohorts are enrolling at the RP2D. Clinical trial information: NCT02637531.

3014 Poster Discussion Session; Displayed in Poster Session (Board #228), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Phase Ib/II study of lacnotuzumab (MCS110) combined with spartalizumab (PDR001) in patients (pts) with advanced tumors. *First Author: Aitana Calvo, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: Tumor-associated macrophages mediate intrinsic/acquired resistance to programmed death-1 (PD-1) inhibitors; these cells can be reduced by inhibiting the colony-stimulating factor-1 (CSF-1)/receptor pathway. Targeting CSF-1 with lacnotuzumab (MCS110), a high-affinity, humanized mAb, combined with spartalizumab (PDR001), a humanized anti-PD-1 mAb, is hypothesized to result in synergistic antitumor activity. **Methods:** This Phase Ib/II study (NCT02807844) assesses lacnotuzumab with spartalizumab in pts with advanced melanoma, endometrial, pancreatic (PC), or triple-negative breast cancer. During dose escalation, pts received lacnotuzumab at 1 or 3 mg/kg with 100 mg spartalizumab, or 3, 5, 7.5, or 10 mg/kg lacnotuzumab with 300 mg spartalizumab, every 3 weeks. For the Phase Ib part, primary endpoints are safety, tolerability, and recommended Phase II dose; secondary endpoints include antitumor activity and PK. Tumor biopsies are collected before and during treatment. **Results:** At data cut-off 24 Nov 2017, 50 pts (median age 60 years) were enrolled at 6 combination dose levels. The most common (≥30%) all-grade AEs regardless of study drug relationship were increased aspartate aminotransferase (AST; 32%), nausea (32%), vomiting (32%), asthenia (30%), and fatigue (30%); the most common (≥10%) Grade ≥3 AEs were increased AST (12%), asthenia (10%), and hyponatremia (10%). Frequent AEs suspected as drug-related were periorbital edema* (30%), increased AST (24%), and increased blood creatine phosphokinase (24%), which was the most frequent Grade ≥3 AE suspected as drug-related (6%). By RECIST 1.1, there was 1 partial response (PR); stable disease (SD) was 19% (9/48). By immune-related response criteria, disease control rate (irPR or irSD) was 27% (13/48); of note, 6/13 had PC. Out of 30 pts with PC, 1 pt achieved PR (on study for 346 days) and 2 pts had durable SD (on study for 328 and 319 days, respectively). PK and biomarker studies are ongoing. **Conclusions:** Lacnotuzumab with spartalizumab was well tolerated overall. Preliminary antitumor activity, notably in the PC cohort, was observed. Ongoing studies are evaluating this combination. *Includes eyelid edema and face edema. Clinical trial information: NCT02807844.

3015 Poster Discussion Session; Displayed in Poster Session (Board #229), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Predicting outcomes of advanced non-small cell lung cancer patients treated with PD-1/PDL-1 inhibitors: Independent international validation of the iSEND model. *First Author: Wungki Park, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: There is an unmet need for affordable and readily available biomarkers to predict outcomes to PD-1/PD-L1 inhibitors (PD-1/L1i) in advanced non-small cell lung cancer patients (aNSCLC pts). We previously developed a multivariate risk prediction model called the iSEND in a cohort of 159 patients with aNSCLC pts (n = 159) treated with nivolumab in second-line or above setting (2L+). Here, we report the independent multicentric validation. **Methods:** The iSEND model includes simple clinical and laboratory characteristics: Sex, ECOG performance status, and baseline and post-treatment change after 1st cycle of NLR (Neutrophil-to-Lymphocyte Ratios), intended to reflect reactive increase of the myeloid-lymphoid balance. For independent validation, we used a retrospective cohort of 230 aNSCLC pts from the authors' institutions in the United States, France and Japan who received 2L+ PD-L/L1i. The outcomes for the iSEND Good, Intermediate, and Poor groups were compared. The performance was assessed using receiver operating characteristic (ROC) curves. **Results:** The median follow-up was 15.2 months (M) (95% Confidence Interval [CI]: 12.4-17.9). The median OS for iSEND Good, Intermediate, and Poor was 15.9 M (CI: 2.8-29.0), 12.4 M (CI: 9.6-15.1), and 4.0 M (CI: 3.0-5.0), respectively. And log-rank test was significant (p = 0.001). The median Progression Free Survival (PFS) was 2.6 M (CI: 2.0-3.1), 2.9 M (CI: 1.6-4.2), and 1.6 M (CI: 1.3-1.8), respectively. (Log-rank: p = 0.002) Time-dependent area under curves (AUC) of the iSEND model for OS at 6, 12, 18, 24, and 36 M were 0.63 (CI: 0.56-0.71), 0.61 (CI: 0.54-0.69), 0.59 (CI: 0.50-0.68), 0.60 (CI: 0.47-0.73), and 0.70 (CI: 58-0.82). The iSEND Poor group had significant correlation with progressive disease compared to the iSEND Good group (HR: 2.7, CI: 1.2-6.1, p = 0.013). **Conclusions:** This study validates the iSEND model in an independent international cohort confirming that it predicts outcomes of aNSCLC pts treated with 2L+ PD-1/L1i. Exploring its validity in a prospective cohort as well as in aNSCLC pts treated with effective myeloid modulating combination strategy is strongly supported and underway.

3016 Poster Discussion Session; Displayed in Poster Session (Board #230), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Medical image computing to assess tumor infiltrating CD8 T cells, tumor immune phenotype and response to anti-PD-1/PD-L1 immunotherapy in prospective phase 1 trials. *First Author: Roger Sun, Gustave Roussy Cancer Campus, Radiation oncology department,, Villejuif, France*

Background: The aim was to develop a radiomic estimator of tumor infiltrating CD8 T-cells, to assess its association with tumor immune phenotype, and to evaluate outcomes of cancer patients enrolled in phase 1 trials of anti-PD-1/PD-L1 monotherapy. **Methods:** Radiomic features were extracted from contrast-enhanced CTs for 135 patients from the prospective trial MOSCATO. For each patient, RNA-seq data were available and used to quantify CD8 T-cells. A radiomic signature of the expression of CD8 T-cells was trained using elastic-net method. Three independent cohorts were used for validation: (I) 119 patients from The Cancer Genome Atlas (TCGA) to validate the association with gene expression, (II) 100 tumors assumed as either immune-inflamed or immune-desert to analyze the association with the immune-phenotype, (III) 137 patients treated with anti-PD-1/PD-L1 monotherapy in phase 1 trials to assess clinical outcome. Clinical responses were defined according to RECIST1.1. Median value of the radiomic score was used to separate patients into two groups to assess the overall survival (OS). **Results:** The final radiomic signature kept eight features from the 83 initial ones, and was associated with the gene expression signature of CD8 T-cells in the TCGA validation set (AUC = 0.67, P = 0.002), and the inflamed tumors in the assumed immune-phenotype cohort (AUC = 0.76, $P < 0.001$). In the cohort of patients treated with immunotherapy, the radiomic score at baseline was higher in patients with objective response (CR + PR) or a controlled disease (SD + CR + PR) at 3 months (P = 0.049 and P = 0.050 respectively) and at 6 months (P = 0.025 and P = 0.013 respectively). OS was higher in patients with a high radiomic score (median OS: 24.3 vs 11.5 mo, HR = 0.58, P = 0.008), which remained significant when taking into account the number of lines of treatment, the Royal-Marsden-Hospital prognostic score, and the volume of the tumor (P = 0.002). **Conclusions:** The radiomic signature of CD8 T-cells was validated in three independent cohorts. It appears promising in estimating tumor immune phenotype and inferring outcomes of patients treated with anti-PD1/PD-L1 in a non-invasive way.

3017 Poster Discussion Session; Displayed in Poster Session (Board #231), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Correlation of survival outcomes with progression heterogeneity in patients (pts) treated with pembrolizumab (pembro). *First Author: Lawrence H. Schwartz, Columbia University College of Physicians and Surgeons, and New York Presbyterian Hospital, New York, NY*

Background: The relevance of RECIST v1.1 measures of progression in pts treated with immunotherapy is unclear. We conducted analyses of KEYNOTE-001 (KN; exploratory) and KN052 (confirmatory) to assess associations of progression heterogeneity by CT imaging with survival outcomes among pts treated with pembro. **Methods:** KN001 and KN052 enrolled pts with advanced melanoma and urothelial cancer, respectively. Blinded independent central review was performed per RECIST v1.1. Beyond RECIST v1.1, pts subgroups (SG) with progressive disease (PD) were defined as *No Growth* (NG; no individual target lesion [TL] Growth (G) $\geq$20% from baseline [BL]) with (NG+) and without (NG–) new metastatic lesions; *Mixed Growth* (MG; any individual TL G $\geq$20% from BL and not aggregate G [AG] $\pm$ new lesion G); and, *AG* (G $\geq$20% from BL $\pm$ new lesion G). SG were assigned at first documented PD. OS between SG was assessed using KM analysis. A Cox model with time-varying covariates related to PD SG and pembro treatment status was used to assess the relative mortality risk between SG on treatment and the effects of discontinuing treatment within each SG. KN001 findings were tested in KN052. **Results:** Of 511 KN001 (N = 655) pts with a post-BL scan, 301 (59%) had RECIST-PD on study, of which 42 (14%) were NG–, 78 (26%) NG+, 75 (25%) MG, and 106 (35%) AG. Median OS was 32.5, 23.2, 16.1, and 8.1 mo, respectively, and 43.6 mo for non-PD. Of 331 KN052 (N = 370) pts with a post-BL scan, 223 (67%) had PD on study, of which 29 (13%) were NG–, 66 (30%) NG+, 35 (16%) MG, and 93 (42%) AG. Median OS was 14.2, 10.2, 6.7, and 5.3 mo, respectively, and not reached for non-PD. Relative to non-PD and consistent with overall study KM estimates, model-derived "on-treatment" HRs were highest for AG, followed by MG, NG+, NG–. Treatment discontinuation was associated with increased mortality risk (HR $>$ 1) in all PD SG, but with differing magnitude. All KN001 findings were confirmed in KN052. Similar analyses will be shown for pts with NSCLC in KN010 (pembro vs docetaxel). **Conclusions:** These analyses suggest there may be distinct populations of PD phenotypes with unique survival outcomes. RECIST v1.1 does not fully capture these PD phenotypes and may not accurately identify treatment failure. Clinical trial information: NCT01295827 for KEYNOTE-001, NCT02335424 for KEYNOTE-052.

3018 Poster Discussion Session; Displayed in Poster Session (Board #232), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

VANCE: First-in-human phase I study of a novel ChAdOx1-MVA 5T4 vaccine in low and intermediate risk prostate cancer. *First Author: Irina Redchenko, The Jenner Institute, University of Oxford, Oxford, United Kingdom*

Background: Prostate cancer (PCa) has been under investigation as a target for antigen-specific immunotherapies in metastatic disease settings. However, neither of the two clinically most advanced PCa vaccines, Sipuleucel-T and ProstVac, induced strong T cell immunity. In our study, we evaluated a novel vaccination platform based on two replication-deficient viruses, chimpanzee adenovirus and MVA, targeting an oncofetal self-antigen 5T4 in early stage PCa. **Methods:** 40 patients, either newly diagnosed with early stage PCa and scheduled for radical prostatectomy or patients with stable disease on active surveillance protocol, were randomised to a "standard" immunisation regimen to receive 3 vaccinations four weeks apart, or to an "accelerated" immunisation protocol to receive 2 vaccinations at one week interval. Study primary endpoints were vaccine safety and immunogenicity. Secondary endpoints included immune infiltration into the prostate and PSA level change secondary to treatment. As exploratory endpoints, phenotype and functionality of antigen-specific T cells and breadth of induced T cell responses were assessed. **Results:** 39 patients completed the study and were eligible for analysis. The vaccine had an excellent safety profile, with the majority of vaccine-related AEs graded as mild. Vaccination-induced 5T4-specific T cell responses were measured in blood by *ex vivo* IFNγ ELISPOT and were detected in the majority of patients. Flow cytometry analysis demonstrated the presence of both CD8+ and CD4+ polyfunctional 5T4-specific T cells in the circulation. 5T4-reactive TILs were isolated from post-treatment prostate tissue. Some of the patients had a transient PSA level increase 2-8 weeks following vaccination possibly indicating an inflammatory response in the target organ. Quantitative immunohistochemical analysis of paired pre- and post-treatment prostate tissue samples will be reported. **Conclusions:** We report for the first time, that *ex vivo* T cell responses to a tumour self-antigen can be elicited in the majority of PCa patients. A Phase II study is starting to test this vaccine in combination with PD1 blockade in early stage and metastatic PCa. Clinical trial information: NCT02390063.

3019 Poster Discussion Session; Displayed in Poster Session (Board #233), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Genetically engineered T-cell therapy for HPV-associated epithelial cancers: A first in human, phase I/II clinical trial. *First Author: Stacey L. Doran, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Engineered T-cell therapy is an emerging treatment for hematological cancers. In epithelial cancers, its study has been limited. Human papillomavirus (HPV)-16+ epithelial cancers constitutively express the HPV E6 oncoprotein. We investigated treatment of metastatic HPV-16+ cancers with T cells that target E6 by an engineered T-cell receptor (E6 T cells). **Methods:** A phase I/II, single-center, clinical trial was conducted. Eligible subjects had a metastatic HPV-16+ cancer from any primary tumor site and had received prior platinum-based therapy. Treatment consisted of a one-time, intravenous infusion of E6 T cells. A lymphocyte-depleting conditioning regimen and systemic aldesleukin were also administered. **Results:** Twelve subjects were treated on this protocol. Dose-limiting toxicity was not encountered (maximum dose was 1.7×10^{11} T cells). Transduction efficiency range was 45-76%. Infused E6 T cells demonstrated engraftment at one month post-treatment in all patients (range 4-53%). Two of nine subjects in the highest dose cohort experienced tumor responses. A subject with a 6-month partial response had complete regression of one lesion and partial regression of two lesions, which were subsequently resected; the subject has no evidence of disease three years after treatment. Resected tumor from this subject demonstrated infiltration by E6 T cells that showed increased expression of the inhibitory molecule PD-1 as compared to E6 T cells in the peripheral blood (26% vs 2%). Genomic analyses were performed on the tumors of two subjects who did not respond to treatment. One subject displayed a frameshift deletion in the interferon-gamma response gene, *IFNGR1*. Another demonstrated loss of heterozygosity (LOH) in chromosome 6 with deletion of *HLA-A*02:01*, the necessary restriction element for this therapy. A subject who responded to treatment did not demonstrate genomic alterations in these pathways. **Conclusions:** Engineered T cells targeting E6 can induce regression of HPV+ epithelial cancers. Treatment resistance may be related to T-cell inhibition by PD-1, tumor evasion by antigen processing and presentation loss, and defects in interferon-response pathways. Clinical trial information: NCT02280811.

3020 Poster Discussion Session; Displayed in Poster Session (Board #234), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Pharmacodynamics (PD) and genomic profiling of pts treated with cabiralizumab (cabira) + nivolumab (NIVO) provide evidence of on-target tumor immune modulations and support future clinical applications. *First Author: Michael Carleton, Bristol-Myers Squibb, Princeton, NJ*

Background: Colony stimulating factor 1 receptor (CSF-1R) signaling supports recruitment, development, and maintenance of immune suppressive macrophages within the tumor. Combining anti–CSF-1R with anti–PD-1 showed enhanced efficacy in preclinical models. Cabira, a humanized IgG4 monoclonal antibody, disrupts CSF-1R binding to ligands CSF-1 and IL-34, thus blocking receptor activation. We report immunohistochemistry (IHC) and transcriptomic evidence of on-target PD effects of cabira + NIVO in treated pts, as well as the first insight into genotypic characteristics of pancreatic tumors exhibiting durable PRs with cabira + NIVO (Wainberg et al. *J Immunother Cancer* 2017;5(suppl 2) [abst 042]). **Methods:** PD activity of cabira + NIVO in pts with advanced tumors treated in a ph 1a/b trial (NCT02526017) was evaluated using peripheral and tumor biomarkers. **Results:** Cabira + NIVO induced increases in serum CSF-1 and decreases in peripheral nonclassical monocytes sustained during the 2-week dose interval. IHC analysis of pre- and on-treatment biopsies across tumor types showed increases in CD8 T-cell infiltrates and decreases in macrophage markers CSF-1R and CD163. Transcriptomes of paired biopsies showed increased CD8 and cytolytic gene signatures with concurrent increased expression of M1 macrophage-associated genes, supporting blockade of CSF-1R–driven M2 responses. Genomic analyses demonstrated 91 of 94 pts with low tumor mutation burden (TMB) below 10 mutations/megabase with only 1 microsatellite instability tumor identified. Responses were observed across tumor types. Of note, in the 4 PRs observed in pts with pancreatic cancer, all were microsatellite stable (MSS) and low TMB. **Conclusions:** Orthogonal IHC and transcriptome-wide analyses demonstrated cabira-mediated CSF-1R blockade in the periphery and tumor microenvironment in pts with advanced cancer. Ongoing analyses include identification of transcriptomic signatures associated with response. These data support further clinical development of cabira + NIVO in multiple indications, including MSS pancreatic cancer (NCT03336216). Clinical trial information: NCT02526017.

3021 Poster Session (Board #235), Mon, 8:00 AM-11:30 AM

CD8 and PD-L1 determination in lung tumor tissue as prognostic biomarker and a predictive marker of anti PD-1 efficacy. *First Author: Jean-David Fumet, Department of Medical Oncology, Center GF Leclerc, Dijon, France*

Background: With recent approval of mAb targeting PD-1 and PD-L1 for non–small cell lung cancer (NSCLC), extensive efforts are under way to develop predictive biomarkers for anti PD-1/PD-L1 response. PD-L1 expression upon histology is currently the only clinically available biomarker, but mRNA immune signatures are also emerging. While the efficacy of these drugs is dependent on CD8 T-cells, no study has evaluated both CD8 and PD-L1 as biomarkers. **Methods:** CD8 and PD-L1 expression was studied by RNA sequencing and immunohistochemistry (IHC). We used RNA sequencing data from The Cancer Genome Atlas (TCGA) lung cancer samples as a prognostic cohort. We validated the results obtained from the transcriptomic data with IHC data using another prognostic cohort of 34 metastatic NSCLC tumor samples untreated by immunotherapy and stained using CD8 and PD-L1. A predictive study was conducted on 85 NSCLC patients treated with nivolumab, for whom outcome was known. To evaluate our signature, we used IFN and Immune Expanded Signature (IES), previously described as gold standards. Data were externally validated using public data (GSE93157). **Results:** In the prognostic TCGA mRNA cohort, we observed that high CD8 expression is associated with better overall survival, while PD-L1 expression is associated with poor prognosis. CD8 and PD-L1 determined upon IHC also had prognostic value in the prognostic cohort. In the predictive cohort, CD8 and PD-L1 expression evaluated using mRNA or IHC are associated with better progression-free survival in patients treated with nivolumab. Use of mRNA improved discrimination when compared with histological measures. A combination of both CD8 and PDL1 variables was highly predictive of outcome and remained significant after adjustment for usual clinical variables (age, sex, histology performance status). This 2-gene signature using CD8 and PD-L1 outperformed both IFN and EIG signatures, even with IHC data. Similar results were obtained in the external validation cohort (GSE93157). **Conclusions:** CD8 and PD-L1 mRNA or IHC could be used to address NSCLC outcomes for patients treated with nivolumab.

3022 Poster Session (Board #236), Mon, 8:00 AM-11:30 AM

Mismatch repair deficiency testing for immune checkpoint therapy: Immunohistochemistry vs microsatellite instability. *First Author: Sucha Sudarsanam, NeoGenomics Laboratories, Aliso Viejo, CA*

Background: DNA mismatch repair deficiency (dMMR) can be tested by immunohistochemistry (IHC) or microsatellite instability (MSI). While either IHC and MSI is adequate for establishing Lynch syndrome, the relevance of discordant results in selecting patients for immune checkpoint treatment is unknown. We investigated MSI and IHC in detecting dMMR and correlated with PD-L1 expression. **Methods:** Community-based practice tissue samples were submitted for PD-L1 expression and dMMR by both IHC and MSI. PD-L1 testing was performed by IHC using clone 22C3, dMMR using IHC against four MMR proteins (MHL1, MSH2, MSH6, and PMS2), and MSI using PCR with five Bethesda markers. **Results:** Of the 396 cases tested for both PD-L1 and dMMR by IHC, 18 (4.5%) were reported dMMR positive. Of the 610 cases tested for both PD-L1 and dMMR by MSI, 27 (4.4%) were dMMR positive. The dMMR positivity was determined as having at least one MMR protein expressed at $\leq$ 6%. There was no statistically significant correlation between PD-L1 expression and the presence or absence of dMMR as detected by IHC. In contrast, patients with MSI had significantly higher PD-L1 positive cells when PD-L1 expression is considered as a continuous variable (P = 0.04), and at cut-offs of 5% (P = 0.003) and 10% (P = 0.004). When a cut-off point of 6% for IHC is used, 8.9% of positive cases by MSI were negative (FN) by IHC and 2.6% of MSI negative cases were positive (FP) by IHC. If a 20% cut-off for IHC is used, FP was at 4.4% but FP was at 3.6%, and if a 30% IHC cut-off is used, FP was at 3.1% and FP was at 5.7%. This difference between cut-off points was statistically significant (P = 0.0008 for 20% and P = 0.0001 for 30% cut-off). **Conclusions:** There is significant correlation between PD-L1 expression and dMMR as detected by MSI, but not by IHC testing. Based on this and the established association between tumor mutation burden and MSI, MSI should be considered the gold standard for dMMR testing for checkpoint blockade therapy consideration.

		MSI			% positive			
	dMMR by IHC cut-off	Pos	Neg	Total	by MSI	by IHC	% IHC FP	% IHC FN
6%	Pos	267	16	283	32.38	31.27	8.9	2.6
	Neg	26	596	622				
20%	Pos	280	22	302	32.38	33.37	4.4	3.6
	Neg	13	590	603				
30%	Pos	284	35	319	32.38	35.25	3.1	5.7
	Neg	9	577	586				
Total		293	612	905				

3023 Poster Session (Board #237), Mon, 8:00 AM-11:30 AM

Relationship between checkpoint molecule B7-H3 and refractoriness to anti-PD-1 therapy in non-small cell lung cancer. *First Author: Kimio Yonesaka, Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan*

Background: While anti-PD-1 therapy improves survival in non-small cell lung cancer (NSCLC), some patients do not respond, indicating the need for alternative strategies. Some cancers express B7-H3, an immune checkpoint molecule. Herein, we evaluated B7-H3 expression and analyzed its relationship with anti-PD-1 therapy efficacy in NSCLC. **Methods:** Eighty-two patients with advanced NSCLC were enrolled in this retrospective study; 50 had been treated with anti-PD-1 therapy. The response rate (RR) and progression-free survival (PFS) were assessed by RECIST v 1.1. B7-H3, PD-L1, and CD8 expression were evaluated by immunohistochemistry; PD-L1 expression levels were scored by tumor proportion score (TPS). For statistical tests, the unpaired t-test was used for continuous variables; Fisher's exact test, categorical variables; and Cox regression and log-rank tests, time to event (two-sided p-values were obtained). **Results:** B7-H3 was positive in 74% of patients and correlated with responsiveness to anti-PD-1 therapy (p = 0.0007). The RR was 88% for B7-H3-negative patients and 29% for B7-H3-positive patients. Multivariate analysis for PFS revealed that PD-L1 expression favorably correlated with PFS [TPS $<$ 50 vs. $\geq$50; HR 3.559, p = 0.006]. In contrast, B7-H3 unfavorably correlated with PFS [negative vs. positive; HR 0.082, p = 0.003]. The median PFS was 427 days for B7-H3-negative patients, but 148 days for B7-H3-positive patients [p = 0.024]. There was no correlation between PD-L1 and B7-H3 expression, indicating these biomarkers were independent. $CD8^+$ T cells were greater in tumors with PD-L1 TPS $\geq$50% than in those with $<$ 50% [median 104 vs. 11/mm^2; p = 0.0038]. However, among patients with PD-L1 TPS $<$ 50%, B7-H3-negative tumors still had more $CD8^+$ T cells than B7-H3-positive tumors [median 47 vs. 8/mm^2; p = 0.0103]. Consistently, patients with PD-L1 TPS $<$ 50% and B7-H3 negativity demonstrated 86% RR. **Conclusions:** NSCLCs lacking B7-H3 had inflammatory microenvironments and responded to anti-PD-1 therapy, despite low PD-L1 expression. Although our sample size was small, our results encouragingly suggest that B7-H3-targeting therapies will enhance the antitumor efficacy of anti-PD-1 antibodies.

3024 Poster Session (Board #238), Mon, 8:00 AM-11:30 AM

Co-mutations of DNA damage response system as predictive biomarker for immune checkpoint blockades. *First Author: Zhijie Wang, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Abstract Background: Selecting appropriate biomarkers for immune checkpoint blockades (ICBs) remains a clinical challenge. Quantitative biomarkers, for instance, PD-L1 expression or tumor mutation burden, are limited by their vague cut-off value, intra-tumor heterogeneity distribution and dynamic alterations. Qualitative biomarkers, including dMMR/MSI-H, are potent predictors, but merely a minority of patients harbor this abnormality. Therefore, a more prevalent biomarker would be highly desirable. In humans, DNA damage response (DDR) system is indispensable in maintaining genomic integrity. We hypothesize genetic mutations of DDR pathways may increase genomic instability and manifest as up-regulated neoantigen load and TMB, contributing to higher susceptibility to immune checkpoint blockades (ICBs). **Methods:** Whole-exome sequencing data from 8552 solid tumors, across 29 cancer types from The Cancer Genome Atlas were included for analysis. The expression signatures of immune genes were compared across distinct DDR subgroups. Statistics concerning the correlation between DDR pathway mutations and treatment outcomes were evaluated in four cohorts treated with ICBs. **Results:** Co-mutations of HRR-MMR or HRR-BER pathways (defined as co-mut +) were correlated with higher neoantigen load and TMB. Co-mut + exhibited anabatic levels of immune gene expression signatures, including genes related to T-effector, IFNγ pathway, T cell receptors and tumor microenvironment. In these four validation cohorts, the progression-free survival (PFS) was longer in co-mut + patients with non-small cell lung cancer (NSCLC) than co-mut – (median, not reached vs. 4.1 months, P = 0.02) and the overall survival was longer in co-mut + melanoma patients than co-mut – (median, 32.4 vs. 10.8 months, P = 0.04). Subgroup analysis of NSCLC cohort demonstrated that co-mut + is predictive to longer PFS in patients with PD-L1 expression $< 50\%$ (median, 8.3 vs. 2.7 months, P = 0.03) or low TMB (median, not reached vs. 3.8 months, P = 0.04). **Conclusions:** Co-mutations of HRR-MMR or HRR-BER are a potential prognostic biomarker for ICBs immunotherapy, and warrant future prospective investigations.

3025 Poster Session (Board #239), Mon, 8:00 AM-11:30 AM

Serum interleukin 8 (IL-8) may serve as a biomarker of response to immuno-oncology (I-O) therapy. *First Author: Michael Carleton, Bristol-Myers Squibb, Princeton, NJ*

Background: Biomarkers are needed to identify pts responsive to I-O therapies. IL-8 is a proinflammatory chemokine that promotes tumor immune escape. High serum IL-8 levels are associated with poor prognosis (Sanmamed et al. *Clin Cancer Res.* 2014); changes in serum IL-8 levels were associated with response to antiPD-1 therapy in a small cohort of pts with melanoma (MEL) and NSCLC (Sanmamed et al. *Ann Oncol.* 2017). Here we report a large, cross-study, retrospective association analysis of baseline (BL) serum IL-8 levels with clinical efficacy and biomarkers in pts receiving nivolumab (NIVO)-based therapy. **Methods:** Data were analyzed from ≈2000 pts with MEL, NSCLC, and renal cell carcinoma enrolled in 8 clinical trials. Serum IL-8 was measured using an immunoassay platform (Myriad RBM, Austin, TX). Correlative efficacy metrics included BL tumor burden, overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). Receiver operating characteristic (ROC) curve analyses for 12-month OS were used to determine IL-8 cutoffs associated with response. Additional tumor and peripheral correlative markers were assessed. **Results:** Quartile stratification of serum IL-8 levels showed that elevated BL IL-8 was associated with poor OS. ROC analysis of NIVO-based therapy from pooled study data identified 23 pg/mL as an IL-8 threshold that could be used to enrich for pts who may be more likely to benefit from I-O. Additional IL-8 correlates were identified, including elevated tumor *CXCL8* mRNA and peripheral neutrophil count, but these were not statistically significant across all indications. Detailed analyses in pts with MEL showed the correlation of BL IL-8 with OS was independent of BL tumor burden or PD-L1 tumor expression. Absolute BL and post-BL IL-8 levels were more strongly associated with OS, PFS, and ORR than changes from BL. **Conclusions:** Association of serum IL-8 with response to NIVO-based therapy suggests that IL-8 may serve as a clinically useful biomarker to select for pts who can benefit from I-O therapy. We hypothesize that IL-8 neutralization in pts with elevated BL IL-8 may restore sensitivity to antiPD-1 therapy; this will be tested clinically with an antiIL-8 antibody (NCT03400332).

3026 Poster Session (Board #240), Mon, 8:00 AM-11:30 AM

Human leukocyte antigen (HLA) B44 supertype and immunotherapy outcomes in non-small cell lung cancer (NSCLC). *First Author: Henry Lu, University of Virginia School of Medicine, Charlottesville, VA*

Background: In melanoma (mel) patients (pts) treated with immune checkpoint inhibitors, presence of HLA class I (HLA-1) B44 supertype (B44+) correlated with survival (Chowell, Science). B44 preferentially binds negatively charged (neg) peptides and those with glutamic acid (E) at the anchor position. Positively charged (pos) peptides impede binding. In mel, B44 benefit was driven by glycine (G) > E changes. We evaluated the predictive role of HLA-I supertypes in NSCLC as neoepitopes are likely different as tranversions (Tv) predominate in smokers compared to transitions (Ti) in mel. **Methods:** 58 advanced NSCLC pts treated with pembrolizumab with 3 years follow up and sufficient PBMCs and/or tumor sample had multiplexed paired-end WES with Illumina HiSeq 2000/3000. HLA typing used BWA-ALN and Athlates software; supertype was determined by 2008 criteria (Sidney, BMC Immunol). Overall survival (OS) and progression-free survival (PFS) were compared by supertype using non-parametric log-rank tests. Tumor variant amino acids (vAA) were identified by GATK best practices, and AA charge was derived from standard charts with stop codons considered uncharged (unc). Ti/Tv and charge change analysis used two-proportion z-tests. Statistical analyses were performed with SPSS V24 (Armonk, NY). **Results:** Of 9 supertypes evaluated, only absence of B44 supertype (B44-) had longer OS [median OS of 14.9 months (m) vs 9.2 m in B44+ (HR 0.55, 95% CI 0.30-0.99, p = 0.048)], driven by B44- smokers [median OS 21.5 m vs 8.5 m in all other pts (HR 0.50, 95% CI 0.26-0.995, p = 0.048)]. PFS and response rate trends were similar to OS. vAA charge changes from unc/pos to neg in 14/384 (3.6%) Tv and 8/192 (4.2%) Ti (NS) and from unc/neg to pos in 48/384 (12.5%) Tv vs 12/192 (6.3%) Ti (p = 0.019). G > E is not possible from Tv. Among pts with evaluated tumors, Ti/Tv, vAA charge, and G > E were as predicted. **Conclusions:** Like mel, the B44 supertype associates with OS in NSCLC, however with the opposite effect direction, driven by favorable OS in B44- smokers. A potential mechanism for these histology-specific results is the greater likelihood of Tv in smokers that may lead to neoepitopes with characteristics less favorable for presentation on HLA B44.

3028 Poster Session (Board #242), Mon, 8:00 AM-11:30 AM

Somatic *STK11/LKB1* mutations to confer resistance to immune checkpoint inhibitors as monotherapy or in combination in advanced NSCLC. *First Author: Maria Jure-Kunkel, MedImmune, Gaithersburg, MD*

Background: Although PD-1/PD-L1 checkpoint blockade has become standard of care for non-small cell lung cancer (NSCLC), some treated patients (pts) do not respond. A deeper understanding of mechanisms of resistance to PD-(L)1 blockade is needed to improve therapeutic decisions. The aim of this study was to identify molecular alterations associated with innate resistance to durvalumab (D) and durvalumab + tremelimumab (D + T) combination therapy in advanced non-squamous (Non-SQ) NSCLC. **Methods:** CP1108/NCT01693562 and ATLANTIC/NCT02087423 were nonrandomized phase 1/2 and 2 trials of D (10 mg/kg, Q2W). D4190C00006/NCT02000947 was a nonrandomized phase Ib trial of D + T (20 mg/kg + 1 mg/kg, Q4W). Circulating tumor DNA (ctDNA) analysis (Guardant360 70 gene cancer panel) was conducted in pre-treatment plasma samples for 119 and 63 Non-SQ NSCLC pts in CP1108 and ATLANTIC, respectively. Targeted sequencing of pre-treatment tumors (FoundationOne CDx™) was conducted in 120 Non-SQ NSCLC pts in D4190C00006. Association of tumor mutations and objective response rate (ORR) by RECIST v1.1 and overall survival (OS) is presented. Immune contexture of *STK11* mt Non-SQ NSCLC tumors was investigated in the TCGA. **Results:** In two independent trials evaluating D as monotherapy (CP1108/Atlantic), and in a D + T combination trial (D4190C00006), reduced ORR and shorter survival were observed in Non-SQ NSCLC pts harboring *STK11* non-synonymous mutant tumors compared to pts harboring *STK11* wild type (wt) tumors (Table 1). In TCGA, STK*11* mutations were not prognostic and were associated with low IFNγ signature and high G-CSF and IL-6 expression. **Conclusions:** In Non-SQ NSCLC, somatic *STK11* mt may confer innate resistance to immune checkpoint inhibitors. Optimal therapeutic combinations for this subset of patients are being explored in HUDSON/NCT03334617. Table 1. ORR and OS in *STK11* mt or wt Non-SQ NSCLC pts treated with D or D + T Clinical trial information: NCT01693562, NCT02087423, NCT02000947.

	ORR (n/N)			Median OS (months)		
	STK11 mt	*STK11* wt	X^2	*STK11* mt (mo.)	*STK11* wt (mo.)	log-rank p
CP1108 (D)	6 (1/15)	16 (17/104)	0.05	4.9	14.2	0.008
Atlantic (D)	0 (0/6)	25 (14/57)				
D4190C00006 (D + T)	4 (1/23)	25 (24/97)	0.02	6.7	15.6	0.001

3029 Poster Session (Board #243), Mon, 8:00 AM-11:30 AM

First-in-human phase 1 study of MK-1248, an anti-human glucocorticoid-induced tumor necrosis factor receptor (GITR) monoclonal antibody, as monotherapy or in combination with pembrolizumab in patients with advanced solid tumors. *First Author: Ravit Geva, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Background: MK-1248 is a humanized IgG4 agonist monoclonal antibody (mAb) that targets GITR. GITR is expressed on regulatory T cells (T_{reg}), resting CD4+ and CD8+ T cells, NK (natural killer) cells and NK T cells. Ligation of GITR decreases T_{reg}-mediated suppression and enhances T cell proliferation, effector functions, and survival. **Methods:** MK-1248 was tested alone or in combination with pembrolizumab at a starting dose of 0.12 mg in both arms. Pembrolizumab dose was fixed at 200 mg. Both study drugs were administered intravenously every 3 weeks. Total number of intended doses of MK-1248 and pembrolizumab was 4 and 35, respectively. The study objective was to determine safety and tolerability, maximum tolerated dose (MTD), pharmacokinetic (PK), and pharmacodynamic (PD) profiles of MK-1248 as a monotherapy and in combination with pembrolizumab. **Results:** Data were available from 37 pts: 20 pts treated with MK-1248 monotherapy and 17 pts treated with MK-1248 + pembrolizumab combination therapy. Tumor types: colorectal cancer (8 pts), melanoma (5 pts), renal cell carcinoma (4 pts) and 20 pts with 16 other solid tumors. Maximum dose of MK-1248 tested: 170 mg (monotherapy) and 60 mg (combination). MK-1248 was well tolerated. Of the 37 pts treated, 36 pts (97.3%) had ≥1 adverse event (AE) and 17 pts (48.6%) had ≥1 treatment-related AE. Common AEs were: vomiting, anemia, decreased appetite, abdominal pain, cough, diarrhea, nausea, fatigue, headache and pyrexia. Infusion related reactions occurred in 6 (16.2%) pts. Eighteen pts had Grade 3-5 AEs (48.6%), 3 (8.1%) were treatment-related. Serious adverse events (SAE) occurred in 6 pts (30.0%) in monotherapy arm and 5 pts (29.4%) in combination arm. No DLT or treatment-related deaths were observed. One CR and 2 PR were observed in the study. **Conclusions:** MK-1248 at the dose up to 170 mg as monotherapy and 60 mg in combination with pembrolizumab was well tolerated with no dose limiting toxicities or treatment-related deaths. Responses were observed when MK-1248 was administered in combination with pembrolizumab. Clinical trial information: NCT02553499.

3030 Poster Session (Board #244), Mon, 8:00 AM-11:30 AM

Underlying host immune dysregulation in cancer patients developing immune-related adverse events. *First Author: David E. Gerber, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Immune checkpoint inhibitors may cause potentially severe immune-related adverse events (irAEs). To determine the role of host immune status in the development of irAEs, we evaluated baseline and post-treatment serum cytokine and IgG levels in patients receiving checkpoint inhibitors. **Methods:** We collected serum from patients treated with checkpoint inhibitors before treatment, after 2-3 weeks, and after 6 weeks. We quantified cytokine profiles using a multiplex panel. Total IgG was determined using ELISA. We analyzed the association between these biomarkers and the presence of irAEs using t tests and ANOVA. **Results:** A total of 78 subjects were enrolled, including 65 cancer patients receiving checkpoint inhibitors and 13 healthy controls. Among cancer patients, mean age was 65 years, 55% were women, and 83% had lung cancer. Immune-related AEs occurred in 35% of cases as follows: pneumonitis (n = 11), endocrinopathy (n = 6), dermatitis (n = 2), arthritis (2), encephalitis (1), complex (2). There was a significant increase in chemokines CXCL9, CXCL10, CXCL11 and CXCL13 in patients at 2 weeks post-immunotherapy and in chemokines CXCL9, CXCL10, CXCL11, CXCL13, IL-10, and CCL26 at 6 weeks post treatment. Patients who developed irAEs had significantly lower levels of CXCL9, CXCL10, CXCL11 and CCL19 at baseline and exhibited far greater increases in CXCL9 and CXCL10 levels at 6 weeks post treatment compared to patients without irAEs ($P< 0.05$ for all analyses). Baseline total serum IgG levels were significantly lower in patients who developed irAEs ($P< 0.05$). Cytokine and IgG levels were stable over time in healthy controls. **Conclusions:** In this study, patients with irAEs had lower baseline levels and greater post-treatment increases in multiple cytokine levels, as well as lower baseline levels in total IgG. Analogous to the elevated risk of autoimmune disease in individuals with HIV/AIDS, these findings suggest that immune dysregulation may be associated with the development of irAEs.

3031 Poster Session (Board #245), Mon, 8:00 AM-11:30 AM

Association of TGF-β responsive signature with anti-tumor effect of vactosertib, a potent, oral TGF-β receptor type I (TGFBRI) inhibitor in patients with advanced solid tumors. *First Author: Vicki Leigh Keedy, Vanderbilt University Medical Center, Nashville, TN*

Background: Stromal signature regulated by TGF-β pathway is one of the major mechanisms of tumor immune surveillance, leading to resistance to immune checkpoint inhibitors (ICI). Moreover, TGF-β responsive signatures (TBRS) of stromal cells have been associated with poor prognosis. Vactosertib (TEW-7197) is a potent, highly selective, oral inhibitor of TGFBR1. The safety, anti-tumor effect of vactosertib and its association with TBRS levels were evaluated in patients with advanced solid tumors. Based on in-house TCGA analysis, high fibroblast TBRS (F-TBRS) levels were seen in pancreatic, lung, colorectal (CMS4 subtype), and stomach (GS subtype) cancers in association with poor prognosis (adjusted hazard ratio 1.27; $P = 1.06 \times 10^{-8}$). **Methods:** 29 patients were enrolled in a phase I modified 3+3 dose-escalating study (NCT02160106) and received vactosertib once daily at the dose range of 30~340 mg for 5 days with 2 days off. RNA sequencing of pre-treatment tumor samples in 16 patients were analyzed to evaluate F-TBRS levels defined as geometric mean values of 171 corresponding gene expressions. **Results:** Vactosertib was safe and well tolerated, and the maximum tolerated dose was not determined. The most common treatment-related AE (TRAE) was fatigue, while G3/4 abdominal pain, AST elevation, and pulmonary edema were each reported in one patient, respectively. One DLT of stroke was seen at 100mg QD. In per-protocol analysis, 6 out of 17 patients who received ≥140 mg achieved stable disease (35.3%) and showed higher F-TBRS levels than those with progressive disease. **Conclusions:** Vactosertib, a potent and highly selective oral TGFBR1 inhibitor, showed excellent safety with the current dosing schedule. Furthermore, since high F-TBRS levels are well recognized as one of the main mechanisms related to resistance to ICI, vactosertib would be an ideal therapeutic strategy in combination with ICIs or conventional anti-tumor therapies for solid tumors with high F-TBRS levels. Clinical trial information: NCT02160106.

3032 Poster Session (Board #246), Mon, 8:00 AM-11:30 AM

Incidence and clinical implications of a new definition of hyperprogression (HPD) with immune checkpoint inhibitors (ICIs) in patients treated in phase 1 (Ph1) trials. *First Author: Ignacio Matos, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: HPD with ICIs has been recently described as progression disease (PD) by RECIST with a ≥ two-fold increase in tumor growth rate experimental vs. reference. However, the implementation of such assessment is challenging and its clinical implications have not been clearly established. **Methods:** Patients (pts) treated with ICIs in Ph1 trials at Vall d´Hebron Institute Oncology (VHIO) were analysed (n = 214). We defined HPD based on RECIST 1.1 as time to treatment failure (TTF) < 2 months (m) and minimum increase in measurable lesions of 10 mm plus: 1) increase of ≥40% (upper decile of our cohort) in target tumor burden compared to baseline or 2) increase of ≥20% plus the appearance of multiple new lesions. The aim of this study was to correlate HPD with overall survival (OS) in pts who achieved PD as best response, by using a Kaplan-Meier analysis. **Results:** From Jan'12 to Oct'17, 214 pts were treated, mostly with antiPD1/PDL1 ICIs (53% in combinations with other ICI). Median age 58y (20-85). Tumor types: melanoma 22%, lung 14%, breast 10%, colon 6%, others 48%. 20% had received prior ICI. Best response was PD in 47% pts (n = 101). In total, 33 pts (15%) were considered HPD, representing 40% of evaluable pts with PD as best response. HPD was not associated with age, tumor type, ICI regimens, previous ICI or metastatic site (Fisher test). Median OS was 4.8 m (95% CI: 3.4-7.3) in HPD group versus 8.7 m (95% CI 6.3-10.2) in non-HPD progressors group (HR = 1.87; 95% CI 1.1-3.3; p = 0.03). Overall, 48 pts (22%) received treatment beyond progression (TBP). Time from initial progression to study discontinuation was 0.4 m (95% CI 0.1-NA) in HPD group versus 0.96 m (95% CI 0.7-1.5) in non-HPD progressors (HR = 2.9; 95% CI 1.4-6.2). Only 10 pts with HPD received further therapy: 2 achieved partial responses with chemotherapy and 1 pt had stabilization with erlotinib, whilst the other 6 pts progressed (4 treated with ICI). **Conclusions:** In our Ph1 Unit population, we established a definition of HPD that is intuitive and easy-to-use in daily clinical practice. Importantly, it correlates with poor OS and represents a clear contra-indication for TBP or switch to alternative ICIs as rescue therapy.

3033 Poster Session (Board #247), Mon, 8:00 AM-11:30 AM

Pilot trial of an Indoleamine 2,3-dioxygenase-1 (IDO1) inhibitor plus a multipeptide melanoma vaccine in patients with advanced melanoma. *First Author: Craig L. Slingluff, University of Virginia School of Medicine, Charlottesville, VA*

Background: Melanoma metastases limit infiltration and function of anti-tumor T cells in part by immunosuppression with IDO1. INCB024360 (epacadostat) is an IDO1 inhibitor that normalizes serum kynurenine/tryptophan (Kyn/Trp) ratios. MELITAC 12.1 multipeptide vaccine induces CD8 T cell responses to melanoma antigens. A clinical trial was designed to test hypotheses that IDO1 inhibition (IDO1i) plus vaccine will be safe, that IDO1i will increase CD8 T cell infiltration into metastases and will enhance immune signatures in tumor, which will be further increased by the vaccine. **Methods:** Patients (pts) with stage IIIB-IV melanoma were treated with INCB024360 days(d) 1-98 (300 mg po bid), and with MELITAC 12.1 emulsified in incomplete Freund's adjuvant d21, 28, 35, 56, 77, 98. Prior checkpoint blockade therapy was allowed. Tumors were biopsied pre-treatment, d21, and d42, when feasible. Safety was assessed by CTCAE v4. The primary immunologic endpoint was tumor infiltration with CD8+ T cells. The biologic effect of INCB024360 on IDO1 function was assessed by serum Kyn/Trp ratio. Clinical outcomes were assessed by RECIST 1.1. **Results:** Eleven eligible pts were enrolled and treated. There were dose-limiting toxicities (DLTs) in 2 pts: grade 3 transaminase elevation, grade 3 syncope, both of which resolved. Six pts had all evident sites of disease resected in protocol biopsies and 1 had non-measurable disease. Of 4 pts with measurable disease beyond d42, best overall responses were PR (1), SD (3). INCB024360 reduced serum Kyn/Trp ratios 44% (mean) by d21 (normalized in 10/11 pts). In 5 pts with evaluable biopsies d0 and d42, with multispectral immunofluorescence histology, CD8 T cell infiltrates increased significantly to d42. **Conclusions:** Combination therapy with INCB024360 and multipeptide vaccine was considered safe with transient DLTs in only 2 patients (18%). INCB024360 normalized serum Kyn/Trp ratios in 91% of patients at 300 mg bid. Clinical activity was observed. There is evidence of enhanced CD8 T cell infiltration with the combination. Ongoing studies will assess the impact of INCB024360 on immune signatures and tumor infiltrating T cell function. Clinical trial information: NCT01961115.

3034 Poster Session (Board #248), Mon, 8:00 AM-11:30 AM

Germinal immunogenetics as a predictor of anti-PD1/PD-L1 treatment outcome. *First Author: Gerard A. Milano, Centre Antoine Lacassagne, Nice, France*

Background: In the context of the checkpoint inhibitors (CPI) era and the strong demand for identification of predictive biomarkers, the role of the host must be considered. We developed a custom-designed panel of single nucleotide polymorphisms (SNPs) of relevant genes implicated in immune response. The prognostic value of this panel was explored in this study. **Methods:** Clinical data of advanced lung carcinoma patients treated by second-line anti-PD(L)1 in Centre Antoine Lacassagne (Nice, France) were collected. High-throughput genotyping of germinal DNA was performed by MassARRAY (AGENA Bioscience) using the custom-panel of 166 SNPs-86 selected genes (minor allelic frequency $>$ 5% in a Caucasian population). Univariate and multivariate analyses for PFS were assessed, respectively, by means of log-rank tests and the Cox proportional hazards model. Multicollinearity was tested between all variables. P values $\leq$ 0.05 were considered statistically significant. **Results:** From October 2014 to April 2017, 48 patients were identified. Median age was 64-years-old; 29 were males (61%), 43 smokers (90%), 34 had radiotherapy (70%), 32 had adenocarcinoma (67%). Median follow-up was 12.5 months (95%CI: 11.0-16.3). All tested SNPs were in Hardy-Weinberg equilibrium. In univariate analyses, 25 individual SNPs significantly discriminated PFS. Multivariate analyses for PFS showed independent CPI prediction for *ICOS* rs11889031 (HR = 8.4 $p < 0.001$), *TLR3* rs3775291 (HR = 4.9; $p < 0.001$), *FAS* rs1800682 (HR = 2.9; p = 0.03), *FAS* rs2234767 (HR = 4.8; p = 0.04), and *INFL4* rs12979860 (HR = 4.3; p = 0.003). These genes and rs are closely involved in immunologic communication and auto immune disease. A composite score of favorable alleles (0-5) was dramatically associated with PFS ($p <$ 0.001), median 2 months (95%CI: 0.6-2.3) for 0-1 (n = 7), median 8.3 months (95%CI: 0.3-13) for 2-3 (n = 29) and median-PFS not reached for 4-5 (n = 12). All SNPs concerned were located in intronic regions, according to https://www.ensembl.org., suggesting a variable impact on alternative splicing. **Conclusions:** This study points to the germinal immunogenetics as a significant piece in the CPI predictors puzzle.

3035 Poster Session (Board #249), Mon, 8:00 AM-11:30 AM

Exploration of baseline derived neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with immune checkpoint inhibitors (ICI) or cytotoxic chemotherapy (CCT). *First Author: Dickran Garo Kazandjian, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Previous studies have suggested the importance of dNLR and LDH as prognostic markers and indicators of inflammation in cancer and other inflammatory diseases. More recently, the lung immune prognostic index (LIPI), the combination of dNLR and LDH, was found to be associated with progression free survival (PFS) and overall survival (OS) in pts with NSCLC treated with ICI but not CCT suggesting its potential use as a predictive marker. We performed an exploratory retrospective analysis of LIPI on pooled clinical trial data from studies evaluating ICI in 2nd line mNSCLC submitted to the FDA. **Methods:** We identified 5 randomized, second line trials (N = 3399) evaluating ICI versus docetaxel submitted to FDA between 2014-2017 for mNSCLC. Only pts with available dNLR/LDH data were included (71.8%). LIPI scores were calculated based on dNLR and LDH values per Mezquita et al. (JAMA Oncol. 2018). Univariate and multivariate COX proportional PFS and OS hazard ratios (HR) were generated for dNLR, LDH, and other major covariates including age, smoking status, histology, and ECOG. Median PFS and OS estimates based on the LIPI score (0,1, or 2) were generated using the Kaplan–Meier method. **Results:** In the final analysis, 1368 ICI and 1072 CCT were evaluable for low (0), intermediate (1), and high (0) LIPI (TABLE). **Conclusions:** This exploratory retrospective analysis indicates that LIPI may be a prognostic biomarker for both ICI and CCT for 2nd line mNSCLC.

		ICI			CCT		
	LIPI (n)	**0 (620)**	**1 (583)**	**2 (165)**	**0 (380)**	**1 (508)**	**2 (184)**
OS	HR (95%CI)		1.71 (1.47,2.00)	2.91 (2.36, 3.59)		1.45 (1.23, 1.71)	2.05 (1.67, 2.53)
	months (95%CI)	15.6 (13.5, 17.6)	8.9 (7.9, 9.7)	4.53 (3.1, 6.2)	10.5 (9.2, 11.8)	7.89 (7.0, 8.7)	5.29 (4.3, 6.3)
PFS	HR (95%CI)		1.34 (1.17, 1.54)	1.7 (1.38, 2.1)		1.37 (1.18, 1.60)	1.79 (1.46, 2.20)
	months (95%CI)	5.7 (4.6, 6.2)	3.5 (2.7, 4.2)	2.1 (1.7, 2.3)	5.4 (4.7, 6.1)	3.7 (3.2, 4.1)	2.4 (2.1, 3.4)

3036 Poster Session (Board #250), Mon, 8:00 AM-11:30 AM

Genomic correlates of response to immune checkpoint blockade in microsatellite stable solid tumors. *First Author: Natalie Vokes, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune checkpoint inhibitors have improved survival in multiple malignancies, but genomic biomarkers for efficacy in microsatellite stable tumors are incompletely characterized. **Methods:** Tumor and germline whole exome sequencing (WES) from pre-treatment tumors in immune checkpoint-treated patients were assembled from 7 published studies and from 78 newly sequenced tumors (total n = 249). Tumor types included were melanoma (n = 151), non-small cell lung cancer (n = 57), bladder cancer (n = 27), head and neck cancer (n = 12), sarcoma (n = 1), and anal cancer (n = 1). The sequencing data were processed through a uniform pipeline, and the results were correlated with clinical outcomes to immune checkpoint therapy to identify tumor genomic features that contribute to response. RECIST (v1.1) was used to define responders as those with complete or partial response, and those with progressive disease as non-responders. **Results:** Although tumor mutational burden was correlated with response, its univariate predictive power in this cohort was low (AUC = 0.66). Further analyses identified additional correlates of response, including individual driver genes in kinase signaling and chromatin regulators, global mutational signatures, and specific HLA-restricted neoantigens. Copy number analysis corroborated associations between specific pathways and absence of response to immunotherapy, including increased copy number events in the interferon-γ pathway in nonresponders (19/123 vs 3/70, p = 0.034). However, many of these molecular features were interrelated and potentially confounded with one-another. Power simulations showed that significantly larger sample sizes are necessary to disentangle these features, highlighting the complexity of identifying genetic driver events that generate an immunoresponsive tumor environment. **Conclusions:** This study represents the largest analysis to date of WES obtained from solid tumors in patients treated with immune checkpoint inhibitors. This work defines a path for gathering insights from multiple cohorts, and advances hypotheses of biological mechanisms and biomarkers of response to immune checkpoint therapy for further study.

3038 Poster Session (Board #252), Mon, 8:00 AM-11:30 AM

Demonstration of anti-tumor immunity via intratumoral regulated platform ad-RTS-hIL-12 in advanced breast cancer and recurrent glioblastoma patients. *First Author: Francois M. Lebel, ZIOPHARM Oncology, Inc., Boston, MA*

Background: Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate expressing IL-12 under the control of an orally administered activator ligand, veledimex (V), through a proprietary RheoSwitch Therapeutic System (RTS) gene switch. This platform reduces systemic toxicity and stimulates anti-cancer T cell immune response. **Methods:** Two open label trials evaluated the tolerability of local inducible IL-12 expression in heavily pretreated patients with metastatic breast cancer (mBC) or recurrent glioblastoma (rGBM). Ad was administered as a single intratumoral injection with V 80 mg PO Qdx7 in mBC and 10-40 mg Qdx15 PO in rGBM. **Results:** We observed local expression of IL-12 and downstream IFNg demonstrating biological activity with a mean increase in tumor cytotoxic T cells ($CD3^+CD8^+$) baseline: 0.4 ± 0.2 to biopsy:1.9±0.8% cells with a mean reduction in T_{reg} ($CD4^+FOXP3^+$) baseline: 0.8 ± 0.4 to biopsy: 0.6±0.3% cells. Sustained increases in tumor IFNg were documented in both mBC (by biopsy at Day 42 post injection) and rGBM (biopsy range:130 - 175 days post injection) while tumor IL-12 returned to baseline and systemic levels of IFNg and IL-12 were undetectable. In mBC, injected and non-injected lesions (abscopal effect) showed a reduction in lesion diameter. In the mBC study, 9 iRECIST evaluable subjects showed PR/stable disease in 5 subjects, for a disease control rate of 44% at Week 6 and 22% at Week 12. In the ongoing rGBM study we observe a mOS of 12.5 months with 5 of 15 subjects alive in the 20 mg V cohort with survival follow up ongoing. Across studies, the adverse event profile of Ad+ V, was predictable, controllable, and fully reversible upon stopping V including a dose response to frequency and severity of cytokine release syndrome. **Conclusions:** Local regulated controlled IL-12 expression using the Ad + V platform in advanced mBC and rGBM patients is promising, eliciting sustained increases in cytotoxic T cells, reduces T_{reg}, including in non-injected lesions (abscopal effect) turning cold tumors hot, with a good safety profile. This platform warrants further evaluation in multiple tumor types in monotherapy and in combination with immune checkpoint inhibitors. Clinical trial information: NCT02026271; NCT02423902.

3039 Poster Session (Board #253), Mon, 8:00 AM-11:30 AM

Outcomes by prior lines of therapy (LoT) in ZUMA-1, the pivotal phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients (Pts) with refractory large B cell lymphoma. *First Author: Frederick Lundry Locke, Moffitt Cancer Center, Tampa, FL*

Background: In ZUMA-1 (NCT02348216), axi-cel, an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, demonstrated significant benefit in patients (pts) with refractory large B cell lymphoma with an objective response rate (ORR) of 82% (complete response [CR] 58%; Neelapu & Locke et al. *NEJM*. 2017). These results supported the recent approval of axi-cel by the US FDA for the treatment of adult pts with relapsed or refractory large B cell lymphoma after ≥ 2 prior lines of systemic therapy. Here, we assessed outcomes of axi-cel by prior lines of therapy (LoT) in pts from Phases 1 and 2 of ZUMA-1. **Methods:** Pts with refractory large B cell lymphoma were leukapheresed and received 2×10^6 CAR T cells/kg after low-dose conditioning (Neelapu & Locke et al. *NEJM* 2017). Pts were evaluated by number of prior LoT: 2 – 3 vs ≥ 4. Autologous stem cell transplant (ASCT) was considered a prior LoT. **Results:** As of 8/11/17, median follow-up was 15.4 mo for the 108 pts treated with axi-cel. Sixty-two (57%) pts had 2 – 3 prior LoT and 43 (40%) had ≥ 4. Pts with 2 – 3 and ≥ 4 prior LoT had median ages of 60 and 55 y, 65% and 47% of pts had ECOG performance status 1, 18% and 42% had prior ASCT, and 76% and 93% had disease stage III/IV, respectively. ORRs were 94% and 67% for pts with 2 – 3 and ≥ 4 prior LoT, respectively, with CR rates of 65% and 53%; 44% and 42% of pts had ongoing responses as of the data cutoff (Table). Overall survival (OS) at 12 mo was 65% and 51% for pts with 2 – 3 and ≥ 4 prior LoT, respectively. Grade ≥ 3 treatment-emergent adverse events were reported for nearly all (100% and 93%) pts with 2 – 3 and ≥ 4 LoT, with similar rates of Grade ≥ 3 cytokine release syndrome (11% and 12%) and neurologic events (32% and 30%). There were 1 and 3 Grade 5 AEs unrelated to disease progression in the 2 – 3 and ≥ 4 LoT groups, respectively. **Conclusions:** Axi-cel demonstrated long-term clinical benefit for pts with refractory large B cell lymphoma regardless of the number of prior LoT. Drs Locke and Neelapu contributed equally. Clinical trial information: NCT02348216.

	LoT	
Response, % (95% CI)	**2 – 3 (n = 62)**	**≥ 4 (n = 43)**
ORR	94 (84 – 98)	67 (51 – 81)
CR rate	65 (51 – 76)	53 (38 – 69)
Ongoing ORR	44 (31 – 57)	42 (27 – 58)
6-mo PFS[a]	49 (36 – 61)	51 (35 – 65)
12-mo OS[a]	65 (51 – 75)	51 (35 – 65)

[a]KM estimate

3040 Poster Session (Board #254), Mon, 8:00 AM-11:30 AM

First-in-human study of KHK2455, a long-acting, potent and selective indoleamine 2,3-dioxygenase 1 (IDO-1) inhibitor, in combination with mogamulizumab (Moga), an anti-CCR4 monoclonal antibody, in patients (pts) with advanced solid tumors. *First Author: Timothy Anthony Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: IDO-1 inhibitors have shown antitumor activity in combination with immunotherapeutic agents in multiple cancers. KHK2455 is a novel and selective oral IDO-1 inhibitor. Unlike other inhibitors, KHK2455 inhibits IDO-1 apo-enzyme, with long-lasting and potent activity. Moga is a monoclonal antibody with enhanced ADCC activity that has shown synergy with KHK2455 in preclinical models. **Methods:** Pts with advanced solid tumors received escalating doses of KHK2455 alone (0.3, 1, 3, and 10 mg once daily) for 4 weeks (Cycle 0), followed by combination with 1 mg/kg weekly of IV Moga for 4 weeks (Cycle 1) and then on Days 1 and 15 (from Cycle 2) in a standard 3+3 Phase I design. Dose escalation was based on safety, tolerability, pharmacokinetics and IDO activity (kynurenine [Kyn] and tryptophan [Trp] levels and *ex vivo* Kyn production). **Results:** 21 pts were enrolled in cohorts that received KHK2455 at 0.3, 1, 3, and 10 mg dose levels. No DLTs were observed. The most frequent adverse events (≥5%) included maculopapular rash, thrush, dysphagia, thrombotic event, and tachycardia, none of which were considered related to KHK2455. One case of rash (Gr 3) was considered related to Moga but not a DLT. Plasma KHK2455 concentrations reached steady state by Day 8 (Cycle 0) and increased dose-dependently. Potent dose-dependent inhibition of IDO activity was demonstrated in plasma samples (67% and 66% inhibition in Kyn concentrations and Kyn:Trp ratio, respectively, compared to baseline) and *ex vivo* stimulation assays (> 95% inhibition in Kyn production) at 10 mg KHK2455, confirming target modulation. Four patients (n = 3 head and neck; n = 1 ovarian) from all dosing groups have achieved durable RECIST disease stabilization for more than 6 months, and one (salivary gland carcinoma) for more than 14 months. **Conclusions:** KHK2455 in combination with Moga is safe and well tolerated at all doses tested, suppresses Kyn production in a dose-dependent and sustained manner, and demonstrates early signals of antitumor activity. These data support the continued development of this promising combination. Clinical trial information: NCT02867007.

3041 Poster Session (Board #255), Mon, 8:00 AM-11:30 AM

Which is better in CD19 CAR-T treatment of r/r B-ALL, CD28 or 4-1BB? A parallel trial under the same manufacturing process. *First Author: Peihua Lu, Hebei Yanda Lu Daopei Hospital, Langfang, China*

Background: Second-generation CARs have been shown to improve the overall functional activity and persistence of CAR-T cells. KYMRIAH and YESCARTA used 4-1BB and CD28 co-stimulatory signaling domains, respectively. **Methods:** A parallel trial under the same manufacturing process to compare the CD28 and 4-1BB CD19 CAR-T. **Results:** This study enrolled 47 relapsed or refractory CD19-positive B-cell acute lymphoblastic leukemia (B-ALL) patients, including 19 patients in CD28 group and 28 patients in 4-1BB group. 47 patients who received at least one infusion treatment and one clinical evaluation were available for assessing safety and efficacy. The overall objective response rate (ORR) was 96%. The ORR of 4-1BB group (100%) was higher than that of CD28 group (89%). All of the patients achieving objective response were MRD negative. CAR-T cell expansion in peripheral blood was detected by Flow cytometry, and the peak of CAR-T cells of 4-1BB group was significantly higher than that of CD28 group. Different degrees of cytokine release syndrome (CRS) occurred in 45 of 47 patients (95%). 5 patients who had grade III-IV of CRS were all in CD28 group. Cytokine release peak in CD28 group was significantly higher than that of the 4-1BB group. 9 patients experienced different levels of neurotoxicity (19%). 5 patients who had grade III-IV of neurotoxicity were all in CD28 group, too. All adverse events were effectively controlled within 1 month. **Conclusions:** The study illustrates that 4-1BB CAR-T cells show enhanced safety, efficacy, and expansion than CD28 CAR-T cells, suggesting a superior therapeutic strategy in the treatment of relapsed or refractory CD19-positive B-ALL patients. Clinical trial information: NCT03173417.

3042 Poster Session (Board #256), Mon, 8:00 AM-11:30 AM

Ex vivo expanded multi-antigen specific lymphocytes for the treatment of solid tumors. *First Author: Amy Houghtelin, Children's National Medical Center, Washington, DC*

Background: Patients with solid tumors refractory to standard therapies have poor prognoses, and most salvage therapies are toxic and ineffective. Antigen-specific T cell therapies offer a promising alternative for targeted therapy with the ability to target multiple antigens in a single product. Hence, we hypothesize that patient-derived tumor-associated antigen-specific T cells (TAA-T) targeting WT1, PRAME, and survivin expressed by pediatric solid tumors can be safely administered to treat patients with relapsed/refractory disease. The objective of this phase I clinical trial is to determine the safety of administering TAA-T to these patients. The secondary objectives include determining disease response and tumor-specific immune reconstitution following infusion. **Methods:** T cells expanded from patient peripheral blood were stimulated weekly with antigen presenting cells pulsed with an overlapping peptide library spanning the TAAs WT1, PRAME, and survivin. Following release testing, patients were infused with TAA-T on a dose escalation study, ranging from 1 x $10^7/m^2$ (dose level 1) to 4 x $10^7/m^2$ (dose level 3). Clinical and immune studies were performed post-infusion to monitor for adverse effects and assess immune and disease responses. **Results:** We have generated TAA-T products from 14 patients (age range 6-54 years) with relapsed/refractory solid tumors (neuroblastoma, osteosarcoma, Wilms tumor, Ewing sarcoma, soft tissue sarcoma, rhabdomyosarcoma). 14 patients have received a median of 2 (range 1-8) infusions without product-related SAEs post-infusion. Epitope spreading was identified in 86% of responding patients. Preliminary outcome data (N = 10) show overall survival of 82% and event-free survival of 54% at 3 months. **Conclusions:** This unique immunotherapeutic has been well tolerated without causing life-threatening adverse events. Despite aggressive and multiply relapsed disease, 75% of patients have demonstrated evidence of disease control after TAA-T with epitope spreading identified in the majority of responding patients post-infusion. These clinical and laboratory data suggest that TAA-T may safely prolong survival in patients with relapsed/refractory solid tumors. Clinical trial information: NCT02789228.

3043 Poster Session (Board #257), Mon, 8:00 AM-11:30 AM

Regression of epithelial cancers in humans following t-cell receptor gene therapy targeting human papillomavirus-16 E7. *First Author: Nisha Nagarsheth, Experimental Transplantation and Immunology Branch, Center for Cancer Research, NIH, Bethesda, MD*

Background: Adoptive T-cell therapy with gene-engineered T cells is an emerging cancer treatment strategy. Study of this approach in epithelial cancers, the most common types of malignancies, has been limited. We initiated a clinical trial of gene-engineered T cells that target human papillomavirus (HPV)-16-E7 for the treatment of patients with metastatic HPV-16+ cancers. **Methods:** The clinical trial was designed as a phase I study with three dose levels (DL) of gene-engineered T cells (DL1: 1 x 10^9, DL2: 1 x 10^{10}, DL3: 1 x 10^{11}). Patients had metastatic HPV-16+ cancers from any primary tumor site. Patients received a single infusion of autologous T cells that were gene-engineered to express an HLA-A*02:01-restricted T-cell receptor that targets HPV-16 E7 (E7 T cells). A lymphocyte-depleting conditioning regimen was administered before treatment. E7 T cell infusion was followed by high-dose systemic aldesleukin. We report the early results of the ongoing study. **Results:** Eight patients were treated. No dose-limiting toxicity, off-target T-cell toxicity, or cytokine-release syndrome occurred. Objective clinical responses were observed in 3/7 evaluable patients. Responses occurred in patients with vulvar, oropharyngeal, and anal cancer. Two of these patients had been previously treated with anti-PD-1 checkpoint blockade. One response occurred at DL1. The patient had extensive metastatic vulvar cancer involving the lungs, retroperitoneum, pelvis, and thigh. She had been previously treated with seven systemic anti-cancer agents. The response lasted 8 months after treatment. Two responses occurred at DL2. One was in a patient with metastatic anal cancer with lung, pleura, and kidney tumors. The response is ongoing after 7 months. In the initial six patients, the E7 TCR was expressed by 90-99% of the infused T cells, and E7 T cells were detectable in the peripheral blood six weeks following treatment (1% to 4% at DL1, 5% to 45% at DL2). **Conclusions:** Tumor regression can occur following treatment of an epithelial cancer with gene-engineered T cells. These findings support continued study of E7 T cells and possibly other types of gene-engineered T cells in epithelial cancers. Clinical trial information: NCI-16-C-0154.

3044 Poster Session (Board #258), Mon, 8:00 AM-11:30 AM

Immunogenicity of tisagenlecleucel in relapsed/ refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL) patients. *First Author: Karen Thudium Mueller, Novartis Institutes for BioMedical Research, East Hanover, NJ*

Background: Tisagenlecleucel, a chimeric antigen receptor (CAR) T-cell therapy, contains a murine single chain variable fragment (mCAR19) binding domain. Humoral immunity to anti-mCAR19 had no impact on safety or efficacy in pediatric r/r B-ALL patients (pts) (Mueller ASH 2017); immunogenicity in r/r DLBCL has not been studied. **Methods:** Tisagenlecleucel immunogenicity was measured in r/r B-ALL (ELIANA [NCT02435849, n = 75]; ENSIGN [NCT02228096, n = 29]) and r/r DLBCL (JULIET [NCT02445248, n = 99]) ≤ 12 months after infusion. Cellular immunity was measured in PBMCs and tested for mCAR19 peptide-activated T cell responses by stimulated intracellular interferon-gamma production. Anti-mCAR19 antibodies (Ig) were measured by flow cytometry at baseline and after treatment. Treatment-induced Ig was defined as the ratio of postbaseline Ig levels to baseline. The impact of preexisting and treatment-induced Ig and T-cell activation on cellular kinetics, efficacy and safety were determined. **Results:** 84.6% of r/r B-ALL and 91.4% of r/r DLBCL pts had preexisting humoral immunogenicity. Treatment-induced humoral immunogenicity occurred in 34.6% of r/r B-ALL and 5% of r/r DLBCL pts. No relationship was found between tisagenlecleucel expansion ($AUC_{0\text{-}28d}$) and preexisting humoral responses in r/r B-ALL (r^2= 0.002) or r/r DLBCL (r^2= 0.008), or treatment-induced humoral responses in r/r B-ALL (r^2= 0.006). Results for C_{max} were similar. Treatment induced humoral responses did not impact expansion or persistence of CARs in B-ALL, but sample size prevented correlation analysis in DLBCL as only 5% of pts had treatment-induced Ig. Preexisting humoral immunity did not appear to impact transgene persistence, duration of response, event-free survival or safety in either indication. T-cell responses were consistent over time with net responses < 1% at baseline and postinfusion for the majority of pts. T-cell responses did not appear to impact transgene expansion or persistence or pt outcomes. **Conclusions:** Preexisting/treatment-induced humoral and antigen-specific cellular immunity did not impact tisagenlecleucel expansion, persistence, efficacy or safety. Clinical trial information: NCT02435849, NCT02228096, NCT02445248.

3045 Poster Session (Board #259), Mon, 8:00 AM-11:30 AM

Durable clinical responses observed from non-Hodgkin lymphoma patients treated with autologous CAR-T cells targeting CD19. *First Author: Yarong Liu, HRAIN Biotechnology, Shanghai, China*

Background: Cellular immunotherapy based on chimeric antigen receptor (CAR)-engineered T (CAR-T) cells has shown to be one of the most promising immunotherapeutic strategies for cancer treatment. Herein we report an encouraging result from a phase 1 clinical trial to evaluate a CD19 CAR-T therapy for treating relapse/refractory B-cell non-Hodgkin's lymphoma (NHL). **Methods:** A phase 1 clinical trial was conducted to evaluate safety and efficacy of CD19 CAR-T therapy for patients with relapsed and/or refractory NHL. A total of 22 patients with $CD19^+$ B-cell NHL at stage III/IV were enrolled in this study; these patients had received 4-12 (median 8) rounds of various chemotherapies prior to the enrollment. All patients were pre-conditioned with Cy (800 mg/m^2) once (d -5) and Flu (25 mg/m^2) daily for 3 days (d -5 to d -3) followed by administration of a total dose of 1x10^6 cells/kg CD19 CAR-T cells via either a single infusion or a 3-day split-dose (10, 30, and 60%) infusion regimen. The efficacy was assessed by RECIST1.1 and the toxicity was evaluated by CTCAE 4.02. The CAR-T cell expansion and persistence were measured by quantitative PCR (qPCR) and flow cytometry. **Results:** Of the 22 patients, only one exhibited over grade 3 cytokine release syndrome (CRS) and was resolved after active treatments. Moreover, no central nervous system toxicity was observed. The overall response rate (ORR) for the 18 evaluable patients was 72.2%. Complete remission (CR) and ORR for six months were both at 36.7%. The median progress-free survival was 4 months (95% confidence interval (CI), 0.5 to 7.5) and a median overall survival was 11 months (95% CI, 4.7 to 17.3). It was observed that local radiation prior to cell therapy could enhance CAR-T cell infiltration. Further analysis revealed a biomarker which could be used to identify beneficial patients. Interestingly, pseudo-progression occurred on some patients and two rounds of CAR-T expansion were seen in several patients. One patient has experienced ongoing CR, B cell deficiency, and persistence of CAR-T cells for > 21 months. **Conclusions:** Our data indicate that this CD19 CAR-T product can offer substantial clinical benefit for NHL patients with manageable toxicities. Clinical trial information: NCT02652910.

3046 Poster Session (Board #260), Mon, 8:00 AM-11:30 AM

A phase I trial of T4 CAR T-cell immunotherapy in head and neck squamous cancer (HNSCC). *First Author: Sophie Papa, Guy's And St Thomas NHS Foundation Trust, London, United Kingdom*

Background: Recent FDA approvals make CAR T-cell therapy a clinical reality for hematologic malignancy. Toxicity and antigen loss-mediated resistance remain problematic. Solid tumors impose additional challenges, foremost the paucity of safe targets. Moreover, CAR T-cells need to home to, penetrate and persist in an active state within a profoundly immunosuppressive tumor microenvironment. To address these issues, we developed T4-immunotherapy: T-cells that co-express: (i) T1E28ζ, a CAR containing a promiscuous ErbB ligand coupled to a CD28+CD3ζ endodomain; and (ii) 4αβ, an IL-4-responsive chimeric cytokine receptor. T1E28ζ engages 8/9 ErbB homo/heterodimers, providing broad anti-tumor scope while minimizing risk of antigen escape. 4αβ enables IL-4-driven selective CAR T-cell enrichment/expansion during manufacture. Pre-clinical data demonstrate potent anti-tumor activity of T4-immunotherapy. However, risk of on-target off-tumor toxicity is significant, due to normal tissues low-level ErbB expression. **Methods:** We undertook a Phase I dose-escalation trial of T4-immunotherapy in HNSCC. T4-immunotherapy was manufactured using a blood draw (40-130mL) in a two-week closed process, employing IL-4 as the sole cytokine stimulus post transduction. CAR T-cell dose was escalated through 5 cohorts from $1x10^7$ -$1x10^9$ $T4^+$ T-cells administered as a single treatment, by multifocal intra-tumoral injection without lymphodepletion. **Results:** Despite a lymphopenia rate of 62%, T4 manufacture was successful in 13/13 cases, yielding 2.5-7.5Bn T-cells (69+/-13% transduced). Treatment-related AEs were ≤ grade 2, with no dose-limiting toxicities (CTCAE v4.0). Frequent AEs were steroid-responsive tumor swelling, pain, pyrexias, chills and fatigue. Circulating $T4^+$ T-cells were undetectable in all patients at all times. At 6-weeks, stable disease (SD) was seen in patients treated with $\geq 10x10^7$ $T4^+$ T-cells. Overall disease control rate was 69% (RECIST 1.1), despite rapidly progressing tumors on trial entry. Subsequent PD1 + oncolytic virus therapy in one patient achieved a rapid complete clinical response. **Conclusions:** These data demonstrate the safe intratumoral administration of T4 in patients with advanced HNSCC. Clinical trial information: NCT01818323.

3047 Poster Session (Board #261), Mon, 8:00 AM-11:30 AM

Acquired resistance to T cell adoptive transfer by inflammation-induced melanoma dedifferentiation. *First Author: Arnav Mehta, Massachusetts General Hospital, Boston, MA*

Background: Many patients that initially respond to cancer immunotherapy with adoptive cell therapy (ACT) using T cell receptor (TCR) engineered autologous T cells eventually develop resistance and experience relapse (termed acquired resistance) through mechanisms that remain poorly understood. **Methods:** We analyzed baseline and on-therapy tumor samples from 15 patients with metastatic melanoma that were treated with transgenic lymphocytes expressing a MART-1 TCR administered with a MART-1 peptide-pulsed dendritic cell vaccine. We studied *in vitro* the effect of inflammatory mediators and MART-1-specific T cells on human patient-derived melanoma cell lines, and performed bulk RNA-sequencing and methylation analysis of melanosome genes to gain further insight into mechanisms of acquired immunotherapy resistance in these cells. **Results:** Progression biopsies of metastatic melanoma lesions in one of the patients demonstrated phenotypic dedifferentiation as a resistance mechanism to ACT, a phenomenon previously only reported in murine models (Landsberg et al., Nature, 2012). After a three month period of tumor regression, the patient presented in relapse with tumors lacking melanocytic antigens (MART-1, gp100) but expressing the inflammation-induced neural crest marker NGFR (or CD271). We validated inflammation-induced tumor dedifferentiation of 8 melanoma cell lines *in vitro* after stimulation with TNFa for 3 days, and identified gene pathways altered in dedifferentiated cells by RNA-sequencing. Gene set enrichment analysis revealed that TNFa treatment enriched for genes involved in epithelial to mesenchymal transition (NES = 1.92, FDR < 0.001) and neural crest stem cell identity (NES = 1.49, FDR = 0.016), and pathways in the innate anti-PD-1 resistance signature (IPRES). TNFa treatment also downregulated genes in the MITF pathway (NES = -2.38, FDR < 0.001). **Conclusions:** Inflammation-induced dedifferentiation is a new mechanism that can lead to acquired resistance to cancer immunotherapy.

3048 Poster Session (Board #262), Mon, 8:00 AM-11:30 AM

Screening of neoantigen-specific T cells and establishment of T-cell receptor-engineered T cells: Implications for head and neck squamous carcinoma. *First Author: Lili Ren, The University of Chicago, Chicago, IL*

Background: Due to the high immune-suppressive condition in tumor microenvironment in growing tumors, the numbers of neoantigen-specific T cells is in general very limited. To improve adoptive T cell transfer (ACT) immunotherapy targeting neoantigens, we attempted to rapidly identify neoantigen-specific T cell receptors (TCRs) and establish T-cell receptor-engineered (TCR-engineered) T cells. **Methods:** To screen the neoantigen-specific T cells, we performed whole exome sequencing (WES) and transcriptome analysis, and selected candidate neoantigen epitopes to induce cytotoxic T lymphocytes (CTLs) in 20 patients with squamous head and neck cancer. 64 potential neoantigen peptides as well as 16 minigenes, each of which were designed to express peptides carrying 20 somatic missense mutations, were examined for induction of neoantigen-reactive cytotoxic T cells *in vitro* using patient-derived dendritic cells and peripheral blood, or expanded TILs isolated from corresponding tumors. Neoantigen-specific T cells were screened by 4-1BB expression levels as well as ELISPOT assay and TCR sequences were determined using isolated T cell clones. We then cloned TCR cDNAs into T lymphocytes and generated the neoantigen-reactive TCR-engineered T cells. **Results:** We have so far confirmed 8 neoantigen-reactive T cells and established 6 TCR-engineered T cells which showed HLA-restricted neoantigen-reactive cytotoxic activity *in vitro*. We also tested HLA A*02:01 restricted engineering T cells with the antigen-negative humanized mice model we generate previously, which showed very specialized antigen reactivity *in vivo*. **Conclusions:** We here demonstrate the establishment of a more effective and rapid protocol to generate neoantigen-specific T cells, identify neoantigen-specific TCRs for individual patients, and establish TCR-engineered T cells applicable for the clinical use.

3049 Poster Session (Board #263), Mon, 8:00 AM-11:30 AM

ET190L1-ARTEMIS T cell therapy to induce complete remission of relapsed and refractory (r/r) B-cell lymphoma with no cytokine release syndrome in the first-in-human clinical study. *First Author: Zhi Tao Ying, Peking University Cancer Hospital & Institute, Beijing, China*

Background: To ameliorate CRS commonly associated with CAR T-cell therapy, we developed a novel T cell therapy, the ARTEMIS platform, which functionally matches the potency of CAR-T cells, but triggers significantly less cytokine release upon target engagement. Herein we describe the first-in-human clinical studies of anti-CD19 ET190L1-ARTEMIS™ T cell therapy in r/r B-cell lymphoma at multiple sites. **Methods:** Patients are assigned to 1 of 3 cohorts: single infusion of ET190L1-ARTEMIS™ T cells at 1, 3 or 6×10^6 cells/kg. The primary objective is to evaluate safety. Additional objectives include assessment of T cell engraftment and tumor response. **Results:** As of Jan 23, 2018, twelve heavily pretreated adult patients received autologous ET190L1-ARTEMIS T cells, 3 in the 1×10^6/kg cohort and 9 in the 3×10^6/kg cohort. Expansion of ARTEMIS T cells after infusion was observed in all patients. No CRS or neurotoxicity was observed. Plasma levels of IL-2, 4, 6, 8, 10, IFNg, TNFa, and GM-CSF were below detection at most time point post-infusion. Vital signs were normal except for 3 patients in the 3×10^6/kg cohort who had transient fever (37.5-39°C) from day 2 to day 4 post-infusion. One patient from the 1×10^6/kg cohort developed a transient skin rash. The overall response rate is 78% (7/9) (See Table 1). Six month follow-up data for the first 9 patients and early data from additional patients will be presented. **Conclusions:** In the studies, ET190L1-ARTEMIS T cell therapy demonstrated a favorable safety profile with no observed CRS or neurotoxicity and shows promising efficacy in r/r lymphoma patients. Durability of the responses will be evaluated with longer follow-up. Based on its observed response rate and lack of CRS and neurotoxicity, the ARTEMIS platform is potentially a major improvement over existing CAR-T cell therapy.

Tumor response (using Cheson criteria) and treatment-related safety events.

			Month Post Dosing				
Patient	Subtype	Dose (Cells/kg)	1	2	3	CRS	Neurotoxicity
1	DLBCL	$1x10^6$	CR	CR	CR	0	0
3	DLBCL		SD	SD	SD	0	0
4	FL		CR	CR	CR	0	0
5	DLBCL	$3x10^6$	PD			0	0
6	DLBCL		PD			0	0
7	FL		CR			0	0
8	DLBCL		CR			0	0
9	MCL		CR			0	0
10	FL		PR			0	0

3050 Poster Session (Board #264), Mon, 8:00 AM-11:30 AM

A phase I trial of PD-1 deficient engineered T cells with CRISPR/Cas9 in patients with advanced non-small cell lung cancer. *First Author: You Lu, Department of Thoracic Oncology, Cancer Center, West China Hospital, West China School of Clinical Medicine, Sichuan University, Chengdu, China*

Background: We performed the first phase I clinical trial (NCT02793856) to assess safety of CRISPR/Cas9-mediated knockout of PD-1 gene in autologous T lymphocytes (PD-$1^{-/-}$ T) therapy in patients with metastatic non-small cell lung cancer (NSCLC). **Methods:** We assigned patients with advanced NSCLC with positive PD-L1 expression who had progressed after 3rd line standard therapeutic regimens. Two patients were enrolled in Pre-A cohort who received PD-$1^{-/-}$ T therapy with 2 x 10^7 cells/kg for one cycle and were observed for another cycle. Then 3 cohorts (A, B, C) enrolled 3 patients in each group receiving PD-$1^{-/-}$ T cells therapy with 1×10^7/kg, 2×10^7/kg, 4×10^7/kg in each cycle, respectively. Patients received PD-$1^{-/-}$ T therapy until disease progression or study withdrawal. Primary outcome was safety. Secondary end points were 8 weeks disease control rate (DCR) and progression-free survival (PFS). In exploratory analyses, next-generation sequencing was performed on PD-1 editing region of T cells and CDR3 region of T-cell receptor. **Results:** Nine patients were enrolled and eight patients received totally 17 cycles of PD-$1^{-/-}$ T therapy. Twenty-three adverse events (AEs) related to PD-$1^{-/-}$ T cell infusion occurred (Table 1). No 3-5 AEs were observed. Of note, one patient in Pre-A group suffered grade 1 arrhythmia (premature beat) that lasted for 42.4 weeks. Seven patients were response evaluable. Two patients experienced stable disease (SD) with 17.6 and 22.0 weeks, respectively. Other 5 patients had progression disease (PD). Eight-week DCR was 28.6% and median PFS was 7.6 weeks. In exploratory data, two patients with SD showed higher diversity of T cell repertoire in PBMC than other 5 patients with PD. **Conclusions:** Patients receiving PD-$1^{-/-}$ T therapy seemed safe. Further larger size studies are warranted to explore effective dose and related immune response. Clinical trial information: NCT02793856.

	Total			Cohort								
	(N = 8)			Pre-A (N = 2)			A (N = 3)			B (N = 3)		
Events Grade	1	2	≥3	1	2	≥3	1	2	≥3	1	2	≥3
Fever	2									2		
Hyperhidrosis	3									3		
Rash	1			1								
Arthralgia	1						1					
Fatigue	2			1			1					
Infusion related reaction		1						1				
Arrhythmia	1			1								
Hypertension	1			1								
Aminotransferase increased	2			1			1					
White blood cell decreased	7						7					
Thrombocytopenia	2									2		
Total	22	1	0	5	0	0	10	1	0	7	0	0
All level events		23			5			11			7	

3051 Poster Session (Board #265), Mon, 8:00 AM-11:30 AM

Correlation of pre-CAR CD19 expression with responses and relapses after CAR T cell therapy. *First Author: Vinodh Pillai, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Chimeric antigen receptor (CAR) T cells targeting CD19 have shown excellent responses in patients with relapsed/refractory B-ALL. However, a subset of patients either do not respond or relapse after CAR T cell therapy, the causes of which are unclear. The use of CD19-directed therapy has increased the incidence of CD19 dim or CD19 negative B-ALL. We assessed whether pre-treatment CD19 expression level or prior targeted therapy impacts response to CAR therapy. **Methods:** Cases of B-ALL treated with CAR therapy from 2012-2017 at Children's Hospital of Philadelphia were evaluated. CD19 in blasts was classified as dim, normal or bright compared to normal B cells by flow cytometry. CD19 expression and immunophenotype of blasts pre and post-CAR therapy were correlated with responses to CAR T cell therapy. Failure to reach an MRD-negative remission was considered as non-response. Presence of aberrant blasts ($>$ 0.01%) at any time point after remission was considered as relapsed disease. **Results:** 150 cases treated with CAR therapy were evaluated of which 10 were non-response (NON), 20 were CD19 positive relapses (CD19PR) and 33 were CD19 negative relapses (CD19NR). 15 patients received prior CD19 targeted therapy. Rate of responses and relapses in CD19dim B-ALL were not significantly different from the CD19 normal/bright group. However, prior CD19-targeted therapy was associated with a significantly higher rate (60%; p = 0.014) of NON and CD19NR compared to 25% in patients who did not receive any prior CD19 targeted therapy. Immunophenotype of CD19PR were identical to that of pre-therapy disease in 85% of cases, consistent with loss of CAR T cells as the etiology of those relapses. Blasts from CD19NR patients did not show any CD19-negative events by flow prior to CAR T cell therapy in 75% of cases suggesting that CD19-negative blasts may be de novo events. **Conclusions:** CAR T cell therapy is effective in B-ALL with dim CD19 expression. Prior targeted therapy is associated with increased non-response and relapse, likely due to CD19 escape. CD19PR after CAR T cell therapy are due to early loss of CAR T cells while CD19NR are likely due to expansion of de novo CD19-negative B lymphoblasts under treatment pressure.

3052 Poster Session (Board #266), Mon, 8:00 AM-11:30 AM

Clinical anti-lymphoma activity and toxicity of T cells expressing a novel anti-CD19 chimeric antigen receptor with fully-human variable regions. *First Author: Jennifer N. Brudno, Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda, MD*

Background: T cells expressing chimeric antigen receptors (CARs) targeting CD19 have powerful activity against B-cell lymphoma. A limitation to CAR T-cell therapy for lymphoma is occurrence of toxicities, especially neurologic toxicities. **Methods:** We designed an anti-CD19 CAR with fully human variable regions (Hu19CAR). This CAR has CD8α hinge and transmembrane domains and a CD28 costimulatory domain; T cells expressing this CAR release relatively low levels of cytokines. A phase I dose-escalation trial was conducted to investigate the safety of Hu19CAR T cells and to assess efficacy for patients with previously treated B-cell lymphoma. Patients received cyclophosphamide and fludarabine chemotherapy to enhance CAR T-cell activity. Two days after the completion of chemotherapy, Hu19CAR T cells were infused. **Results:** Twenty patients have received Hu19CAR T-cell infusions. Of these patients, 75% had lymphoma that was chemotherapy-refractory or relapsed after autologous stem cell transplant. Patients received a median of 4 prior lines of therapy. The overall response rate is 75%, with 55% complete remissions (CRs). CRs were observed in patients with chemotherapy-refractory lymphomas and in patients with double-hit diffuse large B-cell lymphoma. Durations of response currently range from 1 to 17 months. Forty percent of patients are in ongoing remissions. Only one patient experienced greater than Grade 2 neurotoxicity (5%), which is a neurotoxicity rate lower than that of many anti-CD19 CAR trials. This patient had Grade 4 neurotoxicity which reversed in less than 24 hours with corticosteroid therapy. Three patients had Grade 3 cytokine release syndrome (CRS), and 1 patient had Grade 4 CRS; all other patients had Grade 2 or lower CRS. CRS and neurotoxicities resolved completely in all patients. Loss of CD19 expression by lymphoma cells was observed in 4 of the 8 patients who underwent biopsies of recurrent or residual lymphoma after Hu19CAR T-cell infusions. CAR T cells were detected in the blood of all patients at levels ranging from 4-2216 cells/μL. **Conclusions:** Hu19CAR T cells have substantial activity against advanced lymphoma with a low rate of neurotoxicity. Clinical trial information: NCT02659943.

3053 Poster Session (Board #267), Mon, 8:00 AM-11:30 AM

Impact of the influenza vaccination on cancer patients undergoing therapy with immune checkpoint inhibitors (ICI). *First Author: Ragisha Gopalakrishnan, Vanderbilt University Medical Center, Nashville, TN*

Background: Immune checkpoint inhibitors (ICI) are standard of care for many cancer patients (pts). There have been conflicting reports on the effect of the influenza (flu) vaccines (flu-V) on pts being treated with ICI, and some suggest that flu-V may impact survival outcomes in ICI treated pts. **Methods:** We conducted a retrospective review of patients at Vanderbilt Ingram Cancer Center treated with ICI from 2010-2017. Data collected included age, gender, race, cancer type, comorbidities, type of ICI (single v. combo), time of drug administration, time of flu-V, rate of flu prodromal, rate of admissions for flu related complications, rate of immune related adverse events (irAE) and admissions, and the impact of flu-V on PFS and OS. Statistical analysis was performed using Graph PAD prism and SPSS. **Results:** 534 patients were included, 72.1% received flu vaccine. Median age was 54, 76% male, 64.1% stage IV. Cancer types included were lung (37%), melanoma (34%), GU (18%), breast 7.2%, and lymphoma (3.4%). 93% received single agent ICI. Vaccinated and unvaccinated pts (37.4 v. 42.6, p = 0.067) developed equal rates of irAEs. Unvaccinated pts who developed irAEs were more likely to develop pneumonitis (37.23 v. 17.17, p = 0.023) and more likely to be admitted than vaccinated pts (41.53% v. 23.2% p = 0.016). Unvaccinated pts were less likely to experience flu prodrome (32.2 % v 43.7%, p = 0.067), but were more likely to be admitted for influenza related complications (62.4% 23.2 %, p = 0.032). Most common reason for admission was sepsis. Flu-V did not change PFS (vaccinated 47.2 m vs. unvaccinated 43.2 m, p = 0.0621) but improved OS (vaccinated 72 months v. 62 months unvaccinated, p $<$ 0.001). In multivariate analysis, age and abstaining from flu-V were predictive for developing irAEs. Type and stage of malignancy, # of prior lines of therapy, type of ICI, and timing of flu-V was not predictive for developing for irAE. **Conclusions:** Our results suggest that seasonal flu vaccination is safe and beneficial for patients on ICI and reduces the rate of hospital admissions from flu related and irAEs. Furthermore, our study also demonstrates that vaccination with influenza may improve OS in patients receiving ICI.

3054 Poster Session (Board #268), Mon, 8:00 AM-11:30 AM

Safety and activity of programmed cell death-1 gene knockout engineered t cells in patients with previously treated advanced esophageal squamous cell carcinoma: An open-label, single-arm phase I study. *First Author: Zhao Jing, Hangzhou Cancer Hospital, Hangzhou, China*

Background: We designed the clinical trial to investigate the safety and activity of Programmed death-1 (PD-1) knockout engineered T cell in patients with advanced esophageal squamous cell carcinoma (ESCC). **Methods:** Patients (aged ≥18 years) with advanced ESCC whose disease had progressed after at least two systemic therapies were enrolled. Peripheral blood will be collected and PD-1 gene will be knocked out by clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 in the laboratory. T lymphocytes will be selected, expanded and reinfused back into patients after about 2-3 weeks. Response was assessed 4 weeks after each infusion. Patients continued receiving treatment until disease progression, intolerable toxicity, or consent withdrawal. The primary endpoint was to evaluate the safety of PD-1 knockout engineered T cells treatment. **Results:** Between Mar, 2017, and Jan, 2018, we enrolled 21 patients who received at least one cycle PD-1 knockout engineered T cells treatment. Among 21 treated patients, 7 accepted only 1 cycle of cell infusion, 12 accepted 2 cycles, and 2 accepted 3 cycles. Up to the study cutoff date of Jan 31, 2018, the most common adverse events were transient fever (7 patients, the highest was 39.1℃) and chills (3 patients) and moderate skin rash (1 patient). No grade 3 or 4 adverse events were observed in the study. Of the 17 evaluable patients, no complete or partial responses were observed. 6 patients had stable disease, and 11 patients had progressive disease. Disease control rate was 35% (6/17) and median overall survival was 127 days (95% CI 45–209). During the trial, 10 cancer progression related deaths occurred. Immunofluorescence analysis showed that the PD-1 knockout engineered T cells could infiltrate into and persist for a durable time in ESCC that responded to therapy. **Conclusions:** The results showed that PD-1 knockout engineered T cells infusion might be an effective treatment in patients with heavily pretreated advanced ESCC. The treatment was well tolerated with no unexpected safety concerns. The regimen warrant further clinical investigation. Clinical trial information: NCT03081715.

3055 Poster Session (Board #269), Mon, 8:00 AM-11:30 AM

Adoptive cellular immunotherapy with APN401, autologous cbl-b silenced peripheral blood mononuclear cells: Data from a phase I study in patients with solid tumors. *First Author: Hans Loibner, Apeiron Biologics AG, Vienna, Austria*

Background: Casitas-B-lineage lymphoma protein – b (cbl-b), an E3 ubiquitin ligase is an important intracellular checkpoint limiting activation of lymphocytes and NK cells. Silencing of cbl-b enhances T cell and NK cell antitumor activity in mouse tumor models and in-vitro in human immune cells. APN401, an autologous cellular therapy consisting of ex-vivo cbl-b-silenced PBMCs, was evaluated in patients with solid tumors. **Methods:** Patients with metastatic solid tumors not eligible for standard therapies were included. Patients with autoimmune disease or requirement for immunosuppressive drugs were excluded. PBMCs were obtained by leukapheresis and were transfected with cbl-b- siRNA ex vivo by electroporation, and 5, 10 or 50 x 10^5 /PBMCs/kg were infused once shortly thereafter over 30 min. **Results:** 16 patients were treated with APN401. As a consequence of cbl-b silencing, all patient PBMC preparations produced enhanced amounts of cytokines IL-2 and IFN-g upon TCR stimulation in vitro. Moreover, evaluation of patient PBMCs responses to common tumor antigens were stronger over the course of the follow-up period. Four patients (2 pancreas 1colon cancer, 1 renal cancer) had stable disease as best tumor response during the study. The strongest response to tumor antigens was observed in the patient with the best objective clinical response (metastatic colon cancer; disease stabilization > 1 year). Infusions were well tolerated. Dose-limiting toxicities were not observed. Mild chills were the most commonly observed related adverse event, followed by mild anemia and fatigue. There was no immediate hypersensitivity or evidence for autoimmune adverse effects. **Conclusions:** Cbl-b-silenced PBMCs (APN401) from cancer patients respond to TCR stimulation and activation with tumor antigens. Strongest cell activation was seen in the patient with the best objective clinical response. 50 x 10^5 / kg APN401 was safe and well tolerated. Multiple infusions of APN401 are currently clinically tested. Clinical trial information: NCT03087591.

3056 Poster Session (Board #270), Mon, 8:00 AM-11:30 AM

Initial safety assessment of MAGE-A10^{c796}TCR T-cells in two clinical trials. *First Author: Vincent K. Lam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MAGE-A10 is expressed in 10-50% of urothelial, melanoma, head and neck (HNC), and non-small cell lung cancers (NSCLC). Affinity-enhanced autologous MAGE-A10^{c796}T cells directed towards MAGE-A10 tumor antigen in the context of HLA*02 (SPEAR T-cells) are being tested in 2 ongoing clinical trials (NCT02592577: NSCLC/NCT02989064: urothelial, melanoma, HNC). **Methods:** These first-in-human T-cell dose escalation studies utilize a modified 3+3 design to evaluate safety. Patients are enrolled after progression on at least one line of therapy. In the first treatment groups, lymphodepletion with Flu 30 mg/m^2/day and Cy 600 mg/m^2/day (NCT02989064) or Cy 600 mg/m^2/day (NCT02592577) is administered on days -7 to -5. The initial dose is 0.1×10^9 transduced cells; additional dose levels are 1×10^9 and 5×10^9. Dose-limiting toxicities (DLT) are determined regardless of attribution to cell infusion and adjudicated by a Safety Review Committee. Cohort expansion will occur at the maximum tolerated dose. **Results:** 8 patients were treated with 0.1×10^9 MAGE-A10^{c796}TCR T-cells (29Dec17). Adverse events (AEs) in ≥3 patients included anemia, thrombocytopenia, lymphopenia, leukopenia, neutropenia, vomiting, constipation, dyspnea and tachycardia. Grade (G) 3 AEs in ≥2 patients included thrombocytopenia, lymphopenia, leukopenia, neutropenia, anemia, pancytopenia, and hyponatremia; these were not reported as related to T-cell infusion. 1 event of cytokine release syndrome (CRS) and 1 increase in serum amylase were reported as related to T-cell infusion. SAEs included G5 disease progression, G4 CRS, G4 neutropenia, G4 thrombocytopenia, G4 sepsis, G4 abdominal pain, G4 supraglottic airway obstruction, G3 shortness of breath and G2 respiratory failure. There was 1 DLT of G4 CRS in a patient with NSCLC that resolved with tocilizumab and steroids. While no anti-tumor effects were observed at this dose, transduced cells were detectable in peripheral blood. **Conclusions:** MAGE-A10^{c796}TCR T-cells at the 0.1×10^9 transduced cell dose show no evidence of on target or off target toxicity. 1 DLT of CRS was observed. The available data support continued investigation of MAGE-A10^{c796}TCR T-cells at higher doses. Clinical trial information: NCT02592577; NCT02989064.

3057 Poster Session (Board #271), Mon, 8:00 AM-11:30 AM

Association of efficacy and adverse events of special interest of avelumab in the JAVELIN solid tumor and JAVELIN Merkel 200 trials. *First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Immune checkpoint inhibitors (ICIs) are associated with unique adverse events of special interest (AESI), including infusion-related reactions (IRRs) and immune-related AEs (irAEs). It has been observed that patients (pts) responding to treatment might have a higher likelihood of AEs, potentially due to longer treatment duration. Understanding the association between AESIs and efficacy outcomes may improve the assessment of benefit/risk and thus aid in informed treatment decisions. **Methods:** We pooled and analyzed efficacy/safety data from NCT01772004 and NCT02155647. We performed an association analysis between response and IRRs. The association of efficacy and irAEs was analyzed using approaches that accounted for time dependency: Cox models analyzed overall survival under consideration of time-varying indicators for irAEs; multistate models were used to gain insight into underlying mechanisms. **Results:** 1783 pts were included in this analysis. 25.5% of pts had ≥ 1 IRR; 0.7% of pts had a grade 3-4 IRR. 97.3% of pts with IRRs had first onset during the first 3 infusions. No association between response and IRRs was observed. irAEs were observed in 16.8% of pts, most commonly hypothyroidism (6.7%) and rash (6.6%); grade 3-4 irAEs occurred in 2.7% of pts. 2.2% of pts discontinued avelumab treatment due to an irAE. An improved probability of survival was observed for pts who experienced irAEs (HR, 0.74 [95% CI, 0.61-0.88]). The multistate model did not suggest that occurrence of irAEs predicted response; however, responders were more likely to develop irAEs than others who remained on treatment. The discontinuation rate did not increase upon occurrence of irAEs. **Conclusions:** The overall incidence of AESI was low, and most were grade ≤ 2. The occurrence of IRRs did not impair the rate of response. The data suggest a survival benefit for pts who experienced an irAE; however, not having an AE did not preclude a response to avelumab. Continued awareness of irAEs may improve clinical outcomes in all pts, with particular vigilance needed if a pt is responding and remains on treatment. Clinical trial information: NCT01772004, NCT02155647.

3058 Poster Session (Board #272), Mon, 8:00 AM-11:30 AM

Circulating miRNA and extracellular vesicle containing miRNA as response biomarkers of anti PD-1/PD-L1 therapy in non-small-cell lung cancer. *First Author: Takehito Shukuya, The Ohio State University, Division of Medical Oncology, Columbus, OH*

Background: Anti PD-1/PD-L1 antibody is a standard first or second-line treatment for advanced non-small cell lung cancer (NSCLC), and PD-L1 immunohistochemisty is used as a predictive biomarker for therapeutic response. However, because patients with lower PD-L1 expression also show durable response in NSCLC, and the usefulness of PD-L1 immunohistochemisty results has not been shown in the other malignancies, more accurate and non-invasive predictive biomarkers are needed. Circulating miRNA and that packaged in extracellular vesicles (EVs) are considered to play a role in intercellular communication among immune cells and between immune cells and tumor cells. **Methods:** Pretreatment plasma of advanced NSCLC patients treated with single agent anti PD-1 or PD-L1 antibody was used in this study. Circulating miRNA was extracted from plasma by miRNAeasy kit (QIAGEN). EVs were isolated using size-exclusion chromatography column (Izon), and miRNA was extracted by miRNAeasy kit. Modified small-RNA library construction was used to make small RNA sequencing libraries, and sequenced on a NextSeq 500 sequencer (Illumina). The sequencing results were analyzed with sRNAnalyzer (http://srnanalyzer.systemsbiology.net/). **Results:** Samples from 14 responders (patients who showed PR or SD $\geq$ 6 months) and 15 non-responders (patients who showed PD in RECIST) were analyzed. Extraction of EVs was confirmed by electron microscopy. Quality and quantity of circulating miRNA and EV encapsulated miRNA were assessed by Bioanalyzer. In total, 26 circulating miRNAs ($p = 0.0030 – 0.049$) and 4 EV associated miRNAs ($p = 0.019 – 0.043$) showed significant concentration differences between responders and non-responders. Of these, 2 miRNAs were in common. **Conclusions:** Circulating miRNA and EV containing miRNA have potential as predictive biomarkers for anti PD-1/PD-L1 treatment response. We are in the process of identifying and validating circulating miRNA and EV miRNA signatures associated with response to anti PD-1/PD-L1 therapy.

3059 Poster Session (Board #273), Mon, 8:00 AM-11:30 AM

Activity of ramucirumab (R) with pembrolizumab (P) by PD-L1 expression in advanced solid tumors: Phase 1a/b study in later lines of therapy. *First Author: Roy S. Herbst, Yale University School of Medicine, New Haven, CT*

Background: R (anti-VEGFR2) and P (anti-PD-1) are active in patients (pts) with previously-treated non-small cell lung carcinoma (NSCLC), gastric or gastroesophageal adenocarcinoma (G/GEJ) and urothelial carcinoma (UC). Because PD-L1 expression may be a predictive biomarker, we examined the effect of R + P in relation to PD-L1. **Methods:** Eligible pts had progressive advanced or metastatic G/GEJ, NSCLC and UC, ECOG PS 0-1, and baseline tumor tissue. PD-L1 was assessed using the PD-L1 IHC 22C3 pharmDx assay, where the number of stained tumor cells (tumor proportion score; TPS) or tumor and immune cells (combined positive score; CPS) is relative to total tumor cells. PD-L1 positivity was defined by CPS $\geq$1% in G/GEJ and UC, and defined by TPS $\geq$1% in NSCLC. Primary objective was safety and tolerability of R + P. **Results:** As of 31-July-2017, 92 pts received P 200 mg on Day 1 q3W with R at 10 mg/kg on Day 1 (G/GEJ, n = 17; NSCLC, n = 27; and UC, n = 24) or R at 8 mg/kg, Day 1 and 8 q3W (G/GEJ, n = 24). Baseline demographics and characteristics were as expected for an advanced, previously treated population. Median follow-up duration for G/GEJ, NSCLC, and UC, was 17.9 months (mo), 20.1 mo, and 17.5 mo, respectively. The safety profile was consistent with that of each individual drug, with no additive toxicities. 84 (91%) of 92 pts were evaluable for PD-L1. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) by PD-L1 are shown in the table. 13 pts remained on study treatment (G/GEJ, n = 4; NSCLC, n = 8; and UC, n = 1). Clinical trial information: NCT02443324. NR = not reached **Conclusions:** In previously treated G/GEJ, NSCLC, and UC, R + P appears to provide more benefit in PD-L1 positive compared to PD-L1 negative pts. Randomized trials are warranted. Updated safety and efficacy results will be presented at the meeting.

	G/GEJ (2^{nd}-3^{rd} line)		NSCLC (2^{nd}-4^{th} line)		UC (2^{nd}-4^{th} line)	
PD-L1 status	**< 1% n = 17**	**≥1% n = 22**	**< 1% n = 11**	**≥1% n = 11**	**< 1% n = 11**	**≥1% n = 12**
ORR, n (%)	1 (6)	2 (9)	2 (18)	5 (45)	0	3 (25)
PFS, mo (95% CI)	1.9 (1.3-4.0)	4.6 (2.3-8.5)	9.7 (2.1-13.9)	6.9 (2.8-NR)	1.3 (0.4-1.9)	2.5 (1.2-7.4)
OS, mo (95% CI)	5.2 (1.7-9.7)	14.9 (4.6-NR)	17.0 (10.5-NR)	NR (4.0-NR)	4.8 (0.6-13.9)	6.4 (2.5-NR)

3060 Poster Session (Board #274), Mon, 8:00 AM-11:30 AM

Cost of inpatient admissions for immune-related adverse effects from immune checkpoint inhibitor therapy: A single center experience. *First Author: Jacqueline N. Chu, Massachusetts General Hospital, Boston, MA*

Background: Immune checkpoint inhibitors such as anti-CTLA4 and anti-PD1 antibodies represent a paradigm shift in the treatment of many advanced malignancies. However, immune related adverse effects (irAEs) result in increasing inpatient admissions and the cost burden related to irAEs is unknown. We describe the cost of admissions for irAEs to a tertiary academic center. **Methods:** Data were collected on patients treated with checkpoint inhibitors who were admitted to Massachusetts General Hospital (Feb 2011 to June 2017). Admissions were classified as irAE-related or non irAE-related after review by two independent physicians, including one subspecialist. Admission costs were obtained using our institution's platform, a transition cost accounting system (TSI), to estimate total, variable, and direct costs, which were converted to 2017 USD. **Results:** The annual cumulative cost of all admissions for irAEs rose from $218,700 in 2011 to $1.3 million in 2016. However, the average cost of irAE admissions was significantly lower than that of non-irAE admissions ($3,142/day vs. $8,257/day, $p = 10^{-10}$). irAE cost by therapy was not significantly different. irAE costs by organ varied from $1,990 to $6,674/day. **Conclusions:** Although total costs for irAE admissions have risen almost six-fold from 2011 to 2016, these admissions are less costly compared to other oncologic admissions, possibly because irAEs are more readily intervenable. The added cost burden to usual oncologic care from irAEs may be less than anticipated.

Year	N	Annual cumulative cost of irAE admissions (US$)				
2011	15	218,739				
2012	14	247,592				
2013	21	302,538				
2014	44	774,399				
2015	37	715,601				
2016	59	1,271,187				
Type of admission	**N**	**Cost (US$)**	**95% CI**	**Cost/day (US$)**	**95% CI**	**LOS**
irAE	214	18,819	(16,983-20,654)	3,142	(2,744-3,541)	6.4
non-irAE	658	24,918	(22,612-27,223)	8,257	(6,770-9,745)	6.2
non-irAE (outliers removed)	601	18,092	(17,100-19,083)	4,807	(4,455-5,158)	6.3
Drug	**N**	**Cost (US$)**	**95% CI**	**Cost/day (US$)**	**95% CI**	**LOS**
Ipilimumab + nivolumab	37	16,273	(8,032-24,515)	2,774	(2,443-3,104)	5.4
Nivolumab or pembrolizumab	67	22,374	(17,647-27,100)	3,088	(2,723-3,453)	7.6
Ipilimumab	59	19,433	(13,174-25,692)	3,519	(2,428-4,610)	5.9

3061 Poster Session (Board #275), Mon, 8:00 AM-11:30 AM

Veliparib in combination with nivolumab and platinum doublet chemotherapy (CT) in metastatic/advanced NSCLC. *First Author: Jeffrey Melson Clarke, Duke University Medical Center, Durham, NC*

Background: Veliparib (V), a PARP inhibitor, combined with platinum (Pt) doublet CT has shown promise in a Phase 2 study of NSCLC. Nivolumab (N), a PD-1 inhibitor, has demonstrated single-agent activity in relapsed NSCLC. This is the first study evaluating dose and safety of V combined with N + Pt-doublet CT. **Methods:** This Phase 1, dose-escalation study (NCT 02944396) enrolled adult patients (pts) with metastatic or advanced NSCLC, ECOG 0-1, and no prior cytotoxic CT, anti-PD-1 or PARPi. Primary objective was to establish the recommended Phase 2 dose (RP2D) of oral V BID combined with N (360 mg) and carboplatin (C, AUC 6)/paclitaxel (Pac, 200 mg/m^2) or C (AUC 6)/pemetrexed (Pem, 500 mg/m^2). Combined with N, dose cohorts were 120 mg V + C/Pac or 80-200 mg V + C/Pem for 6 cycles (cycle = 21 d), or until unacceptable toxicity or disease progression, followed by N + Pem maintenance as indicated. DLTs incl. hematologic and non-hematologic AEs delaying treatment (tx), requiring dose modifications, and attributed to V. Safety, PK, and anti-tumor activity by RECIST 1.1 were assessed. **Results:** As of December 15, 2017, 17 pts (median age 61) with Stage IV NSCLC were enrolled (11 non-squamous for V + N + C/Pem; 1 non-squamous and 5 squamous for V + N + C/Pac). Median drug exposure was 105 d (range 3-284). Primary discontinuation of V occurred in 41% due to AE (2), PD (1), physician decision (1), pt withdrawal (1), death (1), or other (1). No DLTs were reported. Tx-emergent AEs incl. fatigue (47%), nausea (35%), anemia (35%), neutropenia (29%) and thrombocytopenia (29%). Grade 3/4 AEs additionally incl. febrile neutropenia, increased lipase, pneumonitis, and rash (6% each). SAEs additionally incl. sinus arrhythmia, acute kidney injury, pleural effusion, pulmonary embolism, and sudden death (6% each). ORR was 27% [95% CI 6, 61] for V + N + C/Pem and 17% [0, 64] for V + N + C/Pac. For V + N + C/Pem, best response was PR (50%) or SD (50%). For V + N + C/Pac, best response was PR (50%). PK data will be presented. **Conclusions:** RP2D is 120 mg for V + N + C/Pac, and has not been determined for V + N + C/Pem (to date, highest tolerated dose is 200 mg). V combined with N + Pt-doublet CT showed anticipated safety signals, with no additional toxicity of V when added to these regimens. Clinical trial information: NCT 02944396.

3062 Poster Session (Board #276), Mon, 8:00 AM-11:30 AM

A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. *First Author: Mallika Lala, Merck & Co, Inc., Rahway, NJ, US*

Background: Pembrolizumab is currently approved for use in multiple cancer indications at a dose of either 200 mg or 2 mg/kg Q3W. An alternative extended dosing regimen would provide convenience and flexibility to patients and prescribers. Robust characterization of pembrolizumab pharmacokinetics (PK) and E-R relationships for efficacy and safety allow the use of model-based approaches to support alternative dosing regimens. **Methods:** The dose for a Q6W schedule was selected by matching exposures with the approved Q3W (200 mg and 2 mg/kg) regimens; efficacy and safety are bridged based on E-R assessments. Exposures were simulated using the established population PK model of pembrolizumab that adequately described PK across multiple tumor types. Regimens are compared on - A) Exposure metrics at steady state: AUCss or time-averaged concentration (Cavg,ss) and trough concentrations (Cmin,ss); B) Predicted clinical endpoints (e.g., objective response rate) in patients with multiple approved tumor types. Safety at the Q6W schedule is bridged by ensuring predicted peak concentrations at steady state (Cmax,ss) are below those at the maximum clinically administered and well-tolerated dose of 10 mg/kg Q2W. **Results:** The 400 mg Q6W dosing regimen had similar predicted exposures (Cavg,ss or AUCss, geometric mean (GM) ~1% higher) compared to those achieved at 200 mg Q3W. Less than 1% subjects had Cmin,ss lower than that for 200 mg Q3W. The GM of predicted Cmax,ss for 400 mg Q6W was ~65% lower than for 10 mg/kg Q2W. Given the similar exposures and established E-R relationships for pembrolizumab over a 5-fold range of clinically tested doses, the clinical outcomes achieved with 400 mg Q6W are predicted to be similar as with 200 mg Q3W across tumor types. **Conclusions:** A 400 mg Q6W dosing regimen of pembrolizumab leads to exposures that are similar to the approved 200 mg Q3W dosing regimen. Based on the robust understanding of pembrolizumab clinical pharmacology, including well-established E-R profiles, such a less frequent dosing regimen is expected to produce similar efficacy, safety, and benefit-risk profile in all clinical treatment settings where 200 mg Q3W pembrolizumab is currently approved.

3063 Poster Session (Board #277), Mon, 8:00 AM-11:30 AM

Hyperprogressive disease (HPD) in early-phase immunotherapy (IO) trials. *First Author: Yada Kanjanapan, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: A subset of patients (pts) treated with immune checkpoint inhibitors experience an accelerated tumor growth rate (TGR) compared with pre-treatment kinetics, known as hyperprogression. The aim of this study was to explore the relationship between HPD, treatment-related toxicity and clinical factors. **Methods:** Consecutive pts enrolled in early-phase trials involving checkpoint inhibitors and/or costimulatory molecules at Princess Margaret Cancer Centre between 8/2012 – 9/2016 with CT scans available for RECIST 1.1 assessment in the pre-IO treatment (reference, REF) and post-IO treatment (experimental, EXP) periods were reviewed. HPD was defined as RECIST progression at the first on-treatment scan and ≥2-fold increase in TGR between EXP and REF periods. Pts who had prior IO were excluded. Treatment-related toxicities requiring systemic corticosteroids, hormone replacement, IO delay or cessation were considered clinically significant adverse events (CSAEs). **Results:** 182/352 pts were eligible for analysis. Median age was 61, 54% were male and ECOG performance status (PS) 0 (32%)/1 (68%). Tumor types were head and neck (18%), gynecological (16%), lung (15%), gastrointestinal (15%), genitourinary (12%), melanoma (8%), sarcoma (7%), endocrine (5%) and breast (4%) cancers. Median prior lines of therapy was 1 (range 0 – 7). Royal Marsden Hospital (RMH) prognostic score was 2 or 3 in 59% of pts. 146 pts (80%) received IO monotherapy. IO agents included checkpoint inhibitors in 97% and/or costimulatory molecules in 10% of pts. 13/182 (7%) had HPD, with TGR EXP 2-14 folds greater than TGR REF. CSAEs occurred in 20% of pts and was not associated with HPD. There was also no association between HPD and age, PS, tumor type, RMH prognostic score or use of single agent vs combination IO. Median follow-up was 8.4 months. One-year survival was 57% in HPD and 53% in non-HPD pts; with no significant differences in survival adjusted for RMH score between the 2 groups (HR 0.75, 95% CI 0.32 – 1.76, p = 0.5). **Conclusions:** We observed a 7% rate of HPD within a range of solid tumors treated IO, comparable to other reports. There was no association between HPD and CSAEs, age, tumour type or type of IO therapy. Further studies are needed to identify predictors of HPD.

3064 Poster Session (Board #278), Mon, 8:00 AM-11:30 AM

Correlation between immune-related adverse events (irAEs) and efficacy in patients with solid tumors treated with immune-checkpoints inhibitors (ICIs). *First Author: Mariona Riudavets, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Background: ICIs are associated with irAEs. We describe the incidence of irAEs in patients with solid tumors receiving ICIs and its correlation with efficacy. **Methods:** We retrospectively analyzed all patients with solid tumors receiving ICIs in our center. IrAEs were graded according CTCAE v4.0. Kaplan Meier and log-rank tests were used to evaluate progression-free (PFS) and overall survivals (OS). Analyses were performed using SPSS v24 package. **Results:** From March 2014 to January 2018, 178 patients received ICIs. Median age was 64.1 [33-88] years, 72% were male. Most frequent tumors were lung (63.5%), bladder (14.6%) and melanoma (11.8%). 96% presented advanced disease. Most common used ICIs were nivolumab (38.2%), pembrolizumab (28.7%) and atezolizumab (17.4%). ICIs were used as monotherapy (74.7%) or in combination with ICI (3.4%), chemotherapy (17.4%) or targeted therapies (4.5%). Median duration of immunotherapy was 6.9 [0.7-46.3] months. 95 (53.4%) patients developed 158 irAEs with a median number per patient of 1.2 [0-4]. Most frequent irAE was rash (24.7%) followed by diarrhea (17.7%), hypothyroidism (9.5%), arthritis (6.9%), hyperthyroidism (3.8%), pneumonitis (3.2%) and mucositis (3.2%). Median time to the onset irAEs was 53.2 [11-490] days. 12 (6.7%) patients presented grade (G) 3-4 irAEs: 5 G-3 diarrhea, 2 G-3-4 liver dysfunction, 1 G-3 pneumonitis, 1 G-3 hypopituitarism, 1 G-3 mucositis, 1 G-3 arthritis and 1 G-3 nephritis. There were 2 (1.1%) treatment-related deaths due to pneumonitis. 21.3% patients required steroids for irAEs management. 8.4% patients discontinued treatment due to irAEs. 73.9% irAEs had improved at the time of analysis. OS was superior in patients with advanced disease experiencing irAEs: 37.3 [95%CI, 19.2-51.4] *vs* 7.8 [95%CI, 4.9-10.8] months ($p < 0.0001$). Similarly, PFS was longer: 7.9 [95%CI, 4.4-11.4] *vs* 2.6 [95%CI, 2.0-3.2] months ($p < 0.0001$). **Conclusions:** There was a significant correlation between presence of irAEs and outcomes in patients with advanced solid tumors treated with ICIs.

3065 Poster Session (Board #279), Mon, 8:00 AM-11:30 AM

A meta-analysis to indirectly compare the safety and efficacy of PD-1 and PD-L1 antibodies across solid tumors using a Bayesian hierarchical model. *First Author: Mythili Koneru, Eli Lilly and Company, New York, NY*

Background: Many PD-1/PD-L1 mAb are in development across a broad range of tumors. The expanded literature provided an opportunity to address a critical question: if PD-1 mAbs targeting the receptor have a different safety/efficacy profile than the PD-L1 mAbs targeting the ligand. Direct comparison of these mAb would be ideal but highly unlikely. **Methods:** We performed a meta-analysis using a Bayesian model to provide indirect comparison based on data in the public domain including PubMed and key medical conference abstracts (eg ASCO, ESMO etc.). Key inclusion/exclusion criteria include patients 1) with any specific solid tumor, 2) PD-L1 status if tested using one of the approved assays, 3) received one of the five approved mAbs as a monotherapy, and 4) with disclosure date between June 4th, 2013 and June 6th, 2017. The search resulted in about 70 clinical trials in 31 tumors and 12,025 patients. The endpoints include ORR, PFS for efficacy and the overall G3/4 AE rate for safety. **Results:** For efficacy, in all solid tumors except for HNSCC, ORR is slightly greater for PD-1 than PD-L1 mAb, with the largest odds ratio (OR) in 2L+ NSCLC favoring the PD-1 mAb [$ORR_{PD\text{-}1}$= 19.8% vs $ORR_{PD\text{-}L1}$= 16.5%, OR = 1.27, 95% CI = (0.96, 1.70)] and the smallest OR in 1L HNSCC favoring the PD-L1 mAb [$ORR_{PD\text{-}1}$= 27.4% vs. $ORR_{PD\text{-}L1}$= 28.7%, OR = 0.975, 95% CI = (0.38, 1.50)]. Overall, there is 81% posterior probability that ORRs are equivalent for PD-1 and PD-L1 mAb. For safety, the Gr 3/4 AE rate (e.g. pneumonitis) is numerically higher for PD-1 than PD-L1 mAb [OR = 1.48, 95% CI = (0.19, 12.39)] across tumors. Overall, there is 79% posterior probability that the safety profile in terms of G3/4 AE rate is equivalent for PD-1 and PD-L1 mAb. **Conclusions:** There was no significant difference between PD-1 and PD-L1 mAb across tumor types for ORR, PFS and Gr 3/4 AE rate. Moreover, when the information was analyzed across tumor types, the small magnitude of the difference relative to the variability across tumor types suggests strong interchangeability of efficacy and safety profile of the antibodies targeting either PD-1 or PD-L1. Ultimately, the variability within this class of antibodies is not likely to be clinically meaningful.

3066 Poster Session (Board #280), Mon, 8:00 AM-11:30 AM

Clinical and pharmacological parameters associated with nivolumab toxicity. *First Author: Laure Hirsch, Department of Medical Oncology, Cochin Hospital, Paris Descartes University, AP-HP, CARPEM, Immunomodulatory Therapies Multidisciplinary Study group (CERTIM), Paris, France*

Background: The occurrence of severe, acute limiting toxicity in patients receiving anti-PD-1 monoclonal antibodies, such as nivolumab, is largely unpredictable. Sarcopenia was found associated with anti-CTLA4 acute toxicity (Daly LE et al, Br J Cancer 2017). We studied the clinical and pharmacological parameters influencing nivolumab toxicity, including body composition. **Methods:** From June 2015 to December 2016, all consecutive patients treated with nivolumab in our institution were prospectively included. We studied the relationship, using logistic regression, between muscle mass, assessed by computed tomography and by Janmahasatian formula, nivolumab trough levels (C_{min}) assayed using ELISA method, and the occurrence of grade 3 or 4 toxicity or any toxicity leading to treatment discontinuation (ALT). Univariate and multivariate analysis were made for parameters associated with nivolumab concentration. **Results:** Out of 92 patients, 81 were analyzable for body composition and 84 for nivolumab pharmacokinetics. The population included 63% males, median age 65 years, a majority had lung cancer (72%). We observed 20 ALT including 4 pneumonitis and 4 colitis in 20 (21.7%) patients and 825 (2.4%) nivolumab infusions. The ALT events were more frequent in sarcopenic patients (OR = 3.29, 95% CI: 0.96-11.28, p = 0.06). Sarcopenic overweight patients were the most susceptible to experience ALT (OR = 5.08, CI: 0.53-48.9; p = 0,16), as already reported by our group in melanoma patients (Heidelberger V et al, Invest N Drugs, 2017). The nivolumab C_{min} was 17.0 $\pm$ 5.9 μg/mL on day 14. In multivariate analysis, low nivolumab C_{min} was independently associated with hypoalbuminemia ($<$ 35g/L) (OR = 0.03, 95% CI: 0.002-0.34, p = 0.005) and sarcopenia (OR = 0.13, 95% CI: 0.03-0.54, p = 0.005). The recycling of albumin and nivolumab is both mediated by the neonatal Fc receptor (FcRn) and therefore albumin levels may reflect the abundance and efficiency of FcRn. **Conclusions:** Body composition influences both nivolumab pharmacokinetics and acute toxicity.

3067 Poster Session (Board #281), Mon, 8:00 AM-11:30 AM

Intestinal microbiota to predict lung cancer patients at risk of immune-related diarrhea. *First Author: Tian Liu, Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China*

Background: Anti-programmed cell death protein-1 (PD-1) antibodies represent an effective treatment for lung cancer. However, previous studies showed that a number of patients treating with anti-PD-1 antibodies experience immune-related diarrhea. Intestinal microbiota plays a vital role in gastrointestinal dysregulation including diarrhea. Nevertheless, The association between intestinal microbiota and immune-related diarrhea is still elusive. Our study aims to identify specific intestinal microbiota as potential biomarkers for immune-related diarrhea in patients treating with anti-PD-1 antibodies. **Methods:** Fecal samples of 26 advanced lung cancer patients were obtained before the first dose of anti-PD-1 antibodies. Based on whether they develop diarrhea or not, the patients were subgroup into progressed to diarrhea(PtD) group and diarrhea-free(D-F) group. Immune-related diarrhea was graded according to CTC version 4.0. And 16S rRNA sequencing was used to profile fecal bacterial composition.The onset of diarrhea and fecal bacterial composition were retrospectively analyzed. **Results:** Of the 26 patients, 8 patients experienced diarrhea after the treatment of anti-PD-1 antibodies. Compared to the diarrhea-free patients, patients with diarrhea had similar microbial richness and diversity based on Alpha diversity analysis. While referring to Beta diversity, weighted-UniFrac PCoA analysis demonstrated significant differences in bacterial composition among the two group. Moreover, At the phylum level, Bacteroidetes were significantly richer in D-F group than that in PtD group, and Firmicutes were poorer. Whereas, Veillonella from Proteobacteria phylum was obviously lower in D-F group than that in PtD group. At the genus level, two families of the Bacteroidetes phylum (Bacteroides and Parabacteroides) and a family of the Firmicutes phylum (Phascolarctobacterium) were more abundant in D-F group. Veillonella from Proteobacteria phylum was lower in D-F group than that in PtD group. **Conclusions:** Intestinal microbiota variation is associated with the onset of immune-related diarrhea. Identifying these biomarkers may help to diagnose and prevent the side effect earlier.

3068 Poster Session (Board #282), Mon, 8:00 AM-11:30 AM

A phase 1 study of ALX148, a CD47 blocker, alone and in combination with established anticancer antibodies in patients with advanced malignancy and non-Hodgkin lymphoma. *First Author: Nehal J. Lakhani, START Midwest, Grand Rapids, MI*

Background: CD47, a marker of self, is a myeloid checkpoint that is upregulated by tumor cells to evade the host's immune response. ALX148 is a fusion protein comprised of an engineered high affinity CD47 binding domain of SIRPα genetically linked to an inactive Fc region of human immunoglobulin. We have previously shown ALX148 blocks CD47 and safely enhances the activity of targeted anticancer antibodies and checkpoint inhibitors through Fc dependent and independent mechanisms in nonclinical models (ASH 2017 #112). **Methods:** As of Feb 07, 2018, 30 patients (pts) were enrolled to escalating dose cohorts of ALX148 (0.3 mg/kg [mpk] IV every week [QW] - 30 mpk every other week [QoW]) as a single agent (Part 1) or in combination with standard regimens of pembrolizumab (P), trastuzumab (T), or rituximab (R) (Part2). The primary endpoint for each Part is first cycle dose limiting toxicity (DLT). Tumor response, pharmacokinetics (PK), and CD47 target occupancy (TO) are also characterized. **Results:** Part 1 results are summarized. 25 pts received single agent ALX148. 22 pts experienced any AE. Maximum CTCAE treatment related AEs that occurred in $>$ 1 pt were Dizziness 2G1; Fatigue 3G1; Headache 4G1; Rash 1G1,1G2; and Thrombocytopenia 2G3. Two pts experienced a DLT (Neutropenia with infection, 3mpk; Thrombocytopenia with significant bleed, 30 mpk). There were 4 pts who reported $\geq$G3 AE (Infection 1G3, 3mpk; Pancreatitis 1G3, 30 mpk; Thrombocytopenia 1G3, 3 mpk and 1G3, 30 mpk; Neutropenia 1G4, 3mpk) and 1G5 Death (30mpk; etiology being investigated). No single agent MTD was identified, and the maximum administered dose (MAD) was 30 mpk QoW. Four pts achieved stable disease including 1 pt with NSCLC who had a 15% tumor reduction. ALX148 demonstrated linear PK at doses $\geq$ 10 mpk QW and full TO at doses $\geq$ 3 mpk QW. To date, 5 Part 2 pts received ALX148 (10 mpk QW) in combination (3 with P; 1 with T; 1 with R). **Conclusions:** ALX148 is generally well tolerated in pts with advanced tumors with favorable PK/TO characteristics at doses evaluated. The MAD of single agent ALX148 is 30 mpk QoW. Accrual to the Part 2 combination cohorts is ongoing. Clinical trial information: NCT03013218.

3069 Poster Session (Board #283), Mon, 8:00 AM-11:30 AM

Can body composition (BC) be predictive for outcomes and severe toxicities (ST) in metastatic solid tumors patients (pts) treated with checkpoint inhibitor (CPI)? An analysis of 145 patients. *First Author: Sophie Cousin, Institut Bergonié, Bordeaux, France*

Background: BC parameters have previously been associated with treatments toxicities, and worst outcomes in metastatic solid tumors pts. We studied association between BC parameters and their changes, with ST and outcomes in pts receiving CPI. **Methods:** Pts consecutively treated with CPI between December 2013 and December 2016 in our institute (Institut Bergonié, Bordeaux, France) for metastatic solid tumor and with a baseline computed tomography (CT0) scan $<$28 days before CPI beginning were included. BC parameters were assessed with Slice-O-Matic software V4.3 (Tomovision, Montreal, Canada), using third lumbar vertebra as standard landmark, normalized for height (cm2/m2). **Results:** 145 pts were included (73 female, median age: 62). 124 had a CT scan after 2 months of CPI (CT2). Tumor type was non small cell lung cancer in 80 (55%) pts. 68 pts had received $>$1 line of chemotherapy before. CPI treatment was: anti PD-1, anti PD-L1, anti PD-L1/CTLA-4 combination in 113, 13, and 19 pts, respectively. ST included: Grade III-V toxicity according to NCI-CTC v4.0, unscheduled hospitalization, definitive CPI treatment discontinuation. 15 pts (10.3%) had ST. None of the baseline clinical, nutritional, and BC parameters was associated with ST. In multivariate analysis, subcutaneous adipose tissue index (SATI) decrease $>$-10% between CT0 and CT2 was significantly associated with occurrence of ST (OR=5.3, p=0.027). Median Overall survival (OS) was 402 days. Median progression free survival (PFS) was 86 days. In multivariate analysis, 3 BC-related parameters were significantly associated with worse OS: body mass index $<$ 25 (HR=2.375, p=0.030), Skeletal muscle index (SMI) decrease $>$-10% (HR=4.603, p=0.007), and visceral adipose tissue index (VATI) decrease $>$-10% (HR=8.470, p=0.030). Only SMI decrease $>$-10% was predictive of PFS (HR=3.643, p=0.001). **Conclusions:** Our results demonstrates that body composition is associated with clinical outcomes of cancer patients treated with CPI. Early decrease of SATI is predictive of ST whereas early decrease of skeletal muscle index and of VATI are associated with worse OS.

3070 Poster Session (Board #284), Mon, 8:00 AM-11:30 AM

Comparative analysis of durable responders on immune checkpoint inhibitors (ICI) versus other systemic therapies: A meta-analysis of phase III trials. *First Author: Elvire Pons-Tostivint, Department of Medical Oncology, Institut Curie, Paris, France*

Background: Durable responses have been reported with ICI. We aimed at quantifying the proportion of patients experiencing a durable response on ICI, and comparing it to the proportion observed with other systemic therapies including targeted therapy and chemotherapy. **Methods:** We retrieved all phase III trials that included at least one ICI arm. The proportion of durable responders was evaluated for each treatment arm by estimating the proportion of patients who had a progression-free survival (PFS) exceeding 3 times the median PFS. The proportion of patients who experienced an overall survival (OS) that exceeded 2 times the median OS was also estimated in each arm, from the published survival curves. The impact of the tumor type and the line of treatment were evaluated. Groups were compared using the Mann-Whitney test. **Results:** 20 phase III trials involving 12,834 pts (8275 in ICI arms) treated for 8 different types of cancer in 44 treatment arms were retrieved. Median follow up was 15 months [range: 5.6-36.6]. Treatment was ICI alone, chemotherapy, a tyrosine kinase inhibitor, a vaccine, a placebo and ICI + chemotherapy in 24 (54.5%), 13 (29.5%), 1 (2.3%), 1 (2.3%), 2 (4.5%), and 3 (7%) arms. The mean median PFS was 3.8 [95%CI: 3-4.7] *vs* 3.5 months [95%CI: 2.9-4.1] in the ICI alone arm and in the control arms. Mean median OS was 13.9 [95%CI: 10.6-17.2] *vs* 9.7 months [95%CI: 7.8-11.6] in the ICI alone arm and in the control arms ($p = 0.01$). The proportion of patients who experienced a durable response defined as a PFS exceeding 3 times the median PFS was 24.6% [95%CI:20.9-28.3] *vs* 11% [95%CI:8.5-13.5] in the ICI alone and control arms, respectively ($p < 0.0001$). The proportion of patients who survived longer than 2 times the median OS was 29.7% [95%CI: 28-31.3] in the ICI alone group *vs* 21.8% [95%CI: 19.4-24.2] in the control group ($p < 0.0001$). The effect was similar even in patients treated beyond the first-line metastatic setting and in non-melanoma tumor types. **Conclusions:** The proportion of patients experiencing a durable response was more than twice higher on ICI than on other treatments, even in patients treated beyond the first-line metastatic setting and in non-melanoma tumor types.

3071 Poster Session (Board #285), Mon, 8:00 AM-11:30 AM

Preliminary results of the first-in-human, dose-finding PROCLAIM-CX-072 trial of the PD-L1 Probody therapeutic CX-072 as monotherapy in patients (pts) with advanced solid tumors. *First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In single-agent trials, antibodies (Abs) targeting programmed cell death ligand 1 (PD-L1) improve survival in many cancers but are associated with immune-related toxicities (most commonly in skin, thyroid, liver, and lung), particularly when administered with other anticancer agents in combination. CX-072 is an anti–PD-L1 Probody therapeutic designed to be preferentially activated by proteases in the tumor microenvironment and not in healthy tissue. Preclinically, Probody therapeutics exhibited anticancer activity of the parent Ab but reduced toxicities in models of autoimmunity. **Methods:** This part (A) of the ongoing phase 1-2 PROCLAIM-CX-072 study (Probody Clinical Assessment In Man; NCT03013491) is evaluating CX-072 as monotherapy in a dose escalation cohort in pts with advanced, heavily pretreated solid tumors. Eligible pts include those who are PD-1, PD-L1, and CTLA-4 inhibitor naive, with immunotherapy (IMT) unavailable as a standard of care (SOC) for their disease. CX-072 is given every 14 days in cohorts of doses ranging from 0.03-30 mg/kg IV. **Results:** Escalation is complete (n=22). Median age is 65 years (range, 32-81); pts had 6 (range, 1-13) prior anticancer treatments. One DLT was observed (grade 3 febrile neutropenia; 3 mg/kg); MTD was not reached. Grade 3-4 treatment-related events were observed in 2 pts: febrile neutropenia/thrombocytopenia (3 mg/kg) and elevated AST/ALT (30 mg/kg). Across all dose levels, best response based on change in target lesions from baseline in 17 evaluable pts included 2 PR (thymoma and PD-L1-negative TNBC), 11 SD, and 4 PD. Target lesions decreased from baseline in 7/17 pts (41%) evaluable as per RECIST v1.1. Target lesions decreased from baseline at dose levels ≥3 mg/kg in 5/8 pts (63%). **Conclusions:** Preliminary data for CX-072 in heavily pretreated pts with IMT-naive solid tumors where checkpoint blockade is unavailable as SOC for their disease show a manageable safety profile with signals of antitumor activity. These data warrant further exploration of CX-072 as monotherapy and in combination with other checkpoint inhibitors or targeted therapies. Clinical trial information: NCT03013491.

3072 Poster Session (Board #286), Mon, 8:00 AM-11:30 AM

Preliminary interim results of the first-in-human, dose-finding PROCLAIM-CX-072 trial of the PD-L1 Probody therapeutic (Pb-Tx) CX-072 in combination with ipilimumab (ipi) in patients (pts) with advanced solid tumors. *First Author: Rachel E. Sanborn, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR*

Background: CX-072 is a Pb-Tx directed against programmed cell death ligand 1 (PD-L1), designed to be preferentially activated by tumor-associated proteases but not in healthy tissue. Preclinically, the combination of a PD-1 Pb-Tx with an anti–CTLA-4 antibody showed comparable efficacy but improved safety compared to the non–Pb-Tx combination control. This dose-escalation cohort of CX-072 + ipi in pts with advanced solid tumors was designed to examine the safety and tolerability of combination therapy. Preliminary safety and antitumor activity are reported. **Methods:** In this ongoing phase 1-2 study (NCT03013491), pts receive CX-072 + ipi in a concomitant dosing schedule (study Part B1). Eligible pts are PD-1, PD-L1, and CTLA-4 inhibitor naive. Planned doses are CX-072 0.3-30 mg/kg IV every 21 days + ipi 3 mg/kg or 10 mg/kg IV every 21 days for 4 cycles, followed by CX-072 monotherapy every 14 days. **Results:** As of data cut (Nov 30, 2017), part B1 enrolled 9 pts. Median age was 44 years (range, 28-70); 6 pts (67%) were male. Median number of prior anticancer treatments was 4 (range, 2-18). At the time of data cut, 6 pts remained on treatment. Median number of doses of CX-072 (0.3 and 1 mg/ kg) and ipi (3 mg/kg) was 2 (range, 2-10) and 2 (range, 2-4), respectively. 1 DLT (grade 3 dyspnea, 0.3 mg/kg CX-072 + 3 mg/kg ipi) was observed. MTD has not been reached and dose escalation continues. Grade 1-2 treatment-related adverse events (TRAEs) occurred in 6 pts (67%). 4 grade 3 TRAEs were experienced by 2 pts (22%) and included colitis, pneumonitis, and AST and ALT increases (0.3 mg/kg CX-072 + 3 mg/kg ipi). At cutoff, 1 of 4 evaluable pts showed target lesion reduction of 31% from baseline (0.3 mg/kg CX-072, anal SCC, MSI stable, and intermediate tumor mutation burden). As of Dec 4, this patient had a confirmed PR with 56% reduction in target lesion. **Conclusions:** Preliminary data for CX-072 + ipi show a manageable safety profile and signals of antitumor activity. The study is ongoing, and all cohorts through 10 mg/kg CX-072, the dose selected for monotherapy cohort expansion, are now enrolled. Escalation of ipi dose to 10 mg/kg is pending. Clinical trial information: NCT03013491.

3073 Poster Session (Board #287), Mon, 8:00 AM-11:30 AM

Quality of life in patients with advanced renal cell carcinoma in the randomized, open-label CheckMate 214 trial. *First Author: David Cella, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: In CheckMate 214, overall survival (OS) with nivolumab + ipilimumab (N+I) was superior to sunitinib (S; HR, 0.63; $P<0.001$) with a manageable safety profile as first-line treatment for intermediate/poor (I/P)-risk patients (pts) with advanced renal cell carcinoma (aRCC). We report analyses of health-related quality of life (HRQoL). **Methods:** Pts were randomized 1:1 to receive N 3 mg/kg + I 1 mg/kg every 3 wk for 4 doses then N 3 mg/kg every 2 wk, or S 50 mg/d orally for 4 wk (6-wk cycle). Exploratory HRQoL analyses were conducted on RCC-specific symptoms from the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19) and general cancer symptoms were assessed using the Functional Assessment of Cancer Therapy-General (FACT-G) instruments. Analyses used *t* tests (change from baseline [BL] analysis) and mixed-model repeated measures (MMRM; using a predefined 6-m landmark). **Results:** A total of 847 I/P-risk pts were randomized (N+I, 425; S, 422). HRQoL assessment completion rates were >80% in the first 6 m. Statistically significant differences in change from BL on FKSI-19 total scores (mean BL scores: 60.1 [N+I]; 59.1 [S]) favoring N+I were observed at all but 2 post-BL time points through 2 years of follow-up ($P<0.05$). MMRM analysis found a statistically significant difference between arms at 6 m favoring N+I in FKSI-19 total score and most subscores (table). Change from BL results for the FACT-G trended in a similar direction, with N+I scores exceeding those in the S arm throughout 2 years of follow-up. Similarly, MMRM of FACT-G total scores showed significant benefit of N+I at 6 m. **Conclusions:** In addition to the OS benefit and superior safety profile, descriptive data suggest that N+I offers significant and sustained HRQoL improvement vs S in I/P-risk pts with untreated aRCC. Clinical trial information: NCT02231749.

MMRM analysis: FKSI-19.

Domain	Difference N+I vs S (95% CI)
Total	2.63 (1.13–4.13)[a]
DRS	0.75 (0.10–1.40)[a]
DRS-Physical	1.19 (0.28–2.11)[a]
DRS-Emotional	0.10 (−0.06 to 0.27)
Treatment side effects	1.09 (0.79–1.38)[a]
Functional well-being	0.35 (−0.14 to 0.84)

[a] $P<0.05$ CI, confidence interval; DRS, disease-related symptoms

3074 Poster Session (Board #288), Mon, 8:00 AM-11:30 AM

Single-cell RNA-sequencing and -imaging of melanoma ecosystems reveals sources of resistance to immune checkpoint blockade. *First Author: Benjamin Izar, Dana-Farber Cancer Institute, Boston, MA*

Background: While immune checkpoint blockade (ICB) produces durable responses in some patients with melanoma, most patients derive no clinical benefit, and the molecular underpinnings of ICB resistance (ICR) are elusive. **Methods:** We applied single-cell RNA-sequencing (scRNA-Seq) to > 10,000 malignant and non-malignant cells derived from 31 melanoma tumors, including 15 from patients with ICB, 15 treatment-naïve patients, and 1 patient with clinical response. We applied a novel data-driven method to systematically map cancer programs that promote ICR and T cell exclusion. **Results:** We demonstrate that cancer cell-autonomous ICR programs identified by scRNA-Seq predict comprise several putative mechanisms of resistance, including several that have previously not been described. In addition to functional implications, we generated a clinically applicable signature that was predictive of clinical response (per RECIST criteria) and progression-free survival (PFS): one of patients who underwent RNA-seq of matched pre-treatment and progression (ICR) specimens; and another of 112 melanoma patients with pre-treatment RNA-seq who receive anti-PD-1 monotherapy. This scRNA-Seq derived predictive signature was superior to all interrogated previously published signatures. Furthermore, we demonstrated that pharmacological reversal of these oncogenic cell states can be achieved by CDK4/6-inhibition, and explored the impact of this treatment in melanoma at the single cell level. To determine the role of T cell exclusion from the TME as a potential mechanism of ICR, we performed spatially resolved 30-plex single-cell protein analysis of matching FFPE specimens from 16 of patients who also underwent scRNA-seq. While the integration of these data sets is pending, the presented analytical platforms provide a promising approach to understanding drug resistance within preserved tumor ecosystems. **Conclusions:** Our study provides a high-resolution landscape of oncogenic ICR states, identifies clinically predictive signatures, and forms a basis to developing novel therapeutic strategies that could overcome immunotherapy resistance in melanoma.

3075 Poster Session (Board #289), Mon, 8:00 AM-11:30 AM

Phase I open-label, ascending dose trial of AGEN1884, an anti-CTLA-4 monoclonal antibody, in advanced solid malignancies: Dose selection for combination with PD-1 blockade. *First Author: Breelyn A. Wilky, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: AGEN1884 is a novel fully human IgG1 monoclonal antibody targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4). **Objective:** Assess the safety, maximum tolerated dose, and pharmacokinetic (PK) and pharmacodynamic characteristics of AGEN1884 in patients with advanced and refractory malignancies. **Methods:** Patients (≥18 years old) with relapsed/refractory lymphoma or solid cancers without curative treatment options received AGEN1884 at 0.1, 0.3, 1, 3 or 6 mg/kg in a "3+3" trial design. An additional 10 patients were enrolled in both 1 and 3 mg/kg dose expansion cohorts. AGEN1884 was administered intravenously (IV) every 3 weeks for 4 doses and then every 3, 6, or 12 weeks at the Investigator's discretion. **Results:** As of 03Jan2018 data cutoff, 33 patients were enrolled in the following cohorts: 0.1 mg/kg (n = 5, 2 not evaluable [NE] for dose-limiting toxicity [DLT]), 0.3 mg/kg (n = 3), 1 mg/kg (n = 10), 3 mg/kg (n = 12, 2 NE for DLT) and 6 mg/kg (n = 3). Median age was 61 years (range 26–88), baseline ECOG scores were 0 (N = 4), 1 (N = 25), unknown (4), with a median of 10 (range 3–26) prior therapies. As of Jan 31, 2018, no DLT's have been reported. Immune-related adverse events were reported in 10 (30.3%) of patients as follows: 0.1 mg/kg (1 [20.0%]), 0.3 mg/kg (1 [33.3%]), 1 mg/kg (1 [10%]), and 3 mg/kg (6 [50%]) and included hypophysitis, colitis, diarrhea, rash and pruritus. Most were mild-moderate consistent with published reports of other CTLA-4 inhibitors. 6 patients (18.2%) came off study due to disease progression or AE's but none related to treatment. Of 11 subjects evaluable for response, 1 with angiosarcoma treated at 0.1 mg/kg attained a CR at 7 months after achieving a PR. Three subjects with SD: 1 at 0.3 mg/kg with adenoid cystic carcinoma at Week 21 who had SD for 53 weeks; 2 subjects at 3 mg/kg: 1 with breast cancer with SD at Week 6 and 1 with invasive metaplastic breast cancer at Week 12 on study. **Conclusions:** AGEN1884 was well tolerated at 0.1, 0.3, 1 and 3 mg/kg dose levels. Enrollment continues at 6 mg/kg. Updated safety and PK data will be presented. A starting dose level of 1 mg/kg has been selected for combination with PD-1 blockade. Clinical trial information: NCT02694822.

3076 Poster Session (Board #290), Mon, 8:00 AM-11:30 AM

Association between PD1 mRNA and response to anti-PD1 monotherapy across multiple cancers. *First Author: Laia Pare, 1Translational Genomic and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain*

Background: In advanced cancer, the overall response rate (ORR) following anti-PD1 monotherapy is variable (0% to 50%). Here, we hypothesized that this observation is partly explained by different amounts of the drug target (i.e. PD1) in the tumor. **Methods:** RNA-seq data from 10,078 tumors representing 34 cancer-types were obtained from TCGA. The expression of PD1 and 566 immune-related genes/signatures were evaluated. Correlations between each gene/signature and ORRs reported in the literature were calculated. We included only studies of anti-PD1 monotherapy that enrolled at least 20 patients (pts) who were not selected for PDL1 expression. To translate the in-silico findings to the clinical setting, we analyzed the expression of PD1 mRNA using the nCounter platform in 694 formalin-fixed paraffin embedded (FFPE) tumor samples from 16 cancer-types. Finally, we evaluated FFPE-based PD1 mRNA from an independent dataset of 102 pts with advanced solid tumors treated with anti-PD1 monotherapy. **Results:** PD1 expression varied significantly across TCGA ($p < 0.001$) with 0% to 84% of tumors within a cancer-type being PD1-high (H) (defined as %ile 80). Interestingly, % of PD1-H tumors within a cancer-type were found highly correlated with ORRs reported in the literature (correlation coefficient [CC] = 0.91), suggesting that 83% of the differences in the ORR across cancer-types may be explained by the abundance of PD1. Lower CCs were identified with different PD1 cutoffs, other genes/signatures and tumor mutational burden. To translate these findings in clinical samples, the expression of PD1 was evaluated in 773 FFPE tumor samples across 17 cancer-types. Using the optimal cutoff (%ile 80), similar proportions of PD1-H tumors within each cancer-type were identified in our in-house FFPE-based cohort compared to TCGA (CC = 0.92). Finally, the optimal PD1 FFPE-based cutoff was found significantly associated with ORR (PD1-H 42.8% vs. PD1-low 17.6; P = 0.018) in 102 pts with advanced cancer treated with anti-PD1 monotherapy. **Conclusions:** Our findings highlight the strong relationship between PD1 mRNA expression and the activity of anti-PD1 therapies across multiple cancers.

3077 Poster Session (Board #291), Mon, 8:00 AM-11:30 AM

Impact of immune checkpoint inhibitor dose on toxicity, response rate, and survival: A pooled analysis of dose escalation phase 1 trials. *First Author: Shiraj Sen, The University of Texas Southwestern Medical School, Dallas, TX*

Background: PK and PD studies demonstrate drug exposure and target saturation of immune checkpoint inhibitors (ICI) at doses below MTD. MTD remains a primary endpoint in ICI phase 1 trials and the optimal dosing to minimize toxicity and optimize response remains unclear. **Methods:** We analyzed clinical data from pts treated in phase 1 ICI dose escalation trials at MD Anderson Center for Targeted Therapy. Patients were stratified into a low-dose [LDG] (< 33% MTD), medium dose [MDG] (34-66% MTD), high dose [HDG] (67-100% MTD), or very high dose [VHDG] (> 100% MTD) group. Groups were compared for irAE, PFS, OS, ORR (CR + PR), and DCR (CR + PR + SD > 6 months). **Results:** Among 90 pts treated with escalating doses of ICI (57 CTLA4- and 33 PD1-based) between April 2013 and December 2015, median age was 59 years (range: 20-86 years) and 37 (41%) were females. The most common tumor types treated included renal cell carcinoma (n = 23; 25%), melanoma (n = 16; 18%), sarcoma (n = 10; 11%), and GIST (n = 10; 11%). PFS in the LDG (n = 16) was 2.76 months (mo) (95% CI 1.48-NA), MDG (n = 21) was 2.76 mo (95% CI 1.48-NA), HDG (n = 36) was 2.46 mo (95% CI 1.84-3.29), and VHDG (n = 17) was 3.68 mo (95% CI 2.76-NA). Log rank p = 0.22. OS in LDG was 6.18 mo (95% CI 3.45-NA), MDG was 17.05 mo (95% CI 3.94-NA), HDG was 5.16 mo (95% CI 4.24-7.62), and VHDG was 7.49 mo (95% CI 5.59-NA). Log rank p = 0.0070. In all evaluable patients, ORR in LDG, MDG, HDG, and VHDG was 0%, 6%, 6%, and 12% (p = 0.47) and DCR was 62%, 71%, 41%, and 81% (p = .027), respectively. irAE rates in LDG, MDG, HDG, and VHDG were 6%, 10%, 17%, and 29% (p = .045). **Conclusions:** Despite a dose-dependent increase in irAE, we identify no improvement in PFS, OS, or DCR with escalating doses of ICI administered in phase I trials but do detect an improvement in ORR. Prospective dose-/exposure-response relationships and biomarker-driven RP2D are warranted on all ICI dose-escalation phase 1 trials. Lower doses may reduce toxicity and cost without compromising disease control or survival.

Dosing	PFS, months (95% CI)	OS, months (95% CI)	ORR (%)	DCR (%)	irAE (%)
LDG	2.76 (1.48-NA)	6.18 (3.45-NR)	0	62	6
MDG	2.76 (1.84-NA)	17.05 (3.94-NR)	6	71	10
HDG	2.46 (1.84-3.29)	5.16 (4.24-7.62)	6	41	17
VHDG	3.68 (2.76-NA)	7.49 (5.59-NR)	12	81	29

3078 Poster Session (Board #292), Mon, 8:00 AM-11:30 AM

Phase II open-label, multi-centre study of bemcentinib (BGB324), a first-in-class selective AXL inhibitor, in combination with pembrolizumab in patients with advanced NSCLC. *First Author: James Lorens, BerGenBio ASA, Bergen, Norway*

Background: Bemcentinib (BGB324) is a first-in-class, oral, potent and highly selective inhibitor of the AXL tyrosine kinase currently in phase II clinical development across several cancer types. AXL over-expression has been observed in pts failing PD-1 therapy in several cancers whereas AXL inhibition via bemcentinib has shown synergistic effect with checkpoint blockade in pre-clinical models of NSCLC. **Methods:** In this single-arm, two-stage Phase 2 study, pts with documented Stage IV lung adenocarcinoma progressed on a single line of platinum-based chemotherapy chemotherapy and – if applicable – at least one line of licensed therapy for EGFR mutations or ALK re-arrangements received 200 mg/d bemcentinib po and 200 mg/q3wk pembrolizumab iv. Patients were required to consent to a fresh pre-treatment biopsy. Tumour assessments were done 9-weekly. The primary endpoint was objective response. Predefined secondary endpoints included disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. Tumour biopsies were analysed for PD-L1 and AXL, and infiltrating immune cells. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in patients pre-dose and at C2D1. **Results:** As of February 2018, 13 pts (median age 66 years) initiated therapy and 11 pts remain on treatment. Combination therapy was well tolerated with the overall serious adverse event profile being similar to that reported for pembrolizumab monotherapy. 1 of 4 pts (25%) who had reached their first scan showed a PR and another patient (25%) had SD. There were no grade 4 treatment-related events. Dose reduction from 200 to 100 mg/d of bemcentinib as a consequence of adverse events was required in 12% of patients. **Conclusions:** Combination treatment of bemcentinib and pembrolizumab was well tolerated. A preliminary analysis of response to combination treatment during the first stage of this study as well as biomarker correlation will be presented at the meeting. Clinical trial information: NCT03184571.

3079 Poster Session (Board #293), Mon, 8:00 AM-11:30 AM

Autoimmune genetic variants as germline biomarkers of response in melanoma immunotherapy treatment. *First Author: Vylyny Chat, New York University School of Medicine, New York, NY*

Background: Immune checkpoint inhibition (ICI) has improved clinical outcomes for metastatic melanoma patients. However, ~ 60% of patients do not respond to ICI and 65-80% experience immune-related adverse events (irAEs). Currently, the personalized biomarkers predicting ICI efficacy or toxicity are limited. Given the link between immunotherapy, irAEs and autoimmunity, we investigated if the baseline genetic susceptibility to multiple autoimmune diseases can modulate clinical efficacy of ICI. **Methods:** By performing a comprehensive search of autoimmune genome wide association studies, we identified 25 SNPs, each associated with at least 3 autoimmune diseases. Using the Agena MassArray, we genotyped 25 SNPs in 389 Caucasian metastatic melanoma patients receiving ICI treatment (N = 214 anti-CTLA4, N = 175 anti-PD1) at one of our collaborative centers. Multivariate logistic regression adjusting for age at treatment and gender was used to test for association of germline variants with ICI efficacy. **Results:** We identified two variants previously associated with multiple autoimmune diseases that may predict ICI efficacy: rs1893217 in PTPN2 (OR = 0.35; 95%CI = 0.17-0.73; p = 0.005) and rs17388568 in the IL2, IL21 cluster (OR = 3.28; 95%CI = 1.62-6.64; p = 0.0009) were associated with clinical benefits in anti-CTLA4 and anti-PD1 ICI, respectively. These variants predict efficacy in opposite direction - rs1893217 was associated with anti-CTLA4 treatment resistance while rs17388568 was associated with anti-PD1 response sensitivity. **Conclusions:** Our study reports two autoimmune germline variants as potential biomarkers of anti-CTLA4 or anti-PD1 ICI efficacy in melanoma and suggests that underlying genetic susceptibility to autoimmunity may play an important role during ICI treatments. rs1893217 in PTPN2, involved in cytokine signaling, has been associated with colitis, celiac disease, inflammatory bowel, rheumatoid arthritis and type 1 diabetes. Similarly, rs17388568 was mapped to important immune-related genes (IL2, IL21 and ADAD1) and associated with allergy, colitis and type 1 diabetes. Additional genetic and functional validation of these findings is underway in a large collaborative setting.

3080 Poster Session (Board #294), Mon, 8:00 AM-11:30 AM

Safety and efficacy results from a phase I dose-escalation trial of Nintedanib in combination with Pembrolizumab in patients with advanced solid tumors (PEMBIB trial). *First Author: Andreea Varga, Gustave Roussy Cancer Campus, Villejuif, France*

Background: We aimed to determine the safety and activity of the nintedanib +pembrolizumab combination. Nintedanib is an oral angiokinase inhibitor targeting the vascular endothelial, platelet-derived and fibroblast growth factor receptors as well as RET. Pembrolizumab is a highly selective, humanized monoclonal IgG4–kappa isotype antibody against PD-1 designed to block the negative immune regulatory signaling of the PD-1 receptor expressed by T cells. **Methods:** PEMBIB is a monocentric phase Ib trial which evaluated escalating doses of nintedanib (Dose level 1 (DL1) = 150 mg BID; DL2 = 200 mg BID) in combination with intravenous flat dose of pembrolizumab at 200 mg every 21 days in patients with advanced solid tumors using the rolling 6 design. A lead-in monotherapy of nintedanib was performed 7 days prior starting pembrolizumab. The primary objective was to establish MTD of this combination based on DLT occurrence during the first 4 weeks (28 days since C1D1) and to determine the recommended phase 2 dose (RP2D). **Results:** As of November 24, 2016, 13 patients (12 evaluable for DLT) have been enrolled in the escalation part : 2 cervical carcinoma, 1 MSI colorectal cancer, 1 triple negative breast cancer, 2 thymic carcinoma, 1 malignant pleural mesothelioma, 1 peritoneal mesothelioma, 1 gastric adenocarcinoma, 1 renal carcinoma, 1 neuroendocrine tumor, 1 nasopharyngeal cancer. The median age was 54, of these 50% were male, all ECOG 0 (83%) or 1. There were no grade 4-5 toxicities. The adverse events reported for more than 2 patients were alanine & aspartate aminotransferase increase, fatigue, anorexia, diarrhea, nausea, vomiting, hypothyroidism. Three dose-limiting toxicities of liver enzymes elevation were observed in 200 mg BID nintedanib thus recommending 150 mg BID nintedanib for the phase II part. Three patients have developed an objective RECIST partial response (ORR = 25%). **Conclusions:** Toxicity was consistent with the safety profile of each drug. Additional data for safety and efficacy is being further evaluated in the expansion part of this trial. The efficacy of the combination is currently further explored in 8 expansion cohorts of 30 patients. Clinical trial information: NCT02856425.

3081 Poster Session (Board #295), Mon, 8:00 AM-11:30 AM

Role of melanoma cell-intrinsic RIG-I and STING signaling for checkpoint inhibitor-mediated anticancer immunity. *First Author: Simon Heidegger, Klinikum rechts der Isar, Technical University Munich, Munich, Germany*

Background: Strong inter-individual variation in clinical response to immune checkpoint inhibitors (ICB) including anti-CTLA-4 remains a major challenge, but the molecular pathways that modulate ICB efficacy remain ill defined. **Methods:** Using CRISPR/Cas9 technology to generate melanoma cells lines that lack nucleic acid receptors or downstream signaling molecules together with available genetically deficient mouse models, we addressed the importance of nucleic acid receptor signaling in both tumor and host cells for the efficacy of anti-CTLA-4 immunotherapy. **Results:** We demonstrate that anti-CTLA-4 immunotherapy relies on melanoma cell-intrinsic activation of the cytosolic RNA receptor RIG-I (*DDx58*) but not the DNA sensing adaptor protein STING. Mechanistically, RIG-I signaling induced caspase-3-mediated tumor cell death, cross-presentation of tumor-associated antigen by $CD103^+$ dendritic cells, subsequent expansion of tumor antigen-specific $CD8^+$ T cells and the accumulation of $CD8^+$ T cells within the tumor tissue. These processes were independent of tumor-cell derived type I IFN (IFN-I), but additionally required host STING, MAVS and IFN-I signaling. Consistently, therapeutic targeting of RIG-I with 5'-phosphorylated-RNA in both tumor and non-malignant host cells potently augmented the efficacy of CTLA-4 checkpoint blockade. **Conclusions:** Our data are consistent with the finding that expression of RIG-I in human melanomas has been associated with clinical benefit to CTLA-4 blockade and identify activation of RIG-I/MAVS signaling in tumors and their microenvironment as a crucial component for checkpoint inhibitor-mediated immunotherapy of cancer. These findings not only nominate tumor intrinsic RIG-I activity as potential biomarker for treatment response to checkpoint inhibitors, but predict that targeting this pathway may serve as a basis for the development of new combined modality approaches to increase the response rate of checkpoint inhibitor-based immunotherapy, particularly in individuals that do not have a sufficient spontaneous antitumor T-cell immune response.

3082 Poster Session (Board #296), Mon, 8:00 AM-11:30 AM

Allo-immunity and graft rejection after checkpoint inhibitor therapy (CPI) in solid organ transplant (SOT) recipients. *First Author: Noha Abdel-Wahab, Section of Rheumatology & Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The safety of CPI in patients (pts) with prior SOT was never fully assessed because they were always excluded from clinical trials due to the risk of allo-immunity and organ rejection, and being on immunosupresive therapy (IST). **Methods:** We identified from pharmacy records pts who had received CPI between January 2004 and June 2017 at our institution (n = 4,406). Claims data were obtained for all pts from 6 months prior to first infusion to last follow-up or death. ICD 9 & 10 diagnostic codes were used to identify pts with organ transplant (n = 173). Medical records were reviewed to identify SOT pts. We systematically reviewed the literature databases through September 2017 to identify similar pts. **Results:** A total of 24 pts were retrieved, 6 from institutional databases and 18 from literature. Median age was 61.5 (14-79) years; 75% were male; 67% had metastatic melanoma. Other cancer types included cutaneous squamous cell, non-small cell lung, hepatocellular, and duodenal carcinomas. Renal transplant was reported in 67%. Other SOT included liver and heart. Median time to initiation of CPI after SOT was 8 (1-25) years. Most received anti-PD1 agents (79%). At CPI initiation, all pts were kept on prednisone ($\leq$ 10 mg), mTOR inhibitors, or other IST to maintain graft tolerance. Graft rejection occured in 50% of pts (8/16 kidney, 3/6 liver, and 1/2 heart transplants); 92% received anti-PD1 therapy. Median time to rejection was 21 (5-60) days. In 8 pts with biopsies, 6 had a T-cell mediated rejection, and 2 had mixed cellular and antibody infiltrates. Management of rejection included appropriate IST, and 29% remained dependent on dialysis. CPI was discontinued in all pts. Among all rejected cases, only one pt with cardiac transplant recovered. Interestingly, other irAEs occurred mainly in non rejected cases. They all improved with appropriate IST. In melanoma pts, 27% (4/15) responded to CPI. In all pts, death was reported in 35% (n = 8), in 4 pts was due to organ rejection (2 liver and 2 kidney). **Conclusions:** High rejection rate was evident in SOT pts shortly after CPI and was associated with high mortality rate. Further studies are needed to establish the risk-benefit profile in this population.

3084 Poster Session (Board #298), Mon, 8:00 AM-11:30 AM

Neurologic immune related adverse events (irAEs) in patients treated with immune checkpoint blockade. *First Author: Bianca Santomasso, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neurologic irAEs are uncommon but potentially fatal toxicities of immune checkpoint blockade (ICB). Their incidence, clinical and pathologic features, and association with therapy received are poorly understood. **Methods:** An IRB approved retrospective study was conducted to identify neurologic irAEs of all patients (pts) treated with ICB (anti-CTLA4, anti-PD1, anti-PDL1 monotherapy or in combination) from January 2010 to August 2017 at our institution. Clinical, radiologic, and pathologic features of neurotoxicity were collected. We excluded pts with primary CNS tumors or neurologic symptoms that were attributable to their CNS disease. **Results:** Of 4,864 pts who received anti-CTLA4, anti-PD1, or anti-PDL1 either as monotherapy or in combination, neurologic irAEs developed in 81 (1.67%; 95% CI, 1.34% to 2.06%). Clinical, radiographic, and radiologic features of neurotoxicity were diverse. Time to onset ranged from 3 days to 17 months with a median of 2 doses (1 to 20) received. The incidence was higher with combination therapy versus monotherapy (36 of 1,448 [2.49%] v 45 of 3416 [1.32%]; P = 0.0047), and there was no significant difference in incidence among patients age $\leq$ 65 at time of treatment versus patients age $>$ 65 (41 of 2,705 [1.90%] v 40 of 2,159 [1.85%]; P = 0.3692). Of pts who experienced neurotoxicity, 60% (49 of 81) were hospitalized, 5 (10%) in the ICU. Fifty nine percent (48 of 81) had a concurrent non-neurologic irAEs. Sixty nine percent (56 of 81) had grade 1-2 neurologic events and 77% (63 of 81) improved/resolved with drug holding/immunosuppression. Eight patients worsened clinically or died during the course of neurotoxicity treatment. **Conclusions:** Neurologic irAEs have variable clinical presentation and are more common when anti-CTLA-4 or anti-PD1/PD-L1 mAbs are combined with each other or with other checkpoint inhibitors. Incidence is similar among pts of advanced age and younger pts. Most events improve/resolve with drug holding/immunosuppression, but pts may require hospitalization and experience worsening despite immunosuppression. This underscores the need for earlier identification, as patient outcomes may improve with earlier treatment.

3085 Poster Session (Board #299), Mon, 8:00 AM-11:30 AM

Efficacy and immune modulation by BXCL701 a dipeptidyl peptidase inhibitor, NKTR-214 a CD122-biased immune agonist with PD1 blockade in murine pancreatic tumors. *First Author: Luca Rastelli, bioxcel therapeutics, Branford, CT*

Background: BXCL701 targets DPP8/9 and stimulates migration and cytotoxicity of T and NK cells in addition to targeting fibroblast activator protein (FAP) which forms an immunological barrier to the tumor microenvironment. NKTR-214 is a CD122-biased agonist designed to provide sustained signaling through the heterodimeric IL2 receptor pathway (IL2R$\beta\gamma$) to preferentially activate and expand effector CD8+ T and NK cells. NKTR-214 has demonstrated robust anti-tumor activity when combined with anti-PD1 in multiple murine tumor models and recently, with nivolumab in multiple human cancers. We hypothesized that BXCL701 could further potentiate NKTR-214/anti-PD1 anti-tumor activity by removing fibrotic barriers to immune cells. **Methods:** NKTR-214, BXCL701 and anti-PD1 were dosed in mice bearing established (~100mm^3) murine pancreatic tumors (Pan02) as single agents, doublets and the triplet (0.8mg/kg q9d, 20μg qd, and 200 μg qw2 respectively). Tumors were profiled using IHC and multiplex serum cytokine/chemokine analysis. Tumor-free mice were re-challenged with either Pan02 or murine lung tumor (LLC). **Results:** Of the mice treated with the triplet combination, 100% became tumor-free (9/9) by day 21. These animals remained tumor free for more than 60 days when a subset were re-challenged with new tumor cells. Of these, 5/6 mice rejected tumor regrowth suggesting durable immunity after the triplet therapy. IHC of the tumors from satellite animals sacrificed on day 3 revealed that the triplet significantly reduced FAP expression while increasing the number of immune cell infiltrates in the tumor. **Conclusions:** The triplet of NKTR-214, BXCL701 and anti-PD1 provided 100% tumor-free mice in established pancreatic tumors with concomitant reduction in FAP expression. The results suggest that removal of fibrotic barriers to immune infiltration is an important mechanism for overcoming immune escape by tumors otherwise resistant to immune therapy. These results provide therapeutic rationale for treatment of pancreatic cancer patients with this triple combination.

3086 Poster Session (Board #300), Mon, 8:00 AM-11:30 AM

Phase 1/2 open-label, multiple ascending dose trial of AGEN2034, an anti-PD-1 monoclonal antibody, in advanced solid malignancies: Results of dose escalation. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Agenus AGEN2034 is a fully-human IgG4 monoclonal antibody antagonist targeting Programmed Cell Death Protein-1 (PD-1). The objective was to assess safety, MTD, pharmacokinetic (PK) and pharmacodynamics (PD) characteristics of AGEN2034 in patients (pts) with advanced, refractory malignancies. Analyses of PD-1 receptor occupancy on circulating CD8+ and CD4+ effector memory T lymphocytes was completed. **Methods:** Thirty pts were enrolled in escalating dose cohorts of 1, 3, and 10 mg/kg. AGEN2034 is administered intravenously Q2W for up to 2 years with cohorts evaluating q3wk dosing at 6 and 10 mg/kg are underway. **Results:** Ten subjects were enrolled at each dose level. Median age was 58 years (range 23–77) with ECOG 0–1. No DLTs were observed. Immune-related adverse events consistent with this drug class were observed of pneumonitis, colitis, diarrhea, rash and pruritus. 21 of 30 pts had treatment-related adverse events (TRAEs). 13 subjects (43%) discontinued (d/c) due to disease progression and 2 pts d/c due to TRAEs of hepatitis (n = 1) and pneumonitis (n = 1). In 25 evaluable heavily pre-treated pts, three partial responses (two confirmed) were noted in patients with cervical, ovarian and breast cancers in 1mg/kg and 3mg/kg cohorts. At the time of data cut-off, 13 patients had stable disease, including 5 of 5 with ovarian cancer. AGEN2034 demonstrates a dose-proportional C_{max} of 19.6 μg/mL at 1 mg/kg and 73.6 μg/mL at 3 mg/kg in 12 patient samples analyzed in the first two cohorts. Average PD-1 receptor occupancy on circulating CD8+ and CD4+ effector memory T lymphocytes (n = 18) demonstrated $>$ 59% saturation at all dose levels at day 15. **Conclusions:** AGEN2034 is a pharmacologically active, well-tolerated PD-1 antagonist antibody, demonstrating early signals of clinical activity in cervical and ovarian cancers. PK and RO results are comparable to commercial PD-1 antagonists. A phase 2 expansion in pts with relapsed/refractory cervical cancer is underway. Clinical trial information: NCT03104699.

3087 Poster Session (Board #301), Mon, 8:00 AM-11:30 AM

Characterization of immune related hepatitis (irH) from immune checkpoint inhibitors (ICIs). *First Author: Justine Vanessa Cohen, Massachusetts General Hospital, Boston, MA*

Background: Immune related hepatitis (irH) occurs in a subset of patients receiving ICIs. Although the pathologic features of irH have been described, no studies have correlated the histologic findings on liver biopsy with steroid responsiveness. **Methods:** 25 patients with cancer (22 melanoma, 1 cutaneous squamous cell carcinoma, 1 glioblastoma, 1 non-small cell lung cancer) who had a liver biopsy for elevated transaminases were included. 23 patients received anti-PD1, anti-CTLA4 or a combination of ICI with a non-ICI agent. 2 patients underwent biopsies after targeted therapy. Liver biopsies were reviewed for pattern of injury. Steroid response and requirement for secondary immunosuppression was determined from clinical notes. The pattern of hepatic injury was correlated with response to steroids. **Results:** 15 biopsies showed evidence of lobular injury that was often centrizonal, but in some was panlobular, with a histiocytic inflammatory response. In 6, the histiocytes formed granulomas that were loose, well-formed, or fibrin ring type. 5 of the 15 had central vein endothelialitis. Another 3 patients had mild lobular or portal inflammation without typical features of irH. 2 patients had cholestatic patterns, with portal edema, duct injury, or pericholangitis. 2 had fatty liver disease. 3 remaining patients had non-inflammatory patterns of hepatocyte injury such as hepatocyte cytoplasmic rarefaction. 19 (76%) patients required steroids and 6 (24%) required secondary immunosuppression. 11 (73%) of the 15 cases with characteristic irH were steroid responsive (resolution of transaminitis with < 2 months). The 2 cholestatic cases were less responsive to steroids (one required > 2 months of steroids and the other required secondary immunosuppression). Patients with fatty liver and non-inflammatory injury had variable response to steroids. **Conclusions:** ICI hepatitis has a characteristic pattern of lobular injury with histiocytic infiltration, granuloma formation, and endothelialitis on liver biopsy is highly likely to be steroid responsive. A cholestatic pattern of injury predicts less steroid responsiveness. Non-inflammatory hepatic injury on liver biopsy has variable steroid responsiveness.

3088 Poster Session (Board #302), Mon, 8:00 AM-11:30 AM

Identifying new biomarkers and targeted molecules for immunotherapy using targeted RNA next generation sequencing. *First Author: Wanlong Ma, NeoGenomics Laboratories, Aliso Viejo, CA*

Background: Predictive biomarkers for selecting of patients who may benefit or experience serious adverse effects from checkpoint blockade therapy are urgently needed. These biomarkers may vary from one type of tumor to next. Developing a broad approach for the discovery of new tissue-specific predictive biomarkers may also help guide combination therapy. We used targeted RNA sequencing for the discovery of biomarkers that are co-regulated with PD-L1. **Methods:** We used RNA sequencing of 1385 genes to profile tissues from solid tumors and lymphomas and correlated RNA levels with PD-L1 expression as detected by IHC in tumor and inflammatory cells. **Results:** After normalization, adjusting for group effect and multiple hypothesis testing, 21 genes correlated with PD-L1 expression; fourteen genes correlated positively and 7 correlated negatively. Using the first principle component, we demonstrated that these 21 genes are highly redundant in predicting levels of IHC PD-L1 expression and practically any one can be used as a biomarker. Using LASSO to develop a multivariate model, we demonstrated that RNA levels of *CD274*, *PLAU* (*uPA*), and *RAC1* are independent biomarkers predictive of IHC PD-L1 expression. **Conclusions:** RNA expression, measured using targeted NGS, is a reliable alternative to IHC PD-L1 expression testing. We showed that RNA levels of *CD274*, which codes for PD-L1, and 20 other genes can be used interchangeably in predicting IHC PD-L1 expression. Further, as RNA expression of *PLAU* and *RAC1* are independent from *CD274*, targeting *PLAU* and *RAC1* in combination with PD-L1 inhibitors potentially may augment the therapeutic effects of anti-PD-L1 therapy.

	% PD-L1 in Tumor		
	q-value		q-value
CD274	0.0000	*CD74*	0.0019
PLAU	0.0001	*CHD6*	0.0020
PDCD1LG2	0.0001	*RASGRP1*	0.0020
STAT1	0.0007	*KANK1*	0.0026
IRF1	0.0013	*CIITA*	0.0029
CCNB1IP1	0.0014	*MBTD1*	0.0030
MIR4683	0.0014	*C10*	0.0073
SOD2	0.0014	*PLCB4*	0.0079
FAS	0.0018	*IGF1R*	0.0079
GBP2	0.0018	*SIRT1*	0.0079
IL21R	0.0018		

3089 Poster Session (Board #303), Mon, 8:00 AM-11:30 AM

Pelareorep to promote the expression of a IFN-gamma-related gene signature that predicts response to checkpoint blockade therapy. *First Author: Grey A Wilkinson, Oncolytics Biotech Inc., Calgary, AB, Canada*

Background: A clinical study in patients (pts) with metastatic breast cancer (mBC) treated with pelareorep resulted in significant improvements in overall survival. Clinical studies with checkpoint blockade inhibitors (CBIs) have also resulted in noteworthy clinical responses in a small subset of mBC pts. In pts who do not respond to CBIs, the absence of IFN-γ signalling in the tumor microenvironment has been proposed as a key mediator of innate resistance. IFN-γ signalling upregulates the expression of checkpoint ligands and promotes lymphocyte activation and infiltration to the tumor microenvironment. Thus, the expression of IFN-γ-related genes can be used to both facilitate and predict response to CBIs. Given pelareorep's known capacity to promote an inflamed tumor phenotype, we hypothesised that pelareorep could also stimulate the expression of IFN-γ-related genes associated with response to CBIs. **Methods:** Cell lines derived from breast cancer (BC: MCF7, T47D, MD-231), colorectal cancer (CRC: HT-29, SW620), hepatocellular carcinoma, (HCC: SNU-387) and non-small cell lung cancer (NSCLC: H522) were infected with pelareorep at a multiplicity of infection equal to 50. We examined changes in gene expression and conducted cell viability assays at 6, 12, and 18 hours post-infection (including a non-infected control). To monitor changes in gene expression we employed a 780-gene panel (nanoString) to monitor for changes in the expression of key IFN-γ-related and other immunity-related genes. **Results:** All cell lines were susceptible to pelareorep induced cytopathic effect. Strikingly, BC and HCC cells lines significantly upregulated IFN-γ-related genes while CRC and NSCLC cell lines demonstrated only a modest and variable ability to promote IFN-γ pathway activation. Moreover, BC and HCC cells lines also upregulated key chemokines that are known to promote response to immunotherapy. **Conclusions:** These results suggest that various tumor types are amenable to immune priming for CBIs therapy with pelareorep. The role of pelareorep in the treatment of BC and HCC deserves further investigation, particularly in combination with other immunotherapies.

3090 Poster Session (Board #304), Mon, 8:00 AM-11:30 AM

Analysis of inflammatory signatures of cancer spheroids in blood and their role in metastasis. *First Author: Peter Geck, Tufts University School of Medicine, Boston, MA*

Background: Cancer mortality correlates with metastatic progression where genetic/epigenetic changes in the cancer are important. Recent data indicate, however, that the host thrombotic and inflammation responses are also critical in the metastatic process, but not well understood. We performed exploratory observational studies by filter-capturing cancer spheroids/clusters in blood and studied inflammatory signatures. We investigated the hypothesis that thrombotic/inflammatory factors can stabilize circulating cancer stem cell clusters and critical in metastasis. **Methods:** Cancer spheroids were collected from the blood of 25 metastatic patients (clinically verified metastasis; > 6 months post-treatment) and 25 samples from controls. Gene expression studies in the spheroids targeted EpCAM (epithelial cancer origin); SOX2, NANOG and OCT4 (stem cells); platelet specific selectin (Sel-P) and CD41; IL1beta (innate immunity/inflammatory signature); and PD-L1 (tumor immunity) markers. Poisson regression with overdispersion and the NCSS/PASS package was used for statistical calculations. **Results:** Flow cytometry detected cancer spheroids in 60 % of metastatic blood samples, while only 5 % in primary non-metastatic samples. Filtration collected circulating cancer stem cell spheroids in 72.7 % of metastatic patients and a striking 95.5 % of them showed markers for immune/inflammatory response. In contrast, filtration found circulating cancer stem cell spheroids in only 15.8 % of the non-metastatic samples and only 5.2% showed immune/inflammation response. On the other hand, 90 % of the primary cancer patients were positive for non-cancer related thrombo-embolic micro-clusters (epithelial negative). As it was not found in healthy controls, it may indicate upregulated innate immunity as early as the primary cancer **Conclusions:** The findings support our previous results that circulating cancer spheroids may disseminate metastasis and suggest that innate immunity/inflammation is critical to stabilize cancer stem cell spheroids in circulation. The new inflammation checkpoint in metastatic progression raises the possibility of anti-inflammation modalities to prevent metastasis.

3091 Poster Session (Board #305), Mon, 8:00 AM-11:30 AM

Phase I trial of BMS-986253, an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors. *First Author: Julie Marie Collins, National Cancer Institute, Bethesda, MD*

Background: BMS-986253 is a novel fully human monoclonal antibody that binds to and inhibits IL-8, a chemokine that promotes immune escape and tumor progression. High serum IL-8 levels correlate with poor prognosis in various tumors (Sanmamed et al. *Clin Cancer Res.* 2014). IL-8 stimulates recruitment of myeloid-derived suppressor cells (MDSCs) and promotes epithelial-mesenchymal transition (EMT) in tumors conferring resistance to immune-mediated killing (David et al. *Vaccines* 2016). We have previously shown the ability of BMS-986253 to reduce mesenchymal features in cancer cells leading to enhanced susceptibility to NK and T cell-mediated lysis, and to decrease the frequency of granulocytic MDSCs in xenograft models. Decreases in serum IL-8 were also associated with response to anti–PD1 therapy in a small cohort of patients with melanoma and NSCLC (Sanmamed et al. *Ann Oncol.* 2017). **Methods:** Patients with metastatic or unresectable locally advanced malignant solid tumors were treated with BMS-986253 monotherapy at 4, 8, 16, or 32 mg/kg IV Q2W in a phase I, open-label, 3+3 dose-escalation study. The primary objective was to determine the safety and tolerability and establish the maximum tolerated dose (MTD). Pharmacokinetics and changes in serum cytokine levels including IL-8 were also evaluated. **Results:** Amongst 15 patients, no serious treatment-related adverse events (TRAEs) were observed and MTD was not identified through 32mg/kg. TRAEs occurred in 5 pts (33%), and all were Grade 1 except for Grade 2 fatigue, hypophosphatemia and hypersomnia in two patients receiving 32mg/kg. Eleven pts (73%) achieved stable disease (per RECIST v1.1) and 4 patients had progressive disease (27%). The progression free survival rate at 24 weeks for all patients was 73% with two-sided 95% CI [44%, 89%]. Reductions in serum IL-8 levels were observed at all dose levels. **Conclusions:** BMS-986253 monotherapy is well tolerated and associated with decreases in serum IL-8 across all doses tested. These data have informed combining this drug with Nivolumab and potentially other agents to evaluate the potential for synergetic activity in selected patient populations. Clinical trial information: NCT02536469.

3092 Poster Session (Board #306), Mon, 8:00 AM-11:30 AM

Single intravenous preoperative administration of the oncolytic virus Pexa-Vec to prime anti-tumor immunity. *First Author: Alan Anthoney, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom*

Background: Oncolytic viruses (OV) constitute a promising modality of cancer therapy. Intra-tumoral administration has yielded encouraging clinical results, but restricted the use of OV to tumors that are readily accessible. Pexa-Vec, a Thymidine Kinase-Deactivated Vaccinia Virus expressing GM-CSF, has been shown previously to successfully target tumor tissue after intravenous administration (Breitbach C.J. *et al.*, 2011). Herein, we report data on the immunostimulatory effects of a single intravenous (*i.v.*) administration of Pexa-Vec prior to surgical resection in patients with advanced solid tumors. **Methods:** Patients with operable tumors received a single *i.v.* administration of $1x10^9$ plaque forming units of Pexa-Vec, 14 days prior to surgical resection. Up to six blood samples were collected pre- and post-injection for each patient. Tumor tissue was collected at surgery for histologic and translational assessments. **Results:** The study included 3 patients with metastatic melanoma and 5 with colorectal cancer metastases to the liver (CRLM). Pexa-Vec injection was well tolerated in all cases. Histologic examination of tumor tissue indicates the presence of virus in tumor at the time of surgery. Of the 3 evaluable CRLM, 2 showed signs of inflammation and fibrosis, within a normal background liver. Phenotyping of peripheral blood mononuclear cells showed robust activation of Natural Killer (NK) and professional antigen presenting cells ($CD14^+$), as well as $CD4^+$ and $CD8^+$ cells, with high CD69 expression. Functional assays revealed increased patient NK cell degranulation in the presence of tumor cell lines. Consistent with cellular markers, Pexa-Vec induced a significant elevation of serum cytokines associated with immune response including IFNα, IL3, IL12p40, IL16, IL18. **Conclusions:** When administered intravenously, Pexa-Vec exhibited a selective persistence in tumor tissues suggesting a targeted oncolytic action in the tumor. Concurrently, Pexa-Vec triggered a robust immune activation of both innate and adaptive immune cells. These data strongly support the rationale for sequential JX-594 and anti-PD-1 viro-immunotherapy, which is the focus of the ongoing study, NCT03071094. Clinical trial information: ISRCTN13913966.

3093 Poster Session (Board #307), Mon, 8:00 AM-11:30 AM

SEA-CD40, a non-fucosylated CD40 agonist: Interim results from a phase 1 study in advanced solid tumors. *First Author: Juneko E. Grilley-Olson, UNC Lineberger Comprehensive Cancer Center/University of North Carolina Chapel Hill, Chapel Hill, NC*

Background: SEA-CD40 is a non-fucosylated, humanized IgG1 monoclonal antibody which binds CD40, an immune-activating TNF receptor. Binding to antigen presenting cells and crosslinking via FcγRIIIa stimulates inflammatory cytokine production and induction of immune co-stimulatory receptors, leading to T-cell activation and antitumor activity. On CD40-expressing malignant cells, SEA-CD40 can induce antibody-dependent cellular cytotoxicity through enhanced NK-cell binding. **Methods:** This is an ongoing phase 1 dose-escalation study in patients (pts) with relapsed/refractory metastatic solid tumors (NCT02376699). Antitumor activity is assessed q4 cycles (~12 wks) by immune-related response criteria and RECIST. **Results:** 48 pts (median age 62 yrs [range, 28–81]; median of 4 prior systemic therapies [range, 1–11]) have received a median of 2 cycles (range, 1–16) of SEA-CD40 at doses 0.6–60 mcg/kg on Day 1 (n = 38), or 30 mcg/kg on Days 1 and 8 (n = 10) IV q3 wks. SEA-CD40 maximum concentrations increased dose-proportionally (10–60 mcg/kg; Day 1 dosing), with mean half-life estimates of 32–95 hrs and no accumulation upon repeat dosing. Dose-limiting toxicities occurred in 5 pts; all were infusion-related reactions (IRRs). Treatment-emergent AEs in ≥25% of pts were IRR (69%), chills (65%), fatigue (54%), nausea (52%), vomiting (35%), and dyspnea and headache (27% each). No treatment-related G5 AEs were reported. Chemokine/cytokine changes and associated immune-trafficking changes observed in the peripheral blood and tumor microenvironment support the proposed mechanisms of action. Best response in 34 efficacy-evaluable pts was 1 PR (basal cell carcinoma) and 10 SD, for a 32% disease control rate (DCR = CR+PR+SD) by RECIST. 5 pts had continued disease control as assessed at Cycle 8 (~6 mos). **Conclusions:** SEA-CD40 monotherapy shows clinical (32% DCR) and biological activity in heavily pre-treated pts with advanced solid tumors. SEA-CD40 has a generally tolerable safety profile; strategies to manage IRRs are being evaluated as dose escalation continues at ≥45 mcg/kg. Combination therapy dose escalation (SEA-CD40 + pembrolizumab) in solid tumors is underway, as is monotherapy dose escalation in lymphomas. Clinical trial information: 02376699.

3094 Poster Session (Board #308), Mon, 8:00 AM-11:30 AM

A phase I/II study of the oncolytic peptide LTX-315 combined with checkpoint inhibition generates *de novo* T-cell responses and clinical benefit in patients with advanced solid tumors. *First Author: James F. Spicer, King's College London, London, United Kingdom*

Background: LTX-315 disintegrates cytoplasmic organelles and induces immunogenic cell death and systemic immune responses preclinically. Systemic efficacy can be enhanced *in vivo* by combination with immune checkpoint inhibitors (ICI). Clinical safety has been demonstrated as a single agent administered intratumorally in a phase I study **Methods:** Patients with heavily pretreated advanced solid tumors were treated twice weekly with intratumoral LTX-315 over 3 weeks; as monotherapy, or in combination with ipilimumab or pembrolizumab. Primary endpoint was safety of LTX-315 combined with ICI. Anti-tumor activity was assessed by using immune-related response criteria (irRC). Immunohistochemistry and gene expression analysis were performed on tumor biopsies pre and post treatment. T-cell receptor (TCR) repertoire in peripheral blood and biopsies was assessed by TCRb-gene sequencing. **Results:** Fifty-nine patients were treated. Eleven experienced LTX-315-related grade 3/4 adverse events, mainly allergic/anaphylaxis, all resolving without sequelae. Out of 36 patients treated with LTX-315 monotherapy, best overall response of SD at 2 months was seen in 28%. Out of 17 TNBC patients treated with LTX-315 plus pembrolizumab, 12 were evaluable, of which 17% had PR, and 25% SD. Six melanoma patients received LTX-315 plus ipilimumab, of those SD was observed in 33%. LTX-315 monotherapy resulted in increased number of CD8+ T-cells in treated lesions in 89% of evaluable biopsied patients. TCR sequencing revealed clonal expansion of T-cells in blood after LTX-315 monotherapy, and 50% of these clones were detected in post-treatment biopsied tumors. **Conclusions:** Intratumoral LTX-315 is generally safe and tolerable when combined with ICI. The combination has anti-tumor activity. LTX-315 monotherapy enhances TIL population and induces polyclonal T-cell responses, demonstrating the potential of LTX-315 as a T-cell primer combined with other immunotherapies. Clinical trial information: NCT01986426.

3095 Poster Session (Board #309), Mon, 8:00 AM-11:30 AM

Pharmacodynamic and clinical activity of RGX-104, a first-in-class immunotherapy targeting the liver-X nuclear hormone receptor (LXR), in patients with refractory malignancies. *First Author: Monica M. Mita, Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA*

Background: RGX-104 is a small-molecule LXR agonist that modulates innate immunity via transcriptional activation of the *ApoE* gene. RGX-104 depletes myeloid derived suppressor cells (MDSCs) and stimulates dendritic cells (DCs), activating cytotoxic lymphocytes (CTLs) with anti-tumor activity as monotherapy and in combination with checkpoint blockade in murine models. **Methods:** We are conducting a Phase 1 dose escalation and expansion study of RGX-104 in patients with refractory solid tumors. Safety, PK, PD, and efficacy are being assessed. **Results:** RGX-104 was dosed orally in 23 patients with a broad array of tumors on 5 cohorts at doses ranging from 120 mg QD for 3 of 4 weeks to 200 mg BID continuously. Following single dosing, PK analysis demonstrated high inter-patient variability with $t_{1/2}$ from 6 – 8 hr. *ApoE* gene expression measured in whole blood leukocytes correlated with RGX-104 dose and exposure, demonstrating robust LXR target engagement. Peripheral immune-cell monitoring revealed substantial MDSC depletion ($CD33^+CD15^+HLA\text{-}DR^{-/low}$; median 78% decrease), DC stimulation ($HLA\text{-}DR^+Lin^-$; median 34% increase in PD-L1) and CTL activation (median 257% increase in $PD\text{-}1^+GITR^+$ $CD8^+$ T-cells) in 10/12 evaluable patients. Peak PD effects began ~2 weeks after RGX-104 initiation. Three patients experienced grade 3-4 neutropenia and 1 patient had grade 3 elevated cholesterol, reversible with a statin, likely on-target adverse events. A patient with a platinum-refractory, high-grade neuroendocrine carcinoma with small cell features had a 53% reduction in index hepatic metastases–a partial response pending confirmation, and 5 patients had stable disease at 8 weeks. **Conclusions:** Proof of principle has been demonstrated for immunologic and anti-tumor activity of the first-in-class LXR-agonist RGX-104 in advanced cancer patients. RGX-104 was well tolerated at doses up to 160mg BID and demonstrated robust PD effects on ApoE expression and relevant immune cell populations. Dose escalation with a PD-1 inhibitor has begun with plans to study RGX-104 both as monotherapy and in combination with a PD-1 inhibitor in select malignancies. Clinical trial information: NCT02922764.

3096 Poster Session (Board #310), Mon, 8:00 AM-11:30 AM

Severe immune-related adverse effects (irAE) requiring hospital admission in patients treated with immune checkpoint inhibitors for advanced malignancy: Temporal trends and clinical significance. *First Author: Kerry Lynn Reynolds, Massachusetts General Hospital, Boston, MA*

Background: Disruption of the immune system using immune checkpoint inhibitors can result in a multitude of immune-related adverse effects (irAE). While irAEs have been well-reported in clinical trials, the impact and magnitude in the real world is unclear. **Methods:** Data was collected on patients with advanced malignancy who experienced a suspected irAE requiring admission to an academic hospital (02/11-06/17). Each case was comprehensively reviewed by a minimum of two reviewers, including one sub-specialist. In addition, oncologists were surveyed regarding their confidence about managing irAEs. **Results:** From 2011-2017, there were 343 hospitalizations for suspected irAEs, and the majority (65%; N = 223) were confirmed irAEs from immunotherapy: PD1 (31.8%), CTLA4 (29.2%), CTLA4 + PD1 (15.7%), PD1 à CTLA4 (14.8%), CTLA4àPD1 (8.5%), and PDL1 (3.1%). The most common irAEs were gastrointestinal (43.9%), pulmonary (16%), hepatic (15%), neurologic (8.9%), endocrine (7.1%), rheumatologic (4%), dermatologic (3%), cardiac (3%), renal (1.8%), and allergy (1.3%). Mean length of stay was 6.4 days, readmission rate for irAE 25%, and inpatient mortality 4%. Majority of patients (92%) required continuation of immunosuppressive medication on discharge. Disposition was to home (87%), skilled facility (8.8%), or hospice (4.2%). Inpatient admissions due to irAEs has increased significantly over time (2016 vs 2011, odds ratio = 3.07; $p < 0.01$). However, a survey (N = 26) revealed that oncologists do not feel very comfortable managing irAEs, and 48% felt irAEs should be managed by different service. **Conclusions:** irAEs from immune checkpoint inhibitors can result in prolonged hospitalizations, need for immunosuppression, inpatient mortality, and high readmission rate. The number of admissions due to irAEs has increased by more than three-fold in the recent years, but comfort level in managing these complications is low. Consequently, there is a critical need for coordinated multidisciplinary approach, comprehensive provider education, and translational research programs for early detection and intervention.

3098 Poster Session (Board #312), Mon, 8:00 AM-11:30 AM

First-in-man study of Ad-sig-hMUC1/ecdCD40L vaccine for immunotherapy of MUC1 overexpressing epithelial cancers. *First Author: Tira Jing Ying Tan, Division of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore*

Background: Ad-sig-hMUC1/ecdCD40L vaccine is an adenoviral vector encoding the human MUC-1 epithelial antigen bound to an immune stimulant, the extracellular domain of the CD40 ligand (CD40L) and an adenovirus signal sequence encoding the secretory signal peptide. Pre-clinical studies have demonstrated efficacy of CD40L in activating endogenous dendritic cells to elicit potent anti-MUC1 immunity. We report results of the dose-escalation cohort in a phase 1 study of Ad-sig-hMUC-1/ecdCD40L vector vaccine. **Methods:** Patients (pts) with advanced adenocarcinoma of the breast, ovary, lung, colon or prostate with tumor overexpressing MUC-1 on immunohistochemistry or elevated serum CA 15-3 were recruited on a 3+3 design phase 1 dose escalation study. Study endpoints were safety, tolerability, maximum tolerated dose (MTD) and antitumor activity. Serum CA 15-3 measurements performed monthly and initial CT evaluation of disease in month 2. Immune biomarkers for analysis included antigen-specific T-cell interferon-gamma Elispot assays, and serum cytokine multiplex assays. **Results:** Eighteen pts were treated, median age 58 (range 34-88 years), 17 females, 1 male, 11 (61%) breast, 6 (33%) ovarian and 1 (6%) lung cancer. Six cohorts of 3 pts recruited. The first 4 cohorts were single injections starting at 1×10^9 viral particles (VP) escalating to 1×10^{11} VP. Cohorts 5 and 6 involved 2 (days 1 and 7) and 3 (days 1, 7 and 21) 1×10^{11} VP injections. The most common adverse events (AE) were injection site reaction 13 (72%) and rash 5 (28%). All drug related AE were of low grades 1-2. There were no dose limiting toxicities and MTD not reached. 16 patients were evaluable for serum CA 15-3, 2 recorded > 30% decline. 13 pts had measurable disease, 5 demonstrated a reduction in tumor size not amounting to partial response. 1 ovarian cancer pt in cohort 5 received 2×10^{11} VP recorded a 60% CA 15-3 decrease and 25% decrease in tumour size. Immune and translational correlates will be reported. **Conclusions:** This first-in-man study of Ad-sig-hMUC-1/ecdCD40L vector vaccine in cancers expressing MUC1 has demonstrated low toxicity and encouraging antitumor activity. Our data supports further clinical evaluation in a larger study cohort. Clinical trial information: NCT02140996.

3099 Poster Session (Board #313), Mon, 8:00 AM-11:30 AM

Cervical microbiome role in outcomes of therapeutic HPV vaccination for cervical intraepithelial neoplasia. *First Author: Rahul Ravilla, University of Arkansas for Medical Science, Little Rock, AR*

Background: Clinical trials have suggested that the gut microbiome can modulate immunotherapy outcomes with checkpoint inhibitors (Kroemer et al, Nat rev immunology. Jan 2018). However, the role of cervical microbiome has not been investigated. We studied the effect of cervical microbiome on outcomes of a novel therapeutic HPV vaccine in women with high grade cervical neoplasia. **Methods:** We collected 65 cervical samples (34 pre-screen and 31 post-vaccination) from 34 women enrolled in a phase 1 therapeutic vaccine trial (Coleman et al. Cancer Immunol Immunotherapy. May 2016). Whole DNA was isolated from cervical Thinprep samples using the Qiagen DNA Mini Kit and amplified by PCR using a bacterial 16sRNA gene primer. eOTUs were identified using V1-V9 16S rRNA gene hybridization with G4 Phylochip™ (Second Genome, South San Francisco, CA). Alpha and beta diversity metrics were calculated. We used PERMANOVA analysis to test for associations of phylogenetic composition with patient demographics; HPV status; HLA type; circulating Th1, Th2, and Treg cells; local TFoxp3 cells and clinical response to the vaccine. Responders and non-responders were defined based on histological regression of cervical lesions. **Results:** Richness ranged from 72 to 365 eOTUs per sample, and Prevotellaceae and Lactobacillaceae were the most abundant families observed. We found that pre-screen samples from vaccine non-responders, as compared to responders, were enriched with the phyla Caldithrix, Nitrospirae and family Mycoplasmataceae and an unclassified family from order Entomoplasmatales. HPV16 status and HLA B40 status were significantly associated with beta diversity. Measures of pre- and post-vaccination alpha and beta diversity were not statistically significantly associated with response to vaccine. Also, we observed no correlations of microbiome metrics with immune parameters. **Conclusions:** Study findings suggest that cervical microbial composition may predict non-responsiveness to a therapeutic vaccine given to treat high-grade cervical neoplasia. Observed associations of cervical microbial composition with HLA B40 and HPV 16 status are of interest but require further investigation. Clinical trial information: NCT01653249.

3100 Poster Session (Board #314), Mon, 8:00 AM-11:30 AM

Utility of comprehensive genomic profiling (CGP) for personal cancer vaccine development via neoantigen analysis. *First Author: Dana Vuzman, KEW, Inc., Cambridge, MA*

Background: Cancer vaccines against neoantigens have shown promise in treating advanced stage cancers [1,2]. Typically, detection of somatic mutations underlying neoantigen expression is done using WES, a cost and time-ineffective platform for routine clinical use. Here, we assess the feasibility of a large NGS panel for use in cancer vaccine development through discovery of somatic mutations and prediction of neoantigen load. **Methods:** Various patient tumor samples with a range of mutational loads [n = 30; mean: 84 mutations, range: 34-248] were profiled using CANCERPLEX, a 435-gene panel for identifying clinically-relevant genomic alterations in cancer [3]. For each mutation, all possible 9- and 10-mer peptides were enumerated. For mutations that result in novel open reading frames (neoORF), peptides overlapping the entire neoORF were considered. The 28 most frequent HLA-A and HLA-B alleles in the Caucasian, African, and Asian populations were used. Peptides were computationally evaluated for binding to HLA using the NetMHCpan-3.0 algorithm [4]. For each neoantigen, the rank relative to the collective mutant and wildtype 9- or 10-mers was determined. Neoantigens were classified as strong binders if $rank_{mutant}/rank_{wt} \geq 0.5$. For each HLA allele, the neoantigen load was calculated as the number of strong binders per given allele. **Results:** The number of neoantigens was significantly correlated with mutational load. The neoantigen load was dependent on the HLA allele binding partner, with HLA alleles B07:02, A33:03, A30:01, and B42:01 predicted to have higher binding affinity. This allele dependent distribution suggests that certain HLA alleles are better binding partners for potential neoantigens or preferential for certain peptide. **Conclusions:** The high number of neoantigens identified suggests that CGP is a feasible alternative to WES for cancer vaccine development. CANCERPLEX accurately detects somatic mutations [3] thus enabling prediction of tumor neoantigens, an emerging biomarker in immune-oncology [5]. Future studies incorporating HLA transcription testing with CGP are warranted to further establish the platform for cancer vaccine development.

TPS3101 Poster Session (Board #315a), Mon, 8:00 AM-11:30 AM

Phase 1, open-label, adaptive biomarker trial that informs the evolution of combination immuno-oncology (IO) therapies (ADVISE), a precision IO approach to personalized medicine. *First Author: Jason J. Luke, University of Chicago Comprehensive Cancer Center, Chicago, IL*

Background: Immune checkpoint inhibitor therapies have revolutionized treatment paradigms for numerous tumor types. However, improved understanding of the tumor microenvironment (TME) and tumor immune biology is needed to enhance and extend benefits to more patients. Personalized pairing of IO agents to the immune biomarkers in the TME of individual patients using pretreatment biopsies could transform cancer care, but the feasibility of using biomarkers to study IO combinations in specific patient populations has not been established. The ADaptiVe biomarker trial that InformS Evolution of therapy (ADVISE; NCT03335540) was designed to assess the clinical feasibility and utility of real-time biomarker data to allow specific IO agents in combination with nivolumab to be selected for individual patients across various tumor-specific cohorts. **Methods:** Approximately 50 patients with selected solid tumors will initially be enrolled. Patients must be ≥ 18 years of age, have an ECOG PS ≤ 1, and have had ≥ 1 prior therapy. Prior IO therapy is permitted; however, patients will not be assigned to receive an IO regimen containing an agent directed against the same target (aside from PD-[L]1). Treatment selection will be driven by biomarker analyses in pretreatment biopsies. Patients will receive nivolumab in combination with a second IO agent that is implicated in tumor immune escape (lirilumab [anti-KIR], relatlimab [antiLAG-3], cabiralizumab [antiCSF-1R], ipilimumab [antiCTLA-4], BMS-986205 [IDO-1 inhibitor], or BMS-986156 [anti-GITR]) or nivolumab with stereotactic body radiation therapy (for noninflamed tumors). The primary endpoint is the ratio of patients with qualified tumor biopsy specimens at baseline providing sufficient biomarker data and analysis time to guide treatment decisions. Other endpoints include safety, preliminary clinical activity, and biomarker analyses. Clinical trial information: NCT03335540.

TPS3102 Poster Session (Board #315b), Mon, 8:00 AM-11:30 AM

ZUMA-2: Phase 2 multicenter study evaluating efficacy of kte-C19 in patients with relapsed/refractory mantle cell lymphoma. *First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mantle cell lymphoma (MCL) is an aggressive B cell malignancy, and accounts for ≈6% of non-Hodgkin lymphomas. Despite high initial response rates, MCL is generally considered incurable, as almost all patients (pts) eventually progress (Cheah et al. *J Clin Oncol.* 2016). Bruton tyrosine kinase (BTK) inhibition can lead to high rates of prolonged responses in relapsed/refractory (R/R) MCL, as noted with ibrutinib (Wang et al. *NEJM.* 2013) and acalabrutinib (Wang et al. *Lancet.* 2017). However, many pts develop ibrutinib-resistance and outcomes to salvage regimens (including investigational agents) are poor with a response rate of 32% and median overall survival of 8.4 months (Cheah et al. *Ann Oncol.* 2015). This phase 2, multicenter, open-label study examines efficacy and safety of KTE-C19, an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in pts with R/R MCL who have progressed on prior chemotherapy, an anti-CD20 antibody, and a BTK inhibitor. **Methods:** ZUMA-2 (NCT02601313) is enrolling pts with R/R MCL sequentially into 2 separate dose level cohorts (~40 pts each). After leukapheresis and manufacturing, pts will receive conditioning chemotherapy with fludarabine 30 mg/m^2/d and cyclophosphamide 500 mg/m^2/d × 3 d and then receive a single infusion of KTE-C19 cells at a dose of 0.5×10^6 CAR T cells/kg. The primary endpoint is objective response rate by Independent Review Committee assessment; secondary and exploratory endpoints include duration of response, progression-free survival, overall survival, incidence of adverse events and levels of CAR T cells and cytokines in blood. Eligible adult pts with pathologically confirmed R/R MCL and an ECOG of 0-1 must have received ≤ 5 prior therapies that must have included an anthracycline or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody therapy, and ibrutinib or acalabrutinib. Pts who received allogenic stem cell transplant or prior CD19-directed therapy or those with clinically significant infection or a history of central nervous system lymphoma or central nervous system disorders are not eligible. Accrual is ongoing. Clinical trial information: NCT02601313.

TPS3103 Poster Session (Board #316a), Mon, 8:00 AM-11:30 AM

A phase 1 multicenter study evaluating KITE-585, an autologous anti-BCMA CAR T-cell therapy, in patients with relapsed/refractory multiple myeloma. *First Author: Robert F. Cornell, Vanderbilt University Medical Center, Nashville, TN*

Background: In the United States there are > 30,000 new cases of multiple myeloma (MM) and an estimated > 12,000 deaths annually (Howlader et al. *SEER Cancer Statistics Review.* 2017). Despite an increasing number of treatment options, the disease remains incurable. KITE-585, an autologous, fully-human anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T cell therapy, potently and specifically targets MM cells in preclinical studies (Adams et al. AACR. 2017 #2135, #4979). This Phase 1, open-label, multicenter, first-in-human study evaluates the safety and efficacy of KITE-585 in patients (pts) with relapsed/refractory MM (RRMM; NCT03318861). **Methods:** Planned enrollment is ≤ 64 pts. After leukapheresis and manufacturing, pts undergo lymphodepleting chemotherapy with fludarabine (30 mg/m^2/d) and cyclophosphamide (300 mg/m^2/d) for 3 d followed by a single infusion of KITE-585. The study follows a standard 3 + 3 cell-dose-escalation design with an option to expand enrollment at doses that have passed dose-limiting toxicity (DLT) criteria. Pts in the first dose cohort will receive 3×10^7 CAR T cells. Pts may receive optional bridging chemotherapy after leukapheresis and before conditioning. The primary endpoint is incidence of adverse events (AEs) defined as DLTs. Secondary endpoints include overall response rate per International Myeloma Working Group criteria, duration of response, progression-free survival, time to next treatment, overall survival, incidence of AEs, and clinically significant changes in laboratory values. Eligible pts (≥ 18 y) must have RRMM (defined as ≥ 3 prior lines of therapy including both a proteasome inhibitor [PI] and an immunomodulatory drug [IMiD] or MM that is refractory to a regimen containing both a PI and an IMiD), an ECOG performance status of ≤ 1, and adequate bone marrow and organ function. BCMA expression is not required for eligibility. Key exclusion criteria include plasma cell leukemia, nonsecretory MM, active infection, a history of central nervous system involvement, active autoimmune disease, or prior allogeneic stem cell transplant. The study opened to accrual in October 2017. Clinical trial information: NCT03318861.

TPS3104 Poster Session (Board #316b), Mon, 8:00 AM-11:30 AM

A phase 1 multicenter study evaluating the safety and efficacy of MHC class II-restricted MAGE-A3/A6 T-cell receptor engineered T cells (KITE-718) in patients with advanced cancers. *First Author: Partow Kebriaei, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Melanoma-associated antigens 3 and 6 (MAGE-A3/A6) are among the most commonly expressed cancer testis antigens in a variety of tumors and are associated with poor disease prognosis. Antitumor activity, including partial and complete responses, has been observed with MHC class II-restricted T cell receptor (TCR)-engineered T cells targeting MAGE-A3 and MAGE-A6 (Lu et al. *J Clin Oncol.* 2017). In this study, the safety and antitumor activity of KITE-718, an autologous TCR-engineered T cell therapy targeting MAGE-A3/A6, will be evaluated in HLA-DPB1*04:01-positive patients with advanced cancers. **Methods:** Phase 1A of the study (NCT03139370) uses a single-patient dose-escalation scheme to evaluate safety and determine the recommended Phase 1B dose of KITE-718, enrolling up to 30 patients. Phase 1B will include ≈45 patients with non-small cell lung cancer, urothelial cancer, and all other MAGE-A3/A6–positive tumors treated at the recommended KITE-718 dose. For both portions of the study, after leukapheresis patients may receive optional bridging therapy prior to conditioning chemotherapy. After manufacturing, patients will receive cyclophosphamide and fludarabine conditioning chemotherapy followed by KITE-718 at a dose of 1×10^6 to 1×10^8 TCR-transduced T cells/kg. Following KITE-718 infusion, patients will receive daily subcutaneous IL-2 therapy for a maximum of 14 days. The primary endpoint for Phase 1A is incidence of adverse events defined as dose-limiting toxicities. The Phase 1B primary endpoint is investigator assessment of objective response rate per modified RECIST v1.1 or IMWG criteria. Secondary endpoints include duration of response, progression-free survival, overall survival, and safety. Patients aged ≥18 y must be HLA-DPB1*04:01–positive, have relapsed/refractory MAGE-A3/A6–positive advanced cancer, ECOG ≤ 1, and adequate bone marrow and organ function. Patients amenable for loco-regional therapy or with history of stroke, myocardial infarction, or symptomatic deep vein thrombosis/pulmonary embolism are not eligible. The study is open and accruing patients. Clinical trial information: NCT03139370.

TPS3105 Poster Session (Board #317a), Mon, 8:00 AM-11:30 AM

A phase 1b/2, multicenter, open-label trial to evaluate the safety of talimogene laherparepvec (T-VEC) injected into primary and metastatic liver tumors alone and in combination with pembrolizumab (pembro) (MASTERKEY-318). *First Author: J. Randolph Hecht, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA*

Background: Combining the intralesional oncolytic immunotherapy T-VEC with systemic immunotherapy may enhance the systemic efficacy of both agents through complementary mechanisms of action. The open-label MASTERKEY-318 study (ClinicalTrials.gov, NCT02509507) was designed to evaluate the safety of intrahepatic injection of T-VEC, with or without intraveneous (IV) pembro, in pts with liver metastases (met) from solid tumors (non-HCC; from breast cancer [BC], colorectal cancer [CRC], gastroesophageal cancer [GEC], melanoma, non-small cell lung cancer [NSCLC], or clear cell renal cell carcinoma [RCC]) or from primary hepatocellular carcinoma (HCC). The study consists of 2 parts. **Methods:** In Part 1, the safety of administering increasing concentrations (Initial 10^6 plaque forming unit [PFU]/mL followed 3 weeks (wk) later by 10^7 PFU/mL or 10^8 PFU/mL q3 wk) and volumes of T-VEC will be determined in the monotherapy and combination (combo) cohorts. The primary objective for Part 1 is to evaluate the maximum tolerated volume and concentration (MTV and MTC) of injection of T-VEC into tumors in the liver alone and in combo (MTC only) with systemic pembro (200 mg IV q3 wk) as measured by incidence of dose limiting toxicities. Once the MTC is determined, Part 2 will evaluate the efficacy and safety of the T-VEC/pembro combo in the respective tumor types. For Part 2, the primary objective is objective response rate and incidence of treatment-emergent and treatment-related adverse events. Key eligibility criteria include age ≥18 years, confirmed BC, CRC, GEC, melanoma, NSCLC, or RCC with liver met or HCC. Generally, non-HCC pts must have received ≥1 prior standard of care systemic therapy for their locally advanced or metastatic disease. However, for the combo cohorts, pts with melanoma or NSCLC do not need to have received prior therapy. Pts must have measurable liver tumors suitable for injection, an Eastern Cooperative Oncology Group performance status of 0 or 1, and life expectancy ≥5 months. MASTERKEY-318 will enroll up to 244 pts from ~50 sites. 21 pts have enrolled onto the monotherapy cohorts so far. Clinical trial information: NCT02509507.

TPS3106 Poster Session (Board #317b), Mon, 8:00 AM-11:30 AM

Phase I adoptive cellular therapy trial with ex-vivo stimulated autologous CD8+ T-cells against multiple targets (ACTolog IMA101) in patients with relapsed and/or refractory solid cancers. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Adoptive cellular therapy (ACT) has demonstrated substantial clinical progresses in hematologic cancers; however, only a small proportion of solid tumor patients have benefited from these advances due to i) lack of suitable immunotherapy targets with high specificity in solid tumors, ii) frequent relapse following immunotherapy to single targets often associated with loss of target expression in the tumor. The ACTolog® concept, utilizing antigen specific T cells (IMA101) against targets identified by the Immatics' proprietary XPRESIDENT® technology, is intended to overcome these limitations by addressing multiple novel tumor antigens per patient. One key defining feature in this trial is the generation of robust T cells, where autologous T cells are primed against the expressed ACTolog targets in the presence of IL-21 followed by HLA tetramer-guided cell sorting and rapid expansion. This process has been shown to result in higher frequencies of central memory T cells, extended *in vivo* persistence, and a more robust clinical response. **Methods:** This study is a first-in-human phase I trial in patients with relapsed or refractory solid tumors expressing up to 4 targets from a warehouse of 8 cancer targets in which autologous T-cell products are manufactured against the most relevant tumor target peptides for individual patients. Key eligibility criteria include: HLA-A*02:01 phenotype, qPCR biomarker positive from a tumor biopsy, RECIST v1.1 measurable lesions, and ECOG status 0 or 1. At baseline, patients will undergo leukapheresis to collect mononuclear cells for manufacturing of IMA101 cells. Patients will receive anti-cancer therapy during the production phase. IMA101 will be infused after lymphodepletion regimen followed by low dose IL2. The primary objective is to assess safety and tolerability of IMA101. Secondary endpoints include overall response rate, PFS and OS. The translational objective includes the assessment of *in vivo* persistence and *ex vivo* characterization of transferred T cells in addition to evaluation of target expression in tumors. Enrollment in the study is currently ongoing. Clinical trial information: NCT02876510.

TPS3107 Poster Session (Board #318a), Mon, 8:00 AM-11:30 AM

A phase 2 study to assess the efficacy and safety of autologous tumor-infiltrating lymphocytes (TIL, LN-145) alone and in combination with anti-PD-L1 inhibitor durvalumab in patients with locally advanced or metastatic NSCLC. *First Author: Sylvia Mina Lee, University of Washington - Seattle Cancer Care Alliance, Seattle, WA*

Background: Adoptive cell therapy with TIL has demonstrated durable complete responses in immunogenic tumors with high mutational burden. Durvalumab, which enhances T-cell antitumor cytotoxicity through blockade of the PD-1/PD-L1 axis, has demonstrated clinical activity in NSCLC. Despite recent advances in the treatment of NSCLC using checkpoint inhibitors, the majority of patients do not respond, leaving an unmet need to improve therapeutic outcomes, warranting this investigation of TIL therapy alone and in combination with durvalumab. IOV-LUN-201 is a phase 2 multicenter, open-label study designed to evaluate the efficacy and safety of autologous LN-145 therapy alone or in combination with durvalumab, for previously-treated, anti-PD-1/PD-L1-naïve NSCLC patients. **Methods:** LN-145 is a preparation of TIL extracted from surgically-resected tumors and manufactured in a 22-day process at a central GMP facility. LN-145 infusion is preceded by a non-myeloablative lymphodepletion regimen of cyclophosphamide and fludarabine, and followed by up to 6 infusions of IV IL-2. Cohort 1 patients receive LN-145 therapy alone. Patients in Cohort 1 who do not receive LN-145 or those who progress following LN-145 therapy can receive durvalumab 1500 mg IV Q4W until progression or unacceptable toxicity. Cohort 2 patients receive durvalumab 2 weeks prior to and 2 weeks after tumor harvest, and then following LN-145 infusion resume durvalumab 1500 mg IV Q4W until progression or unacceptable toxicity. Patients unable to receive LN-145 are allowed to receive durvalumab alone. Patients ≥ 18 years of age must have confirmed stage III/IV NSCLC and have received ≥1 line of prior systemic therapy, excluding anti-PD-1/anti-PD-L1. Other major eligibility criteria include: minimum of 2 tumor lesions, adequate organ function, and ECOG PS 0 or 1. Primary endpoints are efficacy as defined by ORR and safety of LN-145 as a single agent or in combination with durvalumab; secondary endpoints are DOR and PFS per RECIST 1.1, and OS. Key exploratory objectives include CR rate, DCR, immune correlates of response, and HRQoL. Clinical trial information: NCT03419559.

TPS3108 Poster Session (Board #318b), Mon, 8:00 AM-11:30 AM

Evaluating immune checkpoint inhibition in solid tumor patients with homologous recombination repair deficiency. *First Author: Fernando Manuel Vargas Madueno, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Recent studies have shown that patients with mismatch repair deficiency have an increased response rate to immune checkpoint inhibitors (ICI). This led to the tissue-agnostic FDA approval of pembrolizumab (PEM). Stemming from this, we are investigating the interplay between homologous recombination (HR) repair deficiency, another mechanism of DNA repair, and solid tumor response to ICI using an all-inclusive functional immunofluorescence assay of the Fanconi Anemia pathway (FATSI) that we developed and which can be performed in paraffin embedded tumors. **Methods:** This is a phase 2 open-label single center trial evaluating the role of PEM in patients with metastatic solid tumors who have progressed on first-line standard of care chemotherapy and for whom PEM does not have an FDA approved indication. FATSI will be performed in all patients, as well as stool analyses for microbiome composition evaluation. We hypothesize that FATSI negative tumors will be associated with improved responses. Other eligibility criteria include measurable disease by imaging, 18 years of age or older and no previous exposure to ICI. Patients with known microsatellite instability (MSI) high tumors are not eligible. The primary objective is to evaluate the immune-related objective response rate (iORR) achieved in patients with FA Repair Pathway functionally competent and functionally deficient tumors. Secondary objectives include 20-week progression free survival and overall survival. Other exploratory objectives include evaluation of the mutation load, markers of neo-antigenicity, T cell receptor clonotype analyses (before and after treatment) and alterations in HR repair genes. We will utilize a two-stage phase II trial design to detect an iORR $\geq$ 20% in the whole population tested vs. the null hypothesis that the true iORR $\leq$5%, representing a response by chance alone, or other infrequent unknown mechanism. An interim analysis requires that at least 2 of the first 20 evaluable patients enrolled have an objective response. If this occurs, we will accrue 19 additional patients for a total of 39. Enrollment is ongoing and seven patients are currently on treatment. Clinical trial information: NCT03274661.

TPS3109 Poster Session (Board #319a), Mon, 8:00 AM-11:30 AM

Phase 1b/2 study of nivolumab in combination with an anti–IL-8 monoclonal antibody, BMS-986253, in a biomarker-enriched population of patients with advanced cancer. *First Author: Ignacio Melero Bermejo, Clinica Universidad de Navarra, Pamplona, Spain*

Background: Interleukin 8 (IL-8) is a chemokine that has been suggested to play a predominant role in tumor immune escape by promoting an immunosuppressive tumor microenvironment (TME). High levels of serum IL-8 are associated with a poor prognosis in various tumors (Sanmamed, MF, et al. Clin Cancer Res. 2014;20:5697-5707), such as melanoma, non-squamous small cell lung cancer (NSCLC), and renal cell carcinoma, and decreases in serum IL-8 levels have been suggested to be associated with response to antiPD-(L)1 therapy with nivolumab in a small cohort of pts with melanoma and NSCLC (Sanmamed, MF et al. Ann Oncol. 2017;28:1988-1995). Preclinical studies showed synergetic antitumor activity by combining anti-CXCR2 with antiPD-1 vs either agent alone in mouse. BMS-986253 is a fully human-sequence IgG1κ antiIL-8 monoclonal antibody that abrogates signaling through both IL-8 receptors (CXCR1 and CXCR2), resulting in a complete blocking of IL-8 mediated pathway, and as such, can be used to assess the mechanistic role of this pathway in IO resistance. Here we describe a phase 1b/2 study of the combination of BMS-986253 plus nivolumab in a biomarker-enriched population of pts with advanced cancers (NCT03400332). **Methods:** This is a 2-part study with an enrollment of $\approx$ 260 target selected pts, aged $\geq$ 18 y with advanced solid tumors. Pts must have $\geq$ 1 measurable lesion at baseline per RECIST v1.1. Outcomes include safety, tolerability, efficacy, pharmacokinetics, immunogenicity of BMS-986253 plus nivolumab, and measurement of serum IL-8 levels at baseline and during treatment. This study will also explore various peripheral and intra-tumor pharmacodynamic effects of blocking IL-8 in a target selected pt population. Clinical trial information: NCT03400332.

TPS3110 Poster Session (Board #319b), Mon, 8:00 AM-11:30 AM

A phase 3, randomized, open-label, multicenter study to compare the efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma. *First Author: Shukui Qin, People's Liberation Army (PLA) 81 Hospital, Nanjing, China*

Background: Advanced hepatocellular carcinoma (HCC) accounts for 70% of diagnosed HCC. Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). Furthermore, tislelizumab was specifically engineered to minimize F_cgR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors, including HCC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been established for tislelizumab. **Methods:** This global, phase 3, randomized, multicenter, non-inferiority study (NCT03412773) was designed to evaluate the efficacy and safety of tislelizumab compared with sorafenib as a first-line treatment of advanced HCC. Adult patients, aged $\geq$18 years, with unresectable, histologically confirmed HCC, an ECOG score $\leq$1, Child-Pugh A classification, BCLC Stage C disease or BCLC Stage B disease that has relapsed after locoregional therapy, and who have not received prior systemic therapy, are being enrolled. Approximately 640 patients from 100 international centers will be randomized (1:1) to receive tislelizumab 200 mg IV Q3W or sorafenib 400 mg orally BID. The primary outcome of this non-inferiority study is overall survival (OS) of patients treated with tislelizumab compared with OS of patients treated with sorafenib; secondary outcomes include objective response rate, progression-free survival, duration of response, time to progression, and quality-of-life outcomes. Safety/tolerability assessments include monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. Clinical trial information: NCT03412773.

TPS3111 Poster Session (Board #320a), Mon, 8:00 AM-11:30 AM

A phase 3, randomized, open-label study to compare the efficacy of tislelizumab (BGB-A317) versus chemotherapy as second-line therapy for advanced unresectable/metastatic esophageal squamous cell carcinoma (ESCC). *First Author: Lin Shen, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Approximately 40% of patients (pts) with esophageal cancer are diagnosed with advanced unresectable or metastatic disease; the 5-year survival rate for advanced disease is $<$ 5%. Inhibition of programmed cell death protein-1 (PD-1) has demonstrated promising antitumor activity and manageable safety in pts with advanced unresectable or metastatic ESCC. Tislelizumab (also known as BGB-A317), a humanized IgG4 monoclonal antibody, has high affinity and specificity for PD-1. Tislelizumab was specifically engineered to minimize F_cgR binding on macrophages, thus abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and had preliminary antitumor effects in pts with solid tumors, including ESCC. A recommended phase 2 dose of 200 mg administered IV every 3 weeks (Q3W) has been established for tislelizumab. **Methods:** This phase 3, randomized study (NCT03430843) was designed to evaluate the efficacy, safety, and tolerability of tislelizumab compared with chemotherapy for second-line treatment of advanced unresectable/metastatic ESCC. Adult pts, aged $\geq$18 years, with histologically or cytologically confirmed ESCC that has progressed with first-line therapy, have $\geq$1 measurable/evaluable lesion, and have an Eastern Cooperative Oncology score $\leq$1 will be enrolled. Approximately 450 pts will be randomized (1:1) to receive either tislelizumab 200 mg IV Q3W or investigator-chosen chemotherapy (paclitaxel 135–175 mg/m^2 IV Q3W or 100 mg/m^2 IV weekly for 6 weeks with 1 week of rest [Japan only], docetaxel 75 mg/m^2 or 70 mg/m^2 IV Q3W, or irinotecan 125 mg/m^2 IV Q3W). Overall survival is the primary endpoint; secondary endpoints include objective response rate, progression free survival, duration of response, and health-related quality-of-life outcomes. Safety/tolerability will be assessed by monitoring adverse events (AEs), including immune-related AEs, as well as physical examinations, vital signs, and electrocardiograms. Clinical trial information: NCT03430843.

TPS3112 Poster Session (Board #320b), Mon, 8:00 AM-11:30 AM

A phase 3, open-label, multicenter, randomized study to investigate the efficacy and safety of tislelizumab, an anti-PD-1 antibody, versus docetaxel in patients with non-small cell lung cancer who have progressed on a prior platinum-containing regimen. *First Author: Dingzhi Huang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers and has a poor prognosis in later stages. Although lung cancers are not typically immunogenic, recent studies of immune checkpoint inhibitors have shown efficacy in patients with advanced NSCLC. Tislelizumab (also known as BGB-A317) is a humanized, IgG4 monoclonal antibody with high affinity and binding specificity for programmed cell death receptor-1 (PD-1). Furthermore, tislelizumab was specifically engineered to minimize F_cgR binding on macrophages, thereby abrogating antibody-dependent phagocytosis, a potential mechanism of T-cell clearance. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with solid tumors, including NSCLC. A recommended phase 3 dose of 200 mg administered intravenously (IV) every 3 weeks (Q3W) has been identified for tislelizumab. **Methods:** This phase 3, randomized, multicenter study (NCT03358875) was designed to evaluate the efficacy, safety, and tolerability of tislelizumab compared with docetaxel in the second- or third-line treatment of NSCLC. Adult patients aged $\geq$18 years with locally advanced or metastatic NSCLC (Stage IIIB or IV, squamous or non-squamous), who have progressed on $\geq$1 prior platinum-containing therapy, have adequate hematologic and end-organ function, and an ECOG score $\leq$1 are eligible to enroll. Patients with a known EGFR sensitizing/driver mutation or ALK rearrangement are excluded. Approximately 800 patients from ~100 global clinical sites will be randomized (2:1) to receive tislelizumab 200 mg IV Q3W or docetaxel 75 mg/m^2 IV Q3W. Randomization will be stratified by histology, line of therapy, and PD-1 ligand tumor cell expression ($<$ 25% vs $\geq$25% [PD-L1$^+$]). Co-primary endpoints are overall survival in the intent-to-treat population and in the PD-L1$^+$ population; secondary endpoints include objective response rate and health-related quality-of-life outcomes. Clinical trial information: NCT03358875.

TPS3113 Poster Session (Board #321a), Mon, 8:00 AM-11:30 AM

Phase 1/2 study investigating safety, tolerability, pharmacokinetics, and preliminary antitumor activity of anti-PD-L1 monoclonal antibody bgb-A333 alone and in combination with anti-PD-1 monoclonal antibody tislelizumab in patients with advanced solid tumors. *First Author: Jayesh Desai, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Australia*

Background: Programmed cell death-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), play critical roles in the immune modulation of tumor progression. Tislelizumab is a humanized IgG4 monoclonal antibody against PD-1. A first-in-human, phase 1A/1B study (NCT02407990) demonstrated that single-agent tislelizumab was generally well tolerated and showed evidence of antitumor activity in patients with advanced solid tumors at the recommended dose of 200 mg administered every 3 weeks (Q3W). BGB-A333 is a humanized IgG1 monoclonal antibody against PD-L1 which increased functional activities of human T cells in *in vitro* studies, and showed antitumor activity in various cancer xenograft models. BGB-A333 blocks the interaction between PD-L1 and CD80 (B7-1), which in turn release the inhibitory signals to T-cells, enhances T-cell expansion, and prevents T-cell energy induction. Therefore, a combination of anti-PD-1 and anti-PD-L1 can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments. **Methods:** This open-label study (NCT03379259) consists of two phases, each phase consisting of two parts. Phase 1 is designed to investigate the safety and tolerability of the BGB-A333 RP2D alone and in combination with tislelizumab. Phase 1A (BGB-A333 dose escalation) will follow a 3+3 design to establish the RP2D of BGB-A333. Phase 1B (combination dose confirmation) explores safety and tolerability of IV BGB-A333 (determined from dose escalation) in combination with IV tislelizumab (200 mg Q3W). Phase 2 is designed to evaluate the antitumor activity of BGB-A333 alone and in combination with tislelizumab. Phase 2A (BGB-A333 dose expansion) will enroll patients into two cohorts: non-small cell lung cancer and urothelial carcinoma. Phase 2B (combination dose expansion) will enroll patients with specific tumor types, which will be chosen based on data from phase 2A and other studies. The primary endpoint of the phase 2 study is overall response rate. Clinical trial information: NCT03379259.

TPS3114 Poster Session (Board #321b), Mon, 8:00 AM-11:30 AM

A phase 3, double-blind, randomized study of pamiparib versus placebo as maintenance therapy in patients with inoperable, locally advanced, or metastatic gastric cancer that responded to platinum-based first-line chemotherapy. *First Author: Fortunato Ciardiello, University of Campania "Luigi Vanvitelli", Naples, Italy*

Background: Gastric cancer is the fifth most common cancer, and is the third leading cause of cancer deaths worldwide. A subset of gastric cancers exhibit platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) are involved in DNA damage repair, and their inhibition is cytotoxic for cells with HRD. Pamiparib (previously known as BGB-290) is a selective PARP1/2 inhibitor that crosses the blood-brain barrier, has shown potent DNA–PARP trapping, and has demonstrated robust antitumor activity in preclinical models. In early phase clinical studies (NCT02361723; NCT03333915), pamiparib was generally well tolerated and showed promising antitumor activity. These studies also established 60 mg orally twice daily as the recommended pivotal dose. **Methods:** This double-blind, placebo-controlled, randomized, multicenter phase 3 study (NCT03427814) conducted in Asia, Australia, Europe, and North America is designed to compare the efficacy, safety, and tolerability of pamiparib with placebo as maintenance therapy in ~540 patients with advanced gastric cancer who have responded to first-line, platinum-based chemotherapy. Patients who are $\leq$8 weeks after their last platinum dose of first-line chemotherapy will be randomized 1:1 to receive either pamiparib 60 mg twice daily or placebo. Patient randomization will be stratified by genomic loss of heterozygosity status (ie, high versus low), region, and ECOG status. Radiologic assessments will be centrally evaluated per RECIST every 8 weeks after first dose. The primary endpoint is progression-free survival; key secondary endpoints include safety/tolerability, overall survival, objective response rates, and duration of response. Clinical trial information: NCT03427814.

TPS3115 Poster Session (Board #322a), Mon, 8:00 AM-11:30 AM

PROPEL: A phase 1/2 trial of NKTR-214 (CD122-biased agonist) combined with anti-PD-1 (pembrolizumab) or anti-PD-L1 (atezolizumab) in patients (pts) with advanced solid tumors. *First Author: Daniel A. Vaena, West Cancer Center, Germantown, TN*

Background: NKTR-214 is an investigational cytokine designed to target CD122 (IL-2Rβ) expressed on immune cells (CD8$^+$ T cells and NK cells) in order to expand these tumor-killing cells. NKTR-214 monotherapy increases newly proliferative CD8$^+$ T cells and NK cells in tumors and increases cell surface PD-1 and PD-L1 expression, demonstrating a potentially synergistic mechanism with anti-PD-1 therapy. NKTR-214 plus nivolumab resulted in rapid tumor responses in pts with metastatic melanoma (mM), non-small cell lung cancer (mNSCLC), and renal cell carcinoma. Given the early efficacy data and favorable safety profile of NKTR-214 plus nivolumab, PROPEL will evaluate the clinical benefit, safety and tolerability of NKTR-214 combined with pembrolizumab or atezolizumab. **Methods:** PROPEL (NCT03138889) will enroll approximately 60 pts in 2 separate arms concurrently. The first arm will evaluate NKTR-214 plus pembrolizumab in up to 30 select pts with locally advanced or mM, mNSCLC, or locally advanced or metastatic urothelial bladder cancer (UBC) within the FDA-approved pembrolizumab indications and dosage regimen. The second arm will evaluate NKTR-214 plus atezolizumab in up to 30 select pts with locally advanced or metastatic UBC or mNSCLC within the FDA-approved atezolizumab indications and dosage regimen. NKTR-214 is administered intravenously over 30 ($\pm$5) minutes every 3 weeks in an outpatient setting; the first studied dose of NKTR-214 will be 0.006 mg/kg. The primary objectives are to evaluate safety and tolerability and to define the maximum tolerated dose or recommended phase 2 dose of NKTR-214 combined with pembrolizumab or atezolizumab. The secondary objectives are to evaluate preliminary anti-tumor activity and efficacy by assessing overall survival and progression-free survival. In addition, the study will assess the immunological effects of treatment and the association between efficacy measures and PD-L1 expression in tumors. Treatment may continue beyond progression if there is clinical benefit as determined by the investigator. Enrollment is ongoing in the U.S. Clinical trial information: NCT03138889.

TPS3116 Poster Session (Board #322b), Mon, 8:00 AM-11:30 AM

A phase Ib study evaluating the safety and tolerability of durvalumab in combination with eribulin in patients with HER2-negative metastatic breast cancer and recurrent ovarian cancer. *First Author: Chrystal Ann Landry, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Recent studies have revealed only modest responses to single-agent immune checkpoint blockade in metastatic breast cancer (MBC) and recurrent ovarian cancer (ROC) patients as compared to other more immunogenic tumors. Methods to improve response employing the rational combination of cytotoxic chemotherapy with immunotherapies have shown promise. Eribulin (E), a novel microtubule inhibitor, is an effective single-agent chemotherapy in metastatic breast cancer with promising results observed in ovarian cancer patients. Preclinical studies have shown that E may induce intratumoral vascular remodeling through novel anti-vascular activity. It is hypothesized that the combination of E with durvalumab (D), a PD-L1 inhibitor, will result in increased T cell infiltration and activation leading to improved systemic and tumor site immune responses. **Methods:** This is a single center Phase Ib study to evaluate the safety, dose-limiting toxicity (DLT) rate, and the recommended phase II combination dose of E with D. Patients must have metastatic HER-2 negative MBC or ROC, adequate organ function, no prior treatment with E or anti-PD-1/PD-L1, and a history of prior metastatic therapy with no more than 5 prior lines. A 3+3 dose-escalation design is employed to evaluate 3 dose levels of E given by intravenous (IV) injection. The starting dose is 1.1mg/m^2 with dose escalation to 1.4mg/m^2 on day 1 and day 8 of a 21-day cycle. In the event that multiple DLTs are observed at the initial dose level, a dose de-escalation to 0.7 mg/m^2 will be utilized. A fixed dose of D (1.12g by IV) is given on day 1 of each cycle. Secondary objectives include preliminary evaluation of anti-tumor activity as measured by objective response rate, progression-free survival, and overall survival. Responses will be assessed per iRECIST every 9 weeks. Patients will be treated until unacceptable toxicity or disease progression. Optional blood samples will be collected at various time points for quantification and characterization of immune responses and evaluation for potential biomarkers of response. We estimate accrual of 6-12 patients. Clinical trial information: NCT03430518.

TPS3117 Poster Session (Board #323a), Mon, 8:00 AM-11:30 AM

An open label phase I study to evaluate the safety and efficacy of OBP-301 with pembrolizumab in patients with advanced solid tumors. *First Author: Takashi Kojima, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: PD-1 blockade showed promising efficacy in facilitating tumor shrinkage for broad type of cancer patients, but objective response rates are very limited. The antitumor potential of oncolytic adenoviruses has been demonstrated in preclinical and clinical studies. In addition to the specific killing of cancer cells via oncolytic virus, these agents prompt the immune system to stimulate an antitumor immune response. OBP-301 is an oncolytic adenovirus in which gene is modified to be able to selectively replicate in cancer cells by introducing human telomerase reverse transcriptase (hTERT) promotor. Further antitumor effect will be expected activating of two different antitumor immunity by using OBP-301 in combination with pembrolizumab. Therefore, we initiated phase I study to evaluate the safety and efficacy of OBP-301 with pembrolizumab. **Methods:** The major eligibility criteria is patients with advanced or metastatic solid tumor not responded to or intolerant of standard chemotherapies, and with possibility of intratumoral injection. History of anti PD-1/PD-L1/PD-L2 antibody treatment is acceptable. Phase Ia part was designed to determine the recommended dose in a "3+3" cohort-based dose escalation design of OBP-301 (1x10^{10}VP on cohort 1, 1x10^{11}VP on cohort 2 and 1x10^{12}VP on cohort 3) with pembrolizumab (200mg/body q3w). OBP-301 is administered at day1, day15, and, Day29 by intratumoral injection and pembrolizumab is administered at day 8 and thereafter every 3 weeks. Primary endpoint is dose limiting toxicity. Secondary endpoint is response rate, progression free survival, and rate of adverse event. Phase Ib part was designated to evaluate the safety and efficacy of the recommended dose OBP-301 selected in phase Ia part in combination with pembrolizumab in 10 patients. We will also investigate biomarker study using paired samples of both tumor biopsy and blood. The patient enrollment has been started in October 2017. Clinical trial information: NCT03172819.

TPS3118 Poster Session (Board #323b), Mon, 8:00 AM-11:30 AM

A phase I/II Trial of CRISPR-Cas9-mediated PD-1 knockout Epstein-Barr virus cytotoxic lymphocytes (EBV-CTLs) for advanced stage EBV associated malignancies. *First Author: Jia Wei, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: EBV associated malignancies exhibits high amplification of PD-L1 as distinguished from EBV non-associated malignancies (Kim et al. Gastroenterology 2015; Chen et al. Clinical Cancer Research 2013). The up-regulation of PD-L1 restricts antitumor effect of EBV-CTLs by immune tolerance and results in poor prognosis of patients. Our previous work has generated PD-1-disrupted CTLs by CRISPR-Cas9 system which could up-regulate IFN-γ production and enhance cytotoxicity in tumor cell lines and mouse model (Su et al. Oncoimmunology 2016). **Methods:** This phase I/II prospective single center clinical study (clinicaltrials.gov NCT03044743) was designed to evaluate the safety of PD-1 knockout EBV-CTLs in treating EBV positive advanced stage malignancies. Patients included should be pathologically verified EBV positive stage IV gastric carcinoma, nasopharyngeal carcinoma or lymphoma progressed after standard treatment with measurable lesions. Patients will be divided into three groups and receive 2 to 4 cycles of cell therapy according to their tolerance. PD-1 knockout EBV-CTLs from autologous origin will be generated and 2 x 10^^{7}/kg of specific T cells will be infused in one cycle. Each cycle is divided into three administrations, with 20%, 30% and 50% respectively. To modify immune microenvironment, Fludarabine at 30mg/m^2 and cyclophosphamide at 300mg/m^2 will be administered 3 days (intravenous injection, i.v.) before cell infusion. Interleukin-2 will be given daily (i.v.) from the first day of the cell infusion for 5 consecutive days at the dose of 4000,000 international unit (IU)/day to sustain the survival of infused T cells. The adverse events will be evaluated after each cycle by Common Terminology Criteria for Adverse Events (CTCAE v4.0) as primary endpoint. Progression-free survival (PFS), the duration of the normalization of tumor marker and immunological markers will be evaluated as the secondary endpoints. Immunological markers will continuously be examined every two cycles. Clinical trial information: NCT03044743.

TPS3119 Poster Session (Board #324a), Mon, 8:00 AM-11:30 AM

Phase Ib trial of nivolumab combined with metformin for refractory/recurrent solid tumors. *First Author: Toshio Kubo, Center for Clinical Oncology, Okayama University Hospital, Okayama, Japan*

Background: Although immune-checkpoint inhibitors (ICIs) have shown significant survival benefits in several cancers, optimal outcomes have been limited to subsets of patients. We obtained complete regression of an engrafted solid tumor with metformin in a murine syngeneic model. This effect could not be obtained in T cell-deficient SCID mice. These findings suggested that metformin induced immune-mediated reactions. The combination of anti-PD-1 antibody (nivolumab) and metformin resulted in significant tumor regression. This combination also increased the number of tumor-infiltrating CD8 T cells producing IL-2, TNF-α, and IFN-γ, suggesting that this combination induced clinically synergistic antitumor effects. Based on these results, we initiated the following study. Objectives: To investigate the safety, efficacy, and pharmacokinetics of combined treatment with metformin and nivolumab. **Methods:** This was an open-label, phase Ib trial consisting of two parts (part 1 and 2). The recommended dose of metformin combined with nivolumab was determined in part 1, and the safety and efficacy at the optimal dose were examined in part 2. The inclusion criteria were as follows: histologically or cytologically diagnosed refractory/recurrent solid tumors in part 1, and non-small cell lung cancer or pancreatic cancer that was refractory to standard primary treatment in part 2; use of naïve ICIs; a performance status of 0 or 1; $>$ 20 years of age; and adequate organ functions. The primary endpoints were safety, maximum tolerated dose (MTD), and dose limiting toxicity (DLT) in part 1, and pharmacokinetics and adverse event profiles in parts 1 and 2. The secondary endpoints were efficacy, tumor shrinkage, and progression-free survival. Nivolumab (3 mg/kg) was administered intravenously every 2 weeks. In part 1, metformin was started at 750 mg/day, and increased by 750 mg/day up to 2,250 mg/day. The MTD and recommended dose were determined by the 3+3 cohort method. The DLT evaluation period was 4 weeks from the start of administration. A total of 9–18 patients were enrolled in part 1, and 30 patients in part 2. Enrollment began in 2017 and will be complete by 2019. The UMIN registration number is 000028405. Clinical trial information: 000028405.

TPS3120 Poster Session (Board #324b), Mon, 8:00 AM-11:30 AM

An open-label, multidrug, biomarker-directed, multicentre phase II umbrella study in patients with non-small cell lung cancer, who progressed on an anti-PD-1/PD-L1 containing therapy (HUDSON). *First Author: John Heymach, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint inhibitor (ICI) containing regimens have significantly improved survival outcomes in first- and second-line non-small cell lung cancer (NSCLC). However, the majority of patients do not respond or have non-durable responses leading to a new ICI-resistant population. HUDSON addresses the urgent need to identify treatments and understand ICI-resistance for this emerging population. **Methods:** HUDSON is a multicentre, international multi-arm umbrella study that will 1) evaluate therapies to reverse ICI-resistance and 2) define mechanisms of ICI-resistance in NSCLC patients who have progressed following standard-of-care platinum and ICI based therapies. HUDSON is a platform study that consists of two groups; a biomarker matched and a biomarker non-matched group. Within the biomarker matched group, different cohorts will test 1) homologous recombination repair (HRR) defects and 2) LKB1 aberration for response to durvalumab and olaparib (PARP inhibitor), 3) ATM deficiency for response to durvalumab and AZD6738 (ATR inhibitor) and 4) RICTOR amplification for response to durvalumab and vistusertib (mTORC1/2 inhibitor). In the biomarker non-matched group, cohorts will test durvalumab in combination with either i) olaparib, ii) AZD9150 (STAT3 inhibitor) or iii) AZD6738. New cohorts will be added as new translational hypotheses are established. Translational research will be performed on serial peripheral blood samples (including ctDNA) and tumour biopsies. HUDSON enrolls ICI-resistant/refractory patients in a signal searching manner. Biomarker matched and non-matched groups will be opened simultaneously, and all eligible patients can be allocated a treatment option irrespective of their tumour profile. Enrolment is ongoing, Clinical trial information: NCT03334617.

TPS3121 Poster Session (Board #325a), Mon, 8:00 AM-11:30 AM

Trial in progress: Platform phase 1 study investigating the safety of stereotactic body radiotherapy with immuno-oncology agents for the treatment of multiple metastases in advanced solid tumors. *First Author: Corey Christian Foster, Department of Radiation & Cellular Oncology, The University of Chicago Medicine, Chicago, IL*

Background: Stereotactic body radiotherapy (SBRT) and immuno-oncology (IO) have been associated with improved oncologic outcomes when given as monotherapy for advanced solid tumors. Furthermore, preclinical studies have suggested synergistic interactions between SBRT and IO agents with enhanced anti-tumor activity possibly mediated by the induction of CD8+ T-cells. Additionally, patients with advanced melanoma receiving dual IO therapy in the absence of SBRT experienced longer overall survival than patients receiving single-agent IO therapy. Given these findings, it is reasonable to hypothesize that dual IO therapy in combination with SBRT may be more efficacious than any of these treatments alone. However, the safety of multiple IO agents given in combination with SBRT is unknown. **Methods:** The study is a single-center, phase 1, open-label, two-arm, non-randomized clinical trial for patients with advanced solid tumors and at least 1 measurable site of disease after receiving $\leq$ 3 prior systemic therapies. Enrolled patients receive either (1) concurrent nivolumab (anti-PD-1, 240 mg IV flat dose every 2 weeks) + urelemab (anti-CD137, 8 mg flat dose IV every 4 weeks) + SBRT or (2) concurrent nivolumab (240 mg IV flat dose every 2 weeks) + cabiralizumab (anti-CSF1R, 4 mg/kg IV every 2 weeks) + SBRT. SBRT is delivered to 1-4 sites to a maximum target volume of 65 cc/site. Dual IO therapy is continued until progression or fulfilment of discontinuation criteria. We expect 42-72 patients to be enrolled on study until 5 separate organ sites receiving SBRT have accrued at least 6 participants for evaluation of dose-limiting toxicity at the starting dose and a de-escalated dose if necessary. The primary endpoint is dose-limiting toxicity defined as $>$ 33% rate of grade $\geq$3 toxicity. Secondary endpoints include response rate, PFS, and OS. Exploratory analyses include investigation of candidate biomarkers (e.g., PD-L1 status, circulating tumor DNA, gut microbiome data) for treatment efficacy. Enrollment is ongoing. Clinical trial information: NCT03431948.

TPS3122 Poster Session (Board #325b), Mon, 8:00 AM-11:30 AM

Expansion cohort of partially irradiated tumors on a phase 1 trial of pembrolizumab and ablative radiotherapy. *First Author: Sandeep Ramesh BHave, University of Chicago Medicine, Chicago, IL*

Background: Preclinical studies suggest multi-organ site ablative radiation therapy (MOSART) may enhance systemic anti-tumor response through altering the balance of innate and adaptive immunity within the tumor microenvironment and through direct tumor debulking. Previously, we opened a phase I study to evaluate the safety and efficacy of the combination of pembrolizumab with MOSART for patients with metastatic solid tumors. In the first cohort of 73 patients analyzed, the combined therapies were safe in all organ systems studied with no radiation dose reductions (Luke & Lemons et al. J Clin Oncol 2018, in press). Interestingly, large partially irradiated tumors exhibited control similar to smaller completely irradiated tumors (93% vs. 96% at 6 months, p = 0.32). In December 2017, we opened an expansion cohort to formally test the secondary hypothesis that partially irradiated tumors exhibit local control similar to completely irradiated tumors when combined with immunotherapy. **Methods:** We are accruing patients with metastatic disease progressing on standard of care treatment, two or more lesions amenable to MOSART, and have at least one lesion greater than 65cc. Enrollment is currently at six of forty planned subjects, and is actively accruing patients. MOSART dosing is based on NRG BR-001 (30 Gy in 3 fractions for osseous and spinal lesions; 45 Gy in 3 fractions for peripheral lung, liver, and abdominal-pelvic lesions; 50 Gy in 5 fractions for central lung, mediastinal, and cervical lesions). At least two lesions are targeted for each patient and not all sites of disease are treated. The maximum gross tumor volume (GTV) that is completely irradiated is 65cc. Partial tumor irradiation is administered to lesions $>$ 65cc where the target volume is created by performing volume contraction down to 65 cc within the initial radiographically defined GTV. Pembrolizumab 200mg IV Q3W is to be initiated within seven days after final MOSART treatment. RECIST 1.1 will be used used to assess radiated tumor progression. Control (defined as CR, PR, or SD) will be calculated by the Kaplan Meier method and compared between partially irradiated tumors and completely irradiated tumors with the log-rank test. Clinical trial information: NCT02608385.

TPS3123 Poster Session (Board #326a), Mon, 8:00 AM-11:30 AM

A multicenter phase 2 study of nivolumab combined with ipilimumab in patients with pediatric solid tumors in adulthood (GETHI021). *First Author: Xabier Mielgo, Hospital Universitario Fundación Alcorcón, Alcorcón, Spain*

Background: Solid pediatric tumors that appear in adulthood are a heterogeneous group that share some characteristics such as low incidence, lack of standard therapeutic options and reduced survival. Pediatric cancers usually originate from embryonic cells that likely present genetic alterations and epitopes different from mature cells. These may be targeted by the immune system, if properly stimulated by immune checkpoint inhibitors (ICI). Thus, ICIs could achieve a significant activity in these tumors. Here, we present the first phase II clinical trial of nivolumab and ipilimumab in this setting. **Methods:** A multicenter, open-label, single arm Phase II study was designed to evaluate the efficacy, safety and tolerability of the combination of nivolumab and ipilimumab in adult patients ($\geq$18 years) with locally advanced or metastatic childhood malignancies that have progressed or are not candidates to standard therapy. The Spanish Group for Infrequent and Orphan Tumors (GETHI) is the sponsor of the study and 15 associated Spanish centers are participating. Main inclusion criteria are: adult subjects, ECOG PS $\leq$2, no prior anti-PD1 or anti-CTLA4 therapy. Treatment schedule is nivolumab 3 mg/kg IV q2w + ipilimumab 1 mg/kg IV q6w for 6 months or until RECIST v1.1 progression/unacceptable toxicity. Study treatment may continue beyond disease progression and may be extended for a maximum of 24 months if clinical benefit exists. Primary endpoint is objective overall response rate (ORR) according to RECIST v1.1 criteria. Secondary endpoints are toxicity profile, quality of life, PFS and OS. In addition, a comprehensive molecular study to identify potential biomarkers will be performed. Following Simon optimal two-stage design, the first stage includes 30 evaluable patients If ORR is $>$ 10%, the study will continue to a second stage until 89 evaluable patients are recruited. The null hypothesis will be rejected if ORR $\geq$20%. This design yields a type I error rate of 0.05 and power of 80% when true response rate is 0.20. Accrual started in July 2017 and 26 patients have been enrolled up to January 2018. Scheduled recruitment period is 18 months. EudraCT number: 2016-003946-99. Clinical trial information: 2016-003946-99.

TPS3124 Poster Session (Board #326b), Mon, 8:00 AM-11:30 AM

Regorafenib and nivolumab combination therapy for advanced and metastatic solid tumors: Phase I clinical trial (EPOC1603). *First Author: Shota Fukuoka, Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Immune checkpoint inhibitors (CPIs) have shown promising efficacies in several types of malignancies. However, still around half of patients with most tumor types experienced disease progression at the initial tumor assessment. One possible reason for resistance to CPIs is suspected to be based on interaction with cancer niche which include suppressive immune cells such as myeloid-derived suppressor cells (MDSC), regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). Previous in vivo study showed that selective inhibition of VEGF pathway with anti-VEGF antibody or anti-VEGF tyrosine kinase inhibitors (TKIs) suppress tumor growth and decrease MDSC, Tregs and TAMs. In addition, suppression of stem cell factor (SCF)-mediated signaling though c-Kit also decreases MDSC expansion and tumor angiogenesis, which may overcome resistance to CPIs. Therefore, we initiated phase I study to assess efficacy and safety for the combination of nivolumab and regorafenib as a multi-kinase inhibitor targeting both VEGF and SCF signaling. **Methods:** The main eligibility criteria is patients with unresectable recurrent solid tumors who are refractory or intolerant to standard chemotherapy. Primary objective is to examine the safety and tolerability of repeated dosing of regorafenib and nivolumab and to investigate the maximum tolerated dose (MTD) and recommended dose (RD). Dose escalation cohort was designed to determine the recommended expansion cohort dose in a "3+3" cohort-based dose escalation design of regorafenib (80 mg once dairy for 21 days on 7 days off on level 1, 120 mg on level 2 and 160 mg on level 3) with nivolumab (3.0 mg/kg q2w). In expansion cohort, approximately 30 patients with selected solid tumors such as gastric, coloretcal, hepatocellular cancer will be enrolled at the RD. We also investigate several biomarkers using pre- and post-treatment samples from both biopsied tumor and blood. First three patients were enrolled and treated in level 1 as of January 2018. Clinical trial information: NCT03406871.

TPS3125 Poster Session (Board #327a), Mon, 8:00 AM-11:30 AM

A phase I/II study of regorafenib (R) plus avelumab (A) in digestive tumors. *First Author: Sophie Cousin, Institut Bergonié, Bordeaux, France*

Background: Several preclinical studies have shown that simultaneous blockade of programmed death(PD) 1/PD-L1 and neoangiogenesis induces synergistic anti-tumour effect *in vivo*. R is a multikinase inhibitor approved for the treatment of metastatic colorectal (CRC) and gastro intestinal stromal tumor (GIST). A is a PD-L1 inhibitor approved for the treatment of Merkel carcinoma. We hypothesized that R in association with A could be synergistic and feasible in patients (pts) with tumors of the digestive tract. **Methods:** This is a multicenter, prospective phase I/II trial assessing R+A in 4 cohorts of pts with advanced pretreated: A) CRC not MSI-H or MMR-deficient, B) GIST, C) Oesophageal/gastric carcinoma, D) Biliary tract/hepatocellular carcinoma. Primary objectives are to determine the recommended phase II dose (RP2D) of R+A in phase I, and assess the best overall response defined as per RECIST v1.1 with A+R in phase II. In phase I, 2 doses of R will be investigated: 120mg, 160mg, daily, 3 weeks on/1 week off with fixed dose of A: 10mg/kg every 2 weeks. In phase II, all pts will received the RP2D of R with A. Main eligibility criteria are: -adult pts with metastatic, histologically confirmed tumor of 1 of the 4 cohorts, with measurable, progressive disease, after $\geq$ 1 previous line of systemic therapy. Primary endpoint is toxicity according to NCI-CTCAE v4.0 and incidence rate of DLT at each dose level during the first 28 days (I); antitumor activity in terms of best overall response (II). Secondary endpoints encompass: Objective Response Rate (ORR), Progression Free Survival (PFS), Growth modulation index, 6-months,1-year PFS and Overall Survival, PKs, Pharmacodynamics on (I) mandatory blood samples at baseline/on treatment, archived tumor tissue, (II) on optional biopsy at Baseline/after 4 weeks of R+A focusing on TAM, Lymphocytes infiltrates, PD-L1, VEGFR, PDGFR, HIF1alpha expression. Phase I will follow a classical 3+3 design with 2 dose levels and a maximum of 12 pts. A Bayesian approach will be used in phase II, with a maximum sample size of 50 pts/cohort. At each update of interim analysis, a stopping rule for inefficacy will recommend stopping the trial if there is a high predictive probability ($\geq$80%) that ORR is $<$ or = to the futility bound p0 = 20%. Clinical trial information: NCT03475953.

TPS3126 Poster Session (Board #327b), Mon, 8:00 AM-11:30 AM

An open-label, phase 2 study of nivolumab in combination with either rucaparib, docetaxel, or enzalutamide in men with castration-resistant metastatic prostate cancer (mCRPC; CheckMate 9KD). *First Author: Karim Fizazi, Gustave Roussy, Villejuif, France*

Background: Although multiple new agents have been approved for mCRPC over the last decade, median survival remains unsatisfactory at ~12-35 months. Immunotherapy targeted solely at programmed death-1 (PD-1)/PD-1 ligand-1 (PD-L1) interactions has shown limited evidence of antitumor activity in patients (pts) with prostate cancer, likely due to the immunologically "cold" nature of the tumor and low PD-L1 expression on tumor cells. However, if existing prostate cancer treatments can trigger an adaptive immune response, attracting infiltrating immune cells and increasing tumor PD-L1 expression, there is a rationale for combination with anti-PD-1/PD-L1 inhibitors to improve outcomes. The current phase 2 study will evaluate combinations of the PD-1 inhibitor nivolumab with either rucaparib (PARP inhibitor), docetaxel, or enzalutamide (androgen receptor inhibitor) in men aged $\geq$18 years with mCRPC (NCT03338790). **Methods:** Key inclusion criteria: Histologic confirmation of adenocarcinoma of the prostate, evidence of metastatic disease, ongoing androgen deprivation therapy, and evaluable tumor biopsy. Key exclusion criteria: Active brain metastases, active malignancy in prior 3 years (except apparently cured locally-curable cancers), and major surgery $\leq$14 days before treatment assignment. Pts will be assigned to nivolumab + rucaparib, nivolumab + docetaxel, or nivolumab + enzalutamide based on prior systemic treatment history and the presence/absence of measurable disease and homologous recombination deficiency (HRD). Nivolumab, rucaparib, and enzalutamide treatment will continue until disease progression/unacceptable toxicity (nivolumab treatment $\leq$2 years); docetaxel will be given for $\leq$10 cycles. Co-primary endpoints: Objective response per Prostate Cancer Clinical Trials Working Group 3 criteria and prostate-specific antigen response in HRD+ pts and all treated pts; secondary endpoints: Overall survival, progression-free survival, and response kinetics in HRD+ pts and all treated pts, and safety/tolerability in all treated pts. Enrollment began December 2017 with a target of ~300 pts. Clinical trial information: NCT03338790.

TPS3127 Poster Session (Board #328a), Mon, 8:00 AM-11:30 AM

A study of REGN3767, an anti-LAG-3 antibody, alone and in combination with cemiplimab (REGN2810), an anti-PD1 antibody, in advanced cancers. *First Author: Kyriakos P. Papadopoulos, START, San Antonio, TX*

Background: Lymphocyte activation gene 3 (LAG-3) is an immune checkpoint receptor with a biological role in T cell regulation. Analysis of immune-cell infiltrates from human tumors show that a subset of CD4+ and/or CD8+ cells co-express LAG-3 and PD-1 and may be associated with decreased T-cell effector function and tumor escape (Baitsch L et al. *J Clin Investig*. 2011;121:2350-2360; Jie HB et al. *Br J Cancer*. 2013;109:2629-2635.). Preclinical models provide evidence that dual inhibition of LAG-3 and PD-1 blockade offer synergistic anti-tumor effects and suggest a promising immunotherapy combination that warrants clinical investigation (Woo SR et al. *Cancer Res*. 2012;72(4): 917-927). This first in human study will evaluate the safety and efficacy of REGN3767 alone and in combination with cemiplimab in advanced malignancies. **Methods:** Phase 1 study enrolling patients with advanced malignancies. Dose escalation phase employs a modified 3+3 (4+3) design to assess the tolerability and pharmacokinetics (PK) of REGN3767 monotherapy and in combination with cemiplimab. Monotherapy is exploring 4 escalating REGN3767 dose levels. Combination is exploring 3 escalating REGN3767 dose levels. After tolerability and PK evaluation, doses of REGN3767 will be selected for monotherapy and combination therapy tumor-specific expansion cohorts. Solid tumor expansion cohorts will enroll per Simon's two-stage design to evaluate safety and preliminary efficacy. Lymphoma expansion cohorts will enroll 15 patients. Patients who are anti-PD-1/PD-L1 therapy naïve and experienced are eligible for separate cohorts. Patients previously exposed to anti-LAG-3 therapy are not eligible. The primary objectives are the determination of the recommended phase 2 dose (RP2D, dose escalation) and ORR (dose expansion). Secondary objectives include characterization of PK and immunogenicity in all patients, as well as anti-tumor efficacy in dose escalation, and safety in dose expansion. This trial is actively enrolling eligible patients in the US, UK, Ireland, and South Korea. Clinical Trial Information: NCT03005782.

TPS3128 Poster Session (Board #328b), Mon, 8:00 AM-11:30 AM

Phase I study of recombinant interleukin-15 in combination with checkpoint inhibitors nivolumab and ipilimumab in subjects with refractory cancers. *First Author: Geraldine Helen O'Sullivan Coyne, Early Clinical Trials Development Program, DCTD, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Interleukin-15 is a stimulatory cytokine. Recombinant human IL-15 (rhIL-15), a nonglycosylated single-chain peptide, increased circulating CD8+T-cells, NK cells and inflammatory cytokines in clinical trials (Conlon *et al*, 2015. JCO). Simultaneous *in vivo* administration of IL-15 with anti-CTLA-4 and anti-PD-L1 is associated with increased levels of tumor antigen-specific CD8+T cells and T-cell tumor lytic activity, increased antigen-specific IFN-γ release, decreased tumor growth, and improved mouse survival; as well as inhibition of suppressive functions of CD4+CD25+ and CD8+CD122+ regulatory T-cells (Yu *et al*, Proc Natl Acad Sci. 2012). Therefore we postulate the combination of checkpoint inhibitors+rhIL-15, which act on different stages of T-cell activation, will enhance anti-tumor immune responses through T-cell expansion, differentiation, and cytotoxic activity. **Methods:** Open label phase I trial of the rhIL-15+ipilimumab+nivolumab combination following a 3+3 design, with safety lead-in doublets of rhIL-15 +nivolumab (Cohort A) or rhIL-15+ipilimumab (Cohort B). Estimated enrollment: 45 patients (pts). 42-day cycles: rhIL-15 administered subcutaneously on days 1-8 and 22-29 for the first 4 cycles only; nivolumab intravenously (IV) day 8, 22 and 36; ipilimumab IV day 1. Pts must be ≥18 years of age, have histologically confirmed solid tumors that have progressed on standard of care therapy, ECOG PS ≤2. Pts with treated brain metastasis with stable disease ≥4 weeks without requiring steroids/anti-seizure medication, and who do not response on any 2/3 agents, are eligible. Exclusion criteria include grade3 immune related adverse events during prior checkpoint inhibitor treatment, active/chronic autoimmune disease, systemic steroid use or HIV/hepatitis infection. Currently, cohort A has enrolled 1 of 3 planned pts. Assessment of intrinsic apoptosis biomarkers, PD-L1 levels, T-cell phenotypic markers, markers of T-cell activation/inhibition (Zap70 pY493/pY580 SHP2), cell enumeration, proximity of tumor cells to T cells at the maximally tolerated dose using a validated/quantitative immunofluorescence assay, is planned. Clinical trial information: NCT03388632.

TPS3129 Poster Session (Board #329a), Mon, 8:00 AM-11:30 AM

The "INSIGHT" trial: An explorative, open-labeled phase I study to evaluate the feasibility and safety of intra-tumoral, intra-peritoneal, and subcutaneous injections with IMP321 (LAG-3Ig fusion protein) for advanced stage solid tumor entities. *First Author: Daniel Wilhelm Mueller, Institute of Clinical Cancer Research (IKF) at Krankenhaus Nordwest, UCT-University Cancer Center, Frankfurt, Germany*

Background: The INSIGHT study evaluates feasibility and safety of intra-tumoral and intraperitoneal injections of IMP321 (mono-agent) for the treatment of advanced stage solid tumors as well as to generate first efficacy data. This proof-of-concept data could build the basis for further clinical studies exploring the therapeutic potential of active immunotherapy with IMP321 by direct injection into the tumor mass or the peritoneal space. Furthermore, safety and efficacy of combining standard-of-care (SOC) chemo(immuno-)therapies with IMP321 subcutaneous (s.c.) injections in various solid tumor entities will be assessed. IMP321 is a soluble form of the LAG-3 T cell surface receptor with a dual mode of action (MOA) consisting of activation of antigen presenting cells (primary MOA) and prevention of exhaustion of activated T-cells (secondary MOA at high local concentration). **Methods:** This is a prospective investigator initiated phase I trial consisting of three strata. Stratum A: Pretreated patients with solid tumors which are accessible for repeated injections and biopsies receive q2w intra-tumoral injections of IMP321 as a monotherapy. Stratum B: Pretreated patients with solid tumors and additional peritoneal carcinomatosis receive q2w intraperitoneal IMP321 injections via direct injection or a silicon catheter. Both strata are performed in a classical 3 patient cohort study design consisting of intra-patient dose-escalation and consolidation cohorts. Stratum C: Patients with solid tumors treated with SOC chemo(immuno-)therapy in first or second line receive concomitant s.c. IMP321 injections. It is planned to enroll 9 patients each in Stratum A and Stratum B and 20 patients in Stratum C. Main efficacy endpoint is the overall response rate according to RECIST criteria. The trial is accompanied by an extensive biomarker research program. Recruitment has started; currently (Feb 2018) 4 patients have been enrolled (3 Stratum A, 1 Stratum B). Up to now, no DLTs have been observed. ClinicalTrials.gov Identifier: NCT03252938; EudraCT: 2016-002309-20. Clinical trial information: NCT03252938.

TPS3130 Poster Session (Board #329b), Mon, 8:00 AM-11:30 AM

A sequential cohort study of combination immunotherapy with BN-brachyury vaccine, M7824, ALT-803 and epacadostat in metastatic castration-resistant prostate cancer (mCRPC) (QuEST1). *First Author: Jason M. Redman, National Cancer Institute, Bethesda, MD*

Background: Vaccine and checkpoint inhibitor monotherapies infrequently produce objective responses in mCRPC. Combination immunotherapy that 1) facilitates immune recognition of tumor, 2) increases number and function of tumor directed effector cells, and 3) decreases immune suppression in the tumor microenvironment (TME), is a promising strategy to improve outcomes in mCRPC. In pursuit of safety and efficacy, this Quick Efficacy Seeking Trial (QuEST1) will add immunotherapies to sequential study arms. QuEST1 first combines the BN-Brachyury vaccine, targeting a transcription factor involved in epithelial-mesenchymal transition and drug resistance, with a bifunctional agent (M7824) targeting PD-L1 and TGF-β. The next arm adds an IL-15 superagonist (ALT-803) to boost NK and T cell number and function. The final arm adds epacadostat, an IDO1 inhibitor that dampens immune suppression in the TME. **Methods:** Eligibility criteria: prostate cancer, castrate testosterone level, and metastases to bone, organs or lymph nodes. Exclusion criteria: ECOG > 1, immunosuppression, and regular use of narcotic analgesics. QuEST1 will enroll up to 93 patients to sequential arms; each arm evaluates 2-4 treatments. A safety cohort, open to any solid tumor, will assess safety and dose finding for M7824 + ALT-803 (enrolls simultaneously to Arm1). Arm1 will treat 13 pts with BN-Brachyury + M7824. If safety, Arm2 (adds ALT-803) will enroll 13 pts. If safety, Arm3 (adds epacadostat) will enroll 13 pts. Primary endpoints (response definition): objective response by RECISTv1.1 and/or sustained decrease in PSA ≥30% (treatment efficacy). Using a Simon minimax two stage design, if ≥2 of 13 patients in an arm demonstrate efficacy, the arm will expand to n = 25. The fraction of patients who experience efficacy will be reported with two-sided 80% and 95% confidence intervals. Secondary endpoint: PFS. Exploratory endpoints: Correlate immunologic parameters with response (number/function of circulating antigen-specific T cells, immune cell phenotype, sCD40L, sCD20, prostate-specific membrane antigen+ extracellular vesicles (EV) and immune EVs.

TPS3131 Poster Session (Board #330a), Mon, 8:00 AM-11:30 AM

A phase 1/2 study with birinapant in combination with pembrolizumab. *First Author: Russell J. Schilder, Thomas Jefferson University Hospital, Philadelphia, PA*

Background: Birinapant is a bivalent SMAC mimetic with activity against multiple members of the inhibitor of apoptosis protein (IAP) family including cIAP1 and has demonstrated tolerability with robust and durable target engagement in advanced cancers. Synergistic effects of combining birinapant with immune checkpoint inhibitors have been demonstrated in preclinical models, consistent with the reported role of cIAP1 in tumor cells and immune cells (Beug et al., 2017). Based on these observations, a phase 1/2 trial with birinapant and pembrolizumab has been initiated (NCT02587962). **Methods:** In the dose escalation part of this multi-center phase 1/2 study, patients > 18 years with advanced solid tumors without further suitable standard therapeutic options are eligible for inclusion. The primary objective is to determine the safety and tolerability of the recommended phase 2 dose (RP2D) of birinapant in combination with pembrolizumab using a standard 3+3 design. The secondary objective is to assess efficacy by RECIST 1.1. The doses of birinapant to be evaluated are 5.6, 11, 17 and 22 mg/m^2 IV on day 1 and 8 in addition to pembrolizumab 200 mg on day 1 in a 21-day cycle. RP2D will be proposed by the safety review committee. The phase 2 part plans to include 111 patients. The primary objective is to assess the clinical activity of birinapant and pembrolizumab, measured as ORR by RECIST in separate cohorts of microsatellite stable colorectal (N = 28), ovarian (N = 27) and cervical cancer (N = 26). Simon's two-stage design yields a type I error rate of 0.05 and statistical power of 0.80 for each of the three cohorts using a one-sided test based on true response rates of 20% (colorectal cancer), 25% (ovarian cancer) and 30% (cervical cancer). The study will also evaluate an exploratory cohort consisting of five patients each with small cell lung cancer, cholangiocarcinoma, gastroesophageal carcinoma, mesothelioma, head and neck squamous cell carcinoma (check-point inhibitor-naïve and experienced). The phase 2 secondary objectives are safety and tolerability, tumor response, progression-free and overall survival. Exploratory objectives will assess tumor response by iRECIST, pharmacokinetics, pharmacodynamics and predictive biomarkers. Clinical trial information: NCT02587962.

TPS3132 Poster Session (Board #330b), Mon, 8:00 AM-11:30 AM

Phase 1, multicenter, open-label study of single-agent bispecific antibody t-cell engager GBR 1342 in relapsed/refractory multiple myeloma. *First Author: Joshua Ryan Richter, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ*

Background: Therapeutic advances have improved outcomes in multiple myeloma but patients eventually relapse, requiring treatment with agents that are active in refractory disease. CD38, a transmembrane glycoprotein upregulated on myeloma cells, is a validated disease target as evidenced by the anti-myeloma activity of daratumumab, an anti-CD38 human IgG1κ monoclonal antibody. However, not all patients respond and many eventually develop progressive disease to daratumumab monotherapy.[1] GBR 1342, a CD3xCD38 bispecific antibody engineered (using Glenmark's BEAT platform) to direct T-cells to CD38-expressing myeloma cells, has the potential to overcome the limitations of existing therapies. In preclinical studies, GBR 1342 redirected the cytotoxic potential of T-cells to human myeloma cell lines in vitro and in mouse xenograft models. This ongoing, 2-part, first-in-human study aims to: (1) evaluate the safety and maximum tolerable dose (MTD) of GBR 1342 monotherapy in subjects with relapsed/refractory multiple myeloma (>3 prior therapies); and (2) further elucidate the safety, tolerability, and preliminary clinical activity of GBR 1342 at the MTD. **Methods:** In Part 1, intravenous GBR 1342 is administered on Days 1 and 15 in 28-day treatment cycles at escalating doses (Table). The first 4 cohorts consist of a single subject. Subsequent cohorts use a 3+3 enrollment design. In Part 2, 65 evaluable subjects will be treated at the MTD identified in Part 1 until disease progression or unacceptable toxicity occurs. Primary endpoints include AEs (frequency, severity), number of dose-limiting toxicities during Cycle 1 (Part 1), and objective response to GBR 1342 (Part 2). Secondary endpoints include pharmacokinetics and anti-tumor activity of GBR 1342 (progression-free and overall survival). [1]Nijhof IS et al. Blood 2016; doi.org/10.1182. Clinical trial information: NCT03309111.

Dose escalation scheme (doses in ng/kg).

		Cycle 1		Cycle 2		Subsequent Cycle(s)	
	Cohort	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
Single Subject	1	1	3	3	3	3	3
	2	3	10	10	10	10	10
	3	10	30	30	30	30	30
	4	30	60	60	60	60	60
3+3	5	60	100	100	100	100	100
	6	100	200	200	200	200	200
	7	200	400	400	400	400	400
	8	400	600	600	600	600	600
	9	600	800	800	800	800	800
	10	800	1000	1000	1000	1000	1000

TPS3133 Poster Session (Board #331a), Mon, 8:00 AM-11:30 AM

Phase I/II dose escalation and expansion cohort safety and efficacy study of image guided intratumoral CD40 agonistic monoclonal antibody APX005M in combination with systemic pembrolizumab for treatment naive metastatic melanoma. *First Author: Daniel H. Johnson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Checkpoint blockade has become a major modality in the treatment of metastatic melanoma (MM). However, durable remission rates remain low. CD40 activation on antigen presenting cells (APCs) initiates their ability to prime and activate $CD8^+$ T-cells through upregulation of co-stimulatory molecules (ie. CD80, CD86) as well as expression of effector cytokines. Furthermore, CD40 activation cause macrophages to develop a tumoricidal phenotype and increase MHC I expression on tumor cells. Direct IT immune modulation utilizes the tumor as a "vaccine site" to generate a tumor specific immune response. We hypothesize that IT injection of a CD40 Agonist (A), will "immunize" patients (Pts) against melanoma neoantigens through "licensing" of APCs for tumor specific T-cell priming and activation. In mouse models, we have shown that IT administration of the recombinant adenovirus encoding CD40L induces $CD8^+$ T-cell-mediated activity against B16 melanoma and, importantly, also augmented the activity of anti-PD-1. **Methods:** This phase I/II trial (NCT02706353) evaluates the safety, efficacy, and immunological impact of IT administration of APX005M (CD40 A mAb) in combination with pembrolizumab in pts with MM. The phase I escalation is an accelerated 3+3 design. Pts will receive IT APX005M every 3 weeks for a total of 4 doses. Image guidance will allow for injection of visceral, nodal, and soft tissue metastases. The single-arm phase 2 expansion will evaluate the overall response rate (ORR) 12 weeks after treatment initiation. Key inclusion criteria: confirmed, measurable, metastatic cutaneous or mucosal melanoma; and at least 2 injectable lesions. Key exclusion criteria: prior immunotherapy, uveal melanoma, or active autoimmune disease. 26 pts will have 75% power to detect an improvement from a null ORR of 33% to 55%, using a one group chi-square test and assuming a one-sided α–level of 5%. Immune analysis will be performed on pre and on-treatment tumor/liquid biopsies both in injected and non-injected tumors. Dose level 3 of escalation phase has completed with 5 pts enrolled. Clinical trial information: NCT02706353.

TPS3134 Poster Session (Board #331b), Mon, 8:00 AM-11:30 AM

An open-label, phase 1b study of NEO-PV-01 with pembrolizumab plus chemotherapy in patients with advanced or metastatic nonsquamous non-small cell lung cancer. *First Author: Ramaswamy Govindan, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Cancer cells contain unique DNA mutations that result in altered amino acid sequences known as neoantigens. Evidence supports a central role for neoantigens as targets for tumor-directed immune responses. Tumor mutational burden as well as neoantigen load are associated with anti-tumor activity of checkpoint inhibitors. Chemotherapy plus anti-PD1 therapy in NSCLC has demonstrated improved efficacy over chemotherapy alone. This combination reduces early progression and may also modulate the tumor microenvironment. Neoantigen vaccines offer a rational combination partner for these therapies as a highly specific way to induce de novo T cell reactivity and to expand existing T cell responses against neoantigens. Here, we describe a clinical trial combining NEO-PV-01, a personal neoantigen vaccine designed specifically for the molecular profile of each individual's tumor, with anti-PD1 and chemotherapy. **Methods:** NT-002 is a single-arm, phase 1B study evaluating the safety of administering NEO-PV-01 + adjuvant (Poly-ICLC) with pembrolizumab plus carboplatin and pemetrexed in patients with advanced non-small cell lung carcinoma who have received no prior systemic treatment. Patients undergo a baseline tumor biopsy and HLA typing. DNA and RNA sequencing is performed on tumor as well as peripheral blood. NEO-PV-01 is custom designed for each individual patient and contains up to 20 peptides 14-35 amino acids in length. The peptides are pooled into four groups and mixed with Poly-ICLC at the time of administration. On Day 1, patients will begin with 4 treatment cycles of pembrolizumab plus chemotherapy. Beginning on Cycle 5 (Week 12), patients will receive pembrolizumab monotherapy Q3W up to Week 103 without pemetrexed maintenance. Also beginning at Week 12, patients receive five priming immunizations with NEO-PV-01 over a three-week period followed by boosters at Weeks 19 and 23. The primary endpoint is safety. Secondary endpoints are ORR, CBR, PFS, and assessment of response conversion between Week 12 and Week 24. Exploratory endpoints include extensive immune monitoring with antigen-specific analyses of both peripheral blood and tumor. Clinical trial information: NCT03380871.

TPS3135 Poster Session (Board #332a), Mon, 8:00 AM-11:30 AM

HepaVac-101 first-in-man therapeutic cancer vaccine phase I/II clinical trial for hepatocellular carcinoma patients. *First Author: Luigi Buonaguro, IRCCS INT Fondazione, Naples, Italy*

Background: HCC is the third leading cause of death from cancer globally with an extremely variable 5-year survival rate. The HepaVac-101 phase I/II, first-in-man, therapeutic cancer vaccine single-arm clinical trial is performed as part of the HepaVac project, funded by the European Commission's 7th Framework Program under the Grant Agreement Nr. 602893 (www.hepavac.eu). The HepaVac-101 trial identification numbers are NCT03203005 (Clinical trials.gov) and 2015-003389-10 (EudraCT). **and Methods:** The therapeutic cancer vaccine IMA970A is a multi-peptide-based HCC vaccine composed of 16 newly discovered and overexpressed tumor-associated peptides (TUMAPs) directly identified from resected HCC tissues. Of these TUMAPs, 7 are restricted to HLA-A*02, 5 to HLA-A*24 and 4 to HLA class II. CV8102 is a novel RNA based immunostimulatory agent inducing a balanced Th1/Th2 immune response. A total of 40 patients with very early, early and intermediate stage of HCC are enrolled to be treated with a single pre-vaccination infusion of low-dose cyclophosphamide, followed by 9 intradermal vaccinations consisting of IMA970A plus CV8102. The study drugs are applied without concomitant anti-tumor therapy, in order to reduce risk of tumor recurrence/progression in patients having received all indicated standard treatments and without evidence of active disease. The primary endpoints of the HepaVac-101 clinical trial are safety, tolerability, and immunogenicity. Secondary/exploratory endpoints are additional immunological parameters in circulation, infiltrating T-lymphocytes in tumor tissue, biomarkers in blood and tissue, DFS/PFS and OS. Once safety of this vaccination approach has been established in the first 10 patients the addition of a checkpoint inhibitor will be considered. Suitable patients enrolled at Tuebingen are invited to participate in a trial extension investigating an actively personalized vaccine (APVAC). The HepaVac-101 trial is conducted in 6 centers located in 5 European countries. Five centers are actively recruiting patients. As of the time of abstract submission, 4 HCC patients have been screened for HLA haplotype and 1 is eligible for vaccination. Clinical trial information: NCT03203005.

TPS3136 Poster Session (Board #332b), Mon, 8:00 AM-11:30 AM

Phase I/II study of BSK01, an artificial intelligence-driven, peptide-pulsed, mature DC immunotherapy for solid and hematological malignancies. *First Author: Leonardo Mirandola, Kiromic, Inc., Houston, TX*

Background: Despite advances in understanding the biology of hematologic malignancies (HM) and solid malignancies (SM), and the availability of new treatment options, many patients with HM and SM remain incurable. Since the majority of cancer patients display a defective immune response to tumor antigens, the ex vivo activation of dendritic cells (DC), through their exposure to tumor associated antigens, is an attractive and active area of investigation. The choice of the target antigen and the identification of immuno-dominant and immunogenic peptides to drive powerful and specific cellular responses against tumor cells are crucial for the success of cancer vaccines. We have developed a powerful artificial intelligence (AI) computational platform, K.A.I., capable of collecting, normalizing, and analyzing data from multiple data sources, and to prioritize target antigens and immuno-dominant peptides for any given malignancy. **Methods:** Currently, we are conducting 4 clinical trials for solid and hematologic malignancies, both in the consolidation and refractory settings. We hypothesize that treatment of patients with HM or metastatic SM using autologous DC pulsed with immuno-dominant tumor-specific peptide antigens will result in antigen-specific CD4+ T-cell and/or CD8+ CTL responses without significant toxicities. We also hypothesize that the responses generated against specific antigens may translate into clinical anti-tumor activity. Primary Objective: Phase I (6 subjects). To determine safety of intradermal/subcutaneous DC vaccine therapy, low-dose cyclophosphamide and GM-CSF, in patients with metastatic SM or HM. Secondary Objective: Phase II (up to 17 subjects). To determine immune responses associated with intradermal/subcutaneous DC vaccine therapy, low-dose cyclophosphamide and GM-CSF, in patients with metastatic SM or HM who demonstrate a response, or whose disease remains stable, after conventional first-line systemic therapy, or who have failed conventional systemic therapy. The study population is currently drawn from patients at various clinical institutions following contractual agreements. Clinical trial information: NCT02709993; NCT02705703; NCT02224599; NCT02223312.

3500 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine +/- oxaliplatin in locally advanced rectal cancer: Final results of PETACC-6. *First Author: Hans-Joachim Schmoll, Martin Luther University, Halle, Germany*

Background: The PETACC-6 trial investigated the role of oxaliplatin in combination with preoperative capecitabine-based chemoradiation (CRT) and postoperative capecitabine (CT) to improve disease-free survival (DFS) in locally advanced rectal cancer. **Methods:** Between 11/2008 and 09/2011, 1090 patients with rectal adenocarcinoma within 12 cm from the anal verge, T3/4 and/or node-positive, with no evidence of metastatic disease and considered either resectable at the time of entry or expected to become resectable, to 5 weeks preoperative CRT with capecitabine, followed by 6 cycles of adjuvant capecitabine without (arm 1) or with oxaliplatin (arm 2) (before and after surgery). The primary analysis was intent-to-treat and adjusted for stratification factors (clinical T category, nodal status, distance from the tumor to the anal verge and method of locoregional staging) except the center. **Results:** An early release of DFS after a medium follow-up of 31 months per recommendation of the IDMC, did not show any difference between arms (adjusted HR = 1.04, 95% CI: 0.81 -1.33, P = 0.781) (Schmoll H et al, Proc ASCO 2014). We now report on the long-term results for DFS and OS. At median follow-up of 68 months, respectively 157 vs.156 DFS events and 97 vs. 109 deaths were observed in arm 1 and 2. In each arm, 58 patients died due to progressive disease. There is no difference in DFS between arms (adjusted HR = 1.02, 95% CI: 0.82-1.28, P = 0.835) nor in OS (adjusted HR = 1.17, 95% CI: 0.89 – 1.54, P = 0.252). 5-year DFS was 71.3% (95% CI: 67.1% - 75.0%) in arm 1, vs. 70.5% (95% CI: 66.3% - 74.3%) in arm 2. 5-year OS was 83.1 (95% CI: 79.5% - 86.1%) in arm 1, vs. 80.1% (95% CI: 76.2% - 83.4%) in arm 2. No major heterogeneity of the results for DFS according to baseline factors was identified except for the subgroup of non-german patients (N = 357) vs. german patients (N = 737) (p = 0.02 for Cochran's Q test). Adjusted HR was 1.27 (95% CI: 0.96-1.68, p = 0.091) in disfavor of oxaliplatin in german patients while adjusted HR was 0.65 (95% CI: 0.44 – 0.97, p = 0.033) in favor of oxaliplatin in non-german patients. **Conclusions:** Long-term results confirm that the addition of oxaliplatin to capecitabine plus radiotherapy does not improve DFS nor OS in the ITT population. Further prognostic and predictive factors will be defined by a multivariate analysis and be presented at the meeting, in particular the discrepancy of the german and non-german patients will be clarified as well. Clinical trial information: NCT00766155.

3501 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Long-term results of the ADORE trial: Adjuvant oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) versus 5-fluorouracil and leucovorin (FL) after preoperative chemoradiotherapy and surgery for locally advanced rectal cancer. *First Author: Yong Sang Hong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South)*

Background: To report the long-term survival outcomes of the ADORE, a randomized controlled trial, compared adjuvant FOLFOX *vs* FL in patients with resected rectal cancer whose pathologic stages of ypII/III after preoperative chemoradiotherapy (CRT). **Methods:** This is a randomized phase II study accrued patients with curatively resected rectal cancer patients whose postoperative ypStage II/III after preoperative CRT with fluoropyrimidines alone. Patients were randomly assigned (1:1) to receive adjuvant chemotherapy either with FL or FOLFOX for 4 months. Randomization was centrally coordinated and stratified by the ypStage and participating sites. The primary endpoint was disease-free survival (DFS). **Results:** A total of 321 patients were randomly assigned between Nov 2008 and Jun 2012; 161 patients to FL and 160 to FOLFOX. At a median follow-up of 74.1 months (IQR, 56.2 – 88.0), 6-year DFS rate was 68.2% in the FOLFOX arm *vs* 56.8% in the FL arm with an adjusted hazard ratio (HR) of 0.63 (95% CI, 0.43–0.93, p= 0.018) by intention-to-treat analysis. In the subgroup analysis for DFS, patients with ypStage III (HR 0.59 [0.38-0.92], p= 0.019), ypN1b (HR 0.35 [0.14-0.83], p= 0.017), ypN2 (HR 0.47 [0.22-0.99], p= 0.048), high grade histology (HR 0.28 [0.08-0.97], p= 0.045), minimally regressed tumor (0.40 [0.19-0.85], p= 0.016), absence of lymphovascular (HR 0.55 [0.34-0.88], p= 0.013) or perineural invasion (HR 0.53 [0.33-0.86], p= 0.01), male gender (HR 0.62 [0.39-0.98], p= 0.039), and younger than 65 years (HR 0.64 [0.42-0.97], p= 0.034) benefited more from FOLFOX than FL. The 6-year overall survival (OS) rate was 78.1% in the FOLFOX arm *vs* 76.4% in the FL arm (HR 0.73 [0.45-1.19], p= 0.21). In the subgroup analysis for OS, those with ypN2 (HR 0.42 [0.18-0.96], p= 0.04) and minimally regressed tumor (HR 0.42 [0.19-0.97], p= 0.043) benefited from FOLFOX than FL. **Conclusions:** Adjuvant FOLFOX clearly demonstrated improved DFS in rectal cancer patients with ypStage II/III after preoperative CRT. Subgroup analyses provided additional information on the selection of adjuvant candidates. Clinical trial information: NCT00807911.

3502 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

Modified FOLFOX6 with or without radiation in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial. *First Author: Yanhong Deng, Sun Yat-sen University, Guangzhou, China*

Background: The FOWARC trial compared FOLFOX6 with or without Radiation in neoadjuvant treatment of locally advanced rectal cancer to 5-FU chemoradiotherapy. First results of early secondary endpoints have been published (Deng et al., JCO 2016). Here we present the primary endpoint, disease-free survival (DFS) at 3 years. **Methods:** Between 01/2011-02/2015, patients with rectal cancer within 12 cm from the anal verge, clinical stage II-III were randomly assigned to received 5-FU with radiation(RT) (FU-RT arm), or receive mFOLFOX6 with RT (FOLFOX-RT arm), or receive 4-6 cycles of mFOLFOX6 alone (FOLFOX arm), peri-operative RT was allowed if needed. The primary endpoint was DFS at 3 years defined as the interval from randomization to incomplete surgical resection, locaregional or metastatic recurrence or death, whichever occurred first. **Results:** A total of 495 patients were randomly assigned to three arms at 1:1:1 ration. 418 patients who had available follow up and obeyed the treatment protocol, 130 in FU-RT arm, 142 in FOLFOX-RT arm and 146 in FOLFOX arm. The local recurrence rate was 10.0%, 8.5% and 8.9% respectively. After a median follow-up time of 45.2 months, 35 patients in FU-RT arm had a DFS-related event, as compared with 37 patients in FOLFOX-RT arm(HR 1.031, 95% confidence interval 0.657 to 1.620), and 41 in FOLFOX arm (HR 0.960, 95% confidence interval 0.615 to 1.497). The rate of DFS at three years was 76.4±3.8% in FU-RT arm, 77.8±3.5% in FOLFOX-RT arm and 75.7± 3.6% in FOLFOX arm (P = 0.961 by the exact stratified log-rank test). The rate of OS at three years was 93.7±2.2% in FU-RT arm, 92.0±2.3% in FOLFOX-RT arm and 92.2±2.3% in FOLFOX arm (P = 0.961 by the exact stratified log-rank test). **Conclusions:** FOLFOX with or without radiation did not improve significantly improved DFS in patients with advanced rectal cancer. However, FOLFOX alone seems to have identical local recurrence rate and 3-DFS and 3-OS compared to standard FU-RT. Clinical trial information: NCT01211210.

LBA3503 **Oral Abstract Session, Tue, 9:45 AM-12:45 PM**

A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *First Author: François Quenet, Institut Régional du Cancer de Montpellier, Montpellier, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Monday, June 4, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

3504 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Randomized trial of irinotecan and cetuximab (IC) versus irinotecan, cetuximab and ramucirumab (ICR) as 2nd line therapy of advanced colorectal cancer (CRC) following oxaliplatin and bevacizumb based therapy: Result of E7208. *First Author: Howard S. Hochster, Rutger-Cancer Institute, New Brunswick, NJ*

Background: While both anti-VEGF(R) and EGFR antibodies have activity in metastatic RAS wild type CRC, the combination of the two appeared to be detrimental when combined with chemotherapy in unselected CRC patients. We undertook this study to determine whether the anti-VEGFR antibody, ramucirumab, improved activity of Irinotecan and Cetuximab as 2nd line therapy in KRASwt CRC patients, who previously received FOLFOX or CAPOX with bevacizumab (bev) first line therapy, and were now progressing. **Methods:** Patients with advanced and measurable (RECIST 1.1) CRC who had previously been treated with a fluoropyrimidine and oxaliplatin (ox) with bev, and recently showed progression on CT scan were randomized to IC (180 mg/m2 and 500 mg/m2 respectively) or ICR (R = 8 mg/kg) every 2 weeks. After 35 pt were randomized, planned interim analysis showed excess gr 3-5 toxicity for ICR. Therefore a modified ICR (150 mg/m2, 400 mg/m2 and 6 mg/kg) arm was instituted after study hold. Patients were stratified by PS (0 vs 1), progression on ox (Y vs N), and progression within 6 months of last treatment (or longer). 100 patients were then accrued to IC vs mICR, with 85% power to detect improvement in median PFS from 4.5 to 7.65 months (with 15% type I error or $p < 0.15$) by stratified log-rank test. **Results:** Results: 102 patients were randomized and evaluable from June, 2014 - July, 2017. Patients were 65% male, 9% black and 8% Hispanic with med age 60 years, PS 0 = 52%, with 24% progressing while on ox and 15% progressing more than 6 months off rx. Gr 3-4 overall toxicity for IC vs mICR was 47% vs 54% with diarrhea = 10 v 15%; rash = 13 vs 8%; neutropenia = 9 vs 10%. Reasons off study were: 60% progression, 18% adverse events and 10% patient choice. Stratified log rank analysis showed a HR = 0.65 for PFS of mICR vs IC (overall med 5.8 months; p = 0.068), which met primary endpoint of $p < 0.15$. Survival appears to be equal with med = 20.5 months. **Conclusion:** In KRAS selected, wildtype CRC, 2nd line therapy (following ox and bev based treatment), an anti-VEGFR antibody, combined with anti-EGFR and irinotecan, prolongs PFS. This effect is similar to the reported improvement in PFS in other 2nd line anti-VEGF trials and supports the fact that antibodies against these two targets can be combined for additional benefit in the appropriate patient population. This study was coordinated by ECOG-ACRIN & supported by NCI awards: CA180820, CA180794, CA180826, CA180830, CA180888, CA180870, CA189830. Clinical trial information: NCT01079780.

3505 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

First-line FOLFOX plus panitumumab (Pan) followed by 5FU/LV plus Pan or single-agent Pan as maintenance therapy in patients with RAS wild-type metastatic colorectal cancer (mCRC): The VALENTINO study. *First Author: Filippo Pietrantonio, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Since doublets plus anti-EGFRs were continued until progressive disease (PD) in mCRC first-line registration trials, there is scarce evidence if de-escalating treatment intensity after an anti-EGFR-based induction might be not inferior in terms of disease control, while reducing toxicity burden and improving quality of life. In MACRO-2, maintenance with cetuximab alone achieved a 9-month progression-free survival (PFS) rate non inferior than continued mFOLFOX + cetuximab in KRAS ex. 2 wt patients. **Methods:** RAS wt unresectable mCRC patients, stratified for prior adjuvant therapy and metastatic sites (1 vs ≥2), were randomized and received FOLFOX + Pan induction (8 cycles) followed by maintenance with Pan (arm B) or 5FU/LV + Pan (arm A) until PD/unacceptable toxicity/death. The primary endpoint was non-inferiority of PFS of arm B vs A. An overall sample size of 224 subjects (112 per arm) achieved 90% power to detect a 50% 10-month PFS rate in arm A and a maximum 15% difference in arm B, with a significance level of 0.1 and a 15% drop-out rate; non inferiority could be demonstrated if the upper boundary of the one-sided 90% CI of the hazard ratio (HR) was <1.515. Secondary endpoints were safety, quality of life, overall response rate (ORR), duration of response and overall survival. Results: From July 2015 to October 2017, 229 patients were randomized (117 arm A/112 arm B). Baseline characteristics were: males, 68%/66%; median age, 64/64; ECOG PS 0, 71%/72%; previous adjuvant therapy, 14%/18%; single metastatic site, 54%/58%; BRAF mutation, 3%/4%; right-sided primary, 15%/20%. The upper boundary of the one-sided 90% CI for the HR of Pan vs 5FU/LV + Pan was 1.946. At a median follow-up of 13.8 months, 10-m PFS was 52.8% for Pan vs 62.8% for 5FU/LV + Pan, with median time of 10.2 vs 13.0 months, respectively (stratified HR = 1.55, 95% CI: 1.09-2.20; p = 0.011). ORR was 66.6% and 67% in arm A and B, respectively. During maintenance phase, grade ≥3 adverse events (AEs) were mainly diarrhea 3.7%/1.4%; mucositis 6.2%/1.4%; hand-foot syndrome 2.5%/1.4%; neutropenia 2.5%/0%; skin rash 22.2%/13.7%. Overall, grade 1-2 AEs were 75.3%/64.4%. Conclusions: In RAS wild-type mCRC patients, maintenance with Pan alone following induction with FOLFOX + Pan achieves inferior PFS than 5FU/LV + Pan combination. Clinical trial information: NCT02476045.

3506 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Plasma *HER2 (ERBB2)* copy number to predict response to HER2-targeted therapy in metastatic colorectal cancer. *First Author: Alberto Bardelli, Istituto di Candiolo, Fondazione del Piemonte per l'Oncologia, IRCCS, Candiolo, Italy*

Background: The rate of HER2 (*ERBB2*) copy number amplification (CNA) in metastatic colorectal cancer (mCRC) ranges from 2-13%. HERACLES, a phase II trial of trastuzumab and lapatinib (T+L) in HER2-positive mCRC showed response rates of 30%, suggesting HER2 as a viable target in this population. Cell-free circulating tumor DNA (ctDNA) next-generation sequencing (NGS) may be an option for *ERBB2* CNA determination when biopsy is infeasible or tissue is insufficient. Here we determine the sensitivity of plasma CNA (pCNA) detection using a ctDNA NGS assay and suggest a cutoff predictive of response to HER2-targeted therapy. **Methods:** Pre-treatment and progression plasma samples (N = 48) from 26 HER2 FISH-positive patients in the HERACLES study were tested using the Guardant360 assay. We correlated *ERRB2* pCNA with progression free survival (PFS) and best objective response (BOR) on T+L. To establish a threshold for absolute pCNA predicting response, we analyzed *ERBB2* CN relative to panel-wide CNA profile and clonal driver co-occurrence in 819 consecutive mCRC samples tested with Guardant360. **Results:** 46/47 samples with detectable ctDNA were *ERBB2*-amplified based on ctDNA (2.55-122 copies; PPA = 96%, 95% CI 85-99%). A threshold of ≥3 copies of *ERBB2* in circulation allowed identification of 94% of FISH-positive patients, while excluding 86% of all co-occurring *KRAS, NRAS,* and *BRAF* driver mutations in the larger clinical cohort. HERACLES patients below this threshold had reduced PFS (median 4.6 vs. 1.1 months, p = 0.10). Above the threshold, plasma *ERBB2* CNA strongly correlated with BOR (r = 0.5) but weakly with PFS (r = 0.37). **Conclusions:** The ctDNA platform utilized correctly identified 96% of samples as *ERBB2*-amplified and accurately predicted HER2-targeted therapy response rates. Based on the HERACLES and large clinical cohorts, a cutoff of 3 copies of *ERBB2* in plasma is proposed to select patients who will benefit from targeting HER2.

3507 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Actionable fusions in colorectal cancer using a cell-free circulating tumor DNA (ctDNA) assay. *First Author: Katherine Clifton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The presence of gene fusions affects clinical management of patients (pts) with NSCLC, GIST, and CML. Likewise, identification of actionable fusions provides another potential approach to offering effective therapies to pts with advanced colorectal cancer (CRC). Here we detail the frequencies and clinicopathological features of gene fusions in CRC using a comprehensive ctDNA NGS assay. **Methods:** Pts with advanced, pre-treated CRC underwent molecular profiling using a plasma-based ctDNA NGS assay (Guardant360®), which includes testing for fusions in *FGFR2, FGFR3, RET, ALK, NTRK1,* and *ROS1*. Correlations between fusions and clinicopathological features were measured using a Fisher's exact test. Relative frequencies of genomic alterations (point mutations, indels, and splice variants) were compared according to fusion status using an unpaired t-test. **Results:** 45 unique fusions were detected in 41 of 4290 pts tested (0.96%, 95% CI 0.70-1.3%): *RET* (N = 16, 0.37%), *FGFR3* (N = 13, 0.30%), *ALK* (N = 10, 0.23%), *NTRK1* (N = 3, 0.07%), *ROS1* (N = 2, 0.05%), and *FGFR2* (N = 1, 0.02%). Among pts with multiple fusions (N = 4 total), *RET* fusions accounted for 3, all subclonal. Fusions were detected at a median variant frequency of 0.31% (IQR, 0.11-1.5%). FGFR fusions were associated concomitant *RAS* mutations (OR 3.5, P = 0.03). All *NTRK1* fusions were *KRAS/NRAS/BRAF* wild-type. Genomic alterations were more common for the fusion-present cases than non-fusion cases (mean 10.2 vs. 5.1, $P < 0.0001$). **Conclusions:** This is the first large series in CRC patients to demonstrate that plasma-based detection of a broad array of actionable fusions is practical. Fusion presence was associated with a higher mutation frequency, also characteristic of microsatellite instability in CRC. Since these fusions are actionable in other solid tumors, our data provide rationale to utilize ctDNA to identify fusions for targeted therapy trials in metastatic CRC.

3508 Poster Discussion Session; Displayed in Poster Session (Board #1), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Per protocol analysis and final OS update of the FIRE-3 (AIO KRK-0306) study comparing FOLFIRI plus cetuximab vs. FOLFIRI plus bevacizumab. *First Author: Sebastian Stintzing, Ludwig Maximilian University of Munich, Munich, Germany*

Background: FIRE-3 compared 1st-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wt mCRC patients (pts). Extended RAS analysis showed RAS wild-type (RASwt) in tumors of 400 pts. **Methods:** Per protocol analyses were done in all patients that received at least 3 cycles of chemotherapy and who had at least one CT scan following baseline allowing to evaluate of objective response rate (ORR) as the primary endpoint. ORR and early tumor shrinkage (ETS) were compared using Fisher's exact test. Overall survival (OS) was compared using Kaplan-Meier estimation and log-rank tests. Follow up time was calculated using the inverse Kaplan-Meier method. Hazard ratios (HR) were estimated according to the Cox proportional hazard method. **Results:** With data cutoff of July 24th 2017, a total of 400 pts with RASwt tumours were evaluable. The median follow-up time was 70.8 months and 85.3% of OS events have occurred. Of the 400 pts, a total of 351 (87.8%) were evaluable according to the per protocol pre-specified analyses. The final efficacy data is shown in the table below. **Conclusions:** In the per-protocol analysis of RASwt pts treated in FIRE-3, a significantly higher ORR was demonstrated for FOLFIRI plus cetuximab compared to FOLFIRI plus bevacizumab. This advantage relates to a significantly longer OS after more than 85% of OS events had occurred. Clinical trial information: NCT00433927.

	RASwt population (n=400)			RASwt population evaluable according to protocol (n=351)		
	FOLFIRI CET N= 199	FOLFIRI BEV N=201	p	FOLFIRI CET N=169	FOLFIRI BEV N=182	p
ETS, %	68.4	48.9	0.0004* OR: 2.26	70.0	50.3	0.0004* OR: 2.31
ORR, %	65.3	58.7	0.18* OR: 1.33	76.9	64.8	0.01* OR: 1.81
mPFS, mo	10.4	10.5	0.58# HR: 0.95	10.5	10.7	0.80# HR: 0.97
mOS, mo	31.1	25.6	0.01# HR: 0.76	32.5	26.1	0.01# HR: 0.75

CET= cetuximab; BEV= Bevacizumab, RASwt= RAS wild-type; ETS= defined as >20% reduction of tumor diameter at week 6, mPFS= median progression-free survival, mOS= median overall survival; *= two-sided Fisher's exact test p; #= log-rank test p; $= Wilcoxon-Test p, OR = Odds ratio, HR = Hazard Ratio Data on left and right sided primaries will be presented at the conference. The study has been funded by grants from Pfizer and Merck KgaA.

3509 Poster Discussion Session; Displayed in Poster Session (Board #2), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild- type metastatic colorectal cancer m(CRC): A randomized phase II VOLFI trial of the AIO (AIO- KRK0109). *First Author: Michael Geissler, Klinikum Esslingen, Department of Hematology/Oncology, Esslingen, Germany*

Background: Triple chemotherapy with an anti-EGFR reported promising activity with some safety concerns in single arm phase II trials. This trial evaluated activity and safety of mFOLFOXIRI + panitumumab vs FOLFOXIRI in ECOG 0-1, primarily non-resectable mCRC patients. **Methods:** Prospective 2:1 randomized, multi-center, phase II trial comparing mFOLFOXIRI (Ox 85 mg/m2, Iri 150 mg/m2, 5-FU 3000mg/m2 cont. 48h, LV 200 mg/m2) + Panitumumab 6 mg/KG (arm A) with FOLFOXIRI (Ox 85 mg/m2, Iri 165 mg/m2, 5-FU 3200mg/m2 cont. 48h, LV 200 mg/m2; arm B), both arms q2w. Cohort 1: irresectable mCRC; cohort 2: chance of secondary resection of metastatic lesions. Primary endpoint was ORR, secondary endpoints were secondary resection rate (cohort 2), DCR, PFS, OS, toxicity, quality of life (QLQ-C30). Financially supported by an unrestricted grant from Amgen. **Results:** A total of 96 patients were randomized (63 arm A, 33 arm B). ORR was 85.7% in arm A and 54.5% in arm B (p = 0.0013, OR 5.000; 95%-CI 1.870-13.370). DCR was 96.8% in arm A and 78.8% in arm B (p = 0.0071, OR 8.212). ORR in Arm A was 90.6% versus 60.0% (p = 0.0288, OR 6.400) and in Arm B 60.0% versus 50% (p = n.s.) for left and right located CRC, respectively. ORR between arms A and B comparing left and right sided CRC was 90.6% versus 60.0% (p = 0.0039, OR 6.400; 95%-CI 1.889-21.679) and 60.0% versus 50.0% (p = n.s.), respectively. Secondary resections in cohort 2 were 60% (n = 12) and 36.4% (n = 4) in arms A and B, respectively. Treatment related serious adverse advents grade 3-5 occured in 32.8% and 12.1% in arms A and B, respectively (p = 0.0297). Nevertheless, no differences in global health status, functional scales, and symptom scales were reported. **Conclusions:** mFOLFOXIRI plus Panitumumab results in significantly higher response rates compared to FOLFOXIRI in RAS wild-type mCRC. Strong effectivity was observed also in right sided and BRAF mutated CRC. High secondary resection rates could be achieved. Although toxicity (treatment related SAEs) was increased, QL reporting was similar in both arms. Final PFS, AEs, and dosing data will be presented at the meeting. Clinical trial information: NCT01328171.

3510 Poster Discussion Session; Displayed in Poster Session (Board #3), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

REVERCE: Randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan—Biomarker analysis. *First Author: Yasushi Tsuji, Department of Medical Oncology, Tonan Hospital, Sapporo, Japan*

Background: REVERCE demonstrated longer overall survival (OS) with the therapeutic sequence of regorafenib (R) followed by cetuximab (C) ± irinotecan (R-C arm) compared with that of C ± irinotecan followed by R (C-R arm) for patients (pts) with pretreated metastatic colorectal cancer (mCRC; median OS 17.4 vs. 11.6 months, HR 0.61; *Shitara K*, et al. GI Symposium 2018). Biomarker analyses assessed the association of multiple candidate biomarkers with clinical outcomes. **Methods:** Pts with *KRAS* exon 2 wild-type mCRC after failure of fluoropyrimidine, oxaliplatin, and irinotecan treatment were randomized. The primary endpoint was OS. Key secondary endpoints included progression-free survival (PFS) with initial treatment (PFS1), PFS with second treatment (PFS2), safety, and QOL. Sequential biomarker analysis including oncogenic alterations from ctDNA or multiple serum proteins related to the EGF or VEGF pathway was an exploratory endpoint. **Results:** Among the randomized 101 pts, plasma and serum samples were collected from 98 pts. OS HR in the biomarker cohort (n = 98, HR 0.61) and all *RAS/RAF* wild types (n = 86, HR 0.60) at baseline were consistent with that of the overall cohort. R-C arm consistently showed longer OS in all subgroups according to serum proteins biomarkers (median value as cut off). Significant interactions between PlGF or VEGFR-3 level and PFS1 were observed, favoring R over C in higher PlGF and VEGFR-3 level. Among *RAS/RAF* wild types at baseline, emerging *RAS*, *BRAF*, *EGFR S492R* mutations, and *HER2* and *MET* amplification were observed in 1,0,0,2,2 patients after R and 11,1,2,4,4 patients (overlapping) after C. **Conclusions:** This trial consistently showed longer OS with R followed by C versus the reverse sequence for pretreated mCRC pts regardless of biomarker subgroups. Emerging oncogenic alterations are more frequently observed after C treatment than R. Clinical trial information: UMIN000011294.

3511 Poster Discussion Session; Displayed in Poster Session (Board #4), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Anti-EGFR resistant clones decay exponentially after progression: Implications for anti-EGFR rechallenge. *First Author: Christine Megerdichian Parseghian, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Colorectal cancers (CRC) treated with EGFR inhibitor (EGFRi) evolve by a repetitive process of genetic diversification and clonal evolution. After discontinuation of EGFRi, *KRAS/NRAS (RAS)* and *EGFR* resistance mutations no longer have a growth advantage relative to other clones. Yet, the impact of time from the last cycle of EGFRi to decreases in the mutant (MT)/wildtype (WT) allele ratio has not been well defined in mCRC. **Methods:** We analyzed a retrospective cohort of patients at MD Anderson Cancer Center with *RAS/BRAF/EGFR*^{WT} mCRC who had been treated with EGFRi and in whom plasma samples had been collected for sequencing of ctDNA on a platform optimized for very low allele frequencies (AF) (Guardant360). Relative MT allele frequency (rMAF) was defined as ((MT AF) / MT present at the max AF in that assay) and approximates the % of tumor cells shedding the MT of interest into the circulation. rMAF results were normalized to total ctDNA concentration. **Results:** 135 pts were identified. There was an inverse relationship between the rMAF of *RAS* and *EGFR* and time since last treatment, but no change in truncal *APC* and *TP53* inactivating mutations. Our analysis showed that the decline in *RAS/EGFR* rMAF is best described by an exponential decay model (r = 0.93 for *RAS* and 0.94 for *EGFR*). At progression on EGFRi, the median *RAS* rMAF and *EGFR* rMAF were 10.5% and 10.6%, respectively, and these clones exponentially decayed with a half-life of 3.4 mo and 6.9 mo, respectively. Our model predicts that at the time of progression only 30% of the cells in the tumor carry a mutation in *RAS/EGFR/BRAF/MAP2K1*. This suggests that the remaining 70% are driven by undetected autonomous mechanisms of resistance, or paracrine effects. **Conclusions:** We identified that *RAS* and *EGFR* MT alleles decay exponentially over time since last EGFRi. These results provide a molecular explanation for the efficacy of EGFRi rechallenge therapies after a period off EGFR inhibition. The half-life of these clones may help guide timing of rechallenge therapies, and could be monitored by ctDNA. Further, these results suggest that a subclonal tumor population may be exerting resistance through paracrine mechanisms. These data will be validated on an external dataset.

ABSTRACT WITHDRAWN

3513 Poster Discussion Session; Displayed in Poster Session (Board #6), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Distinct impacts of *KRAS*, *NRAS* and *BRAF* mutations on survival of patients with metastatic colorectal cancer. *First Author: Yucai Wang, Mayo Clinic, Rochester, MN*

Background: *RAS* and *BRAF* mutations are associated with lack of response to anti-EGFR therapy and worse survival in patients with metastatic colorectal cancer (mCRC). *NRAS* mutations are less frequent than *KRAS* and *BRAF* mutations. While the prognostic implication of *BRAF* V600E mutations in mCRC is well established, the impact of *NRAS* mutations on outcome is unclear. **Methods:** Patients with mCRC who had *RAS/RAF* mutations tested at Mayo Clinic and MD Anderson Cancer Center between 2012 and 2016 were included in this study. Clinical information was obtained by chart review, and clinical characteristics and survival outcomes were compared among patients with different mutations. Categorical data were analyzed by Chi-square test, and time-to-event data were analyzed by Kaplan-Meier and Cox proportional hazards models. Statistical analysis was done in SPSS (v22). **Results:** In 2953 patients (1076 from Mayo and 1877 from MD Anderson), the mutation frequencies were: *KRAS* 45.6%, *NRAS* 3.8%, *BRAF* V600 8.0% and *BRAF* non-V600 1.3% (all wild-type [WT] 41.3%). 2282 patients with sufficient clinical information available were included for survival analysis, including 951 WT (41.7%), 1080 *KRAS* (47.3%), 91 *NRAS* (4.0%) and 160 *BRAF* V600 (7.0%). Compared with WT, *NRAS* patients were more likely female (47% vs 36%, $P = 0.031$) and had more right-sided cancers (30% vs 20%, $P = 0.031$). *NRAS* and *KRAS* patients did not differ in age, sex, sidedness, or MSI-H/dMMR. Compared with *BRAF*, *NRAS* patients were younger (< 60, 59% vs 44%, $P = 0.018$), had more left-sided cancers (70% vs 29%, $P < 0.001$), and had less MSI-H/dMMR (1% vs 17%, $P = 0.001$). The median follow-up was 42.7 months. The median overall survival (OS) for WT, *KRAS*, *NRAS* and *BRAF* patients were 49.2, 36.2, 30.1 and 22.5 months, respectively ($P < 0.001$). In multivariate analysis adjusting for age, sex and sidedness, *NRAS* patients had worse OS than WT (HR = 1.83 [1.40-2.39], $P < 0.001$) and *KRAS* patients (HR = 1.37 [1.06-1.78], $P = 0.016$). The OS difference between *NRAS* and *BRAF* patients was not statistically significant (HR = 0.81 [0.57-1.14], $P = 0.220$). **Conclusions:** *KRAS*, *NRAS* and *BRAF* mutations have distinct impacts on survival in mCRC. *NRAS* mutations carry a poorer prognosis compared with *KRAS*.

3514 Poster Discussion Session; Displayed in Poster Session (Board #7), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

KEYNOTE-164: Pembrolizumab for patients with advanced microsatellite instability high (MSI-H) colorectal cancer. *First Author: Dung T. Le, Johns Hopkins University, Baltimore, MD*

Background: Pembrolizumab is approved for the treatment of adult and pediatric patients (pts) with previously treated MSI-H cancer regardless of tumor type or site. This approval was based in part on data from cohort A of the phase 2 KEYNOTE-164 (NCT02460198) study of pts with MSI-H CRC after ≥2 prior lines of therapy including fluoropyrimidine, oxaliplatin, and irinotecan. In addition, in Cohort B of KEYNOTE-164, we evaluated the activity of pembrolizumab in pts with metastatic MSI-H CRC treated with ≥1 prior line of therapy. **Methods:** KEYNOTE-164 cohort B enrolled pts with metastatic CRC, MSI-H status confirmed locally by IHC or PCR, and ≥1 prior line of therapy (fluoropyrimidine, oxaliplatin, irinotecan, or anti VEGF/EGFR). Eligible pts received pembrolizumab 200 mg Q3W for 2 years or until progression, unacceptable toxicity, or withdrawal of consent. Tumor response was assessed Q9W per RECIST v1.1 by independent review. The primary endpoint was ORR. Secondary endpoints included DOR, PFS, OS, and safety. **Results:** Of 63 pts enrolled, median age (range) was 59 years (23-83), and 52% were male. Pts had a median of 2 prior therapies, and 94% had ≥1 prior therapy for advanced disease. As of Sep 12, 2017, median (range) duration of follow-up was 12.6 months (0.1-15.4). ORR was 32% (95% CI, 21-45) with 2 CRs and 18 PRs. Median DOR was not reached (NR); 95% of responses were ongoing with DOR ≥6 mo in 75% of responders. Median PFS was 4.1 month (95% CI, 2.1-NR) with a 12-month PFS rate of 41%. Median OS was NR with a 12-month OS rate of 76%. Forty (64%) pts had any grade treatment-related AEs, most commonly (≥10%) fatigue (18%), hypothyroidism (16%), and hyperthyroidism (11%); 7 (11%) pts had grade 3-4 treatment-related AEs of anemia, thrombocytopenia, diarrhea, pneumatosis intestinalis, arthritis, syncope, pneumonitis, and vasculitis (n = 1 each). There were no treatment-related deaths. Twenty (32%) pts had any grade immune-mediated AEs; 2 (3%) pts had grade 3-4 immune-mediated AEs of colitis and pneumonitis (n = 1 each). **Conclusions:** Pembrolizumab provided durable antitumor activity with a manageable safety profile in patients with MSI-H CRC that progressed after ≥1 prior line of therapy. Clinical trial information: NCT02460198.

3515 Poster Discussion Session; Displayed in Poster Session (Board #8), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Tumour-infiltrating CD8$^+$ lymphocytes as a prognostic marker in colorectal cancer: A retrospective, pooled analysis of the QUASAR2 and VICTOR trials. *First Author: Mark Glaire, University of Oxford, Oxford, United Kingdom*

Background: The intensity of the T cell anti-tumour response influences colorectal cancer (CRC) outcome, and may predict benefit from immunomodulatory therapies. However, previous studies have been limited by their modest size, heterogeneous non-experimental populations, and failure to adjust for confounders such as mismatch repair deficiency (MMR-D), *POLE* mutation, and chromosomal instability (CIN). **Methods:** We performed a prospective-retrospective, pooled biomarker study of 1804 CRCs from the QUASAR2 and VICTOR trials. The densities of CD8$^+$ and CD3$^+$ tumour infiltrate were quantified, and their association with clinical outcome analysed by univariable and multivariable Cox proportional hazards regression. **Results:** CD8$^+$ cell density was strongly correlated with CD3$^+$ infiltrate (Spearman rho = 0·65; $P = 2{\cdot}2 \times 10^{-16}$), and was significantly associated with stage II disease ($P = 1{\cdot}5 \times 10^{-4}$), right-sided primary tumour ($P = 4{\cdot}1 \times 10^{-6}$), MMR-D/*POLE* mutation ($P = 4{\cdot}9 \times 10^{-12}$), absence of chromosomal instability (CIN) ($P = 1{\cdot}2 \times 10^{-3}$) and *BRAF* mutation ($P = 3{\cdot}2 \times 10^{-3}$). In the QUASAR2 trial, CD8$^+$ density was a stronger predictor of CRC recurrence than CD3$^+$ alone, and showed similar discriminative ability to both markers in combination. In a pooled analysis of both studies, increasing CD8$^+$ density was associated with significantly reduced risk of tumour relapse and death. Unadjusted estimates of recurrence-free probabilities at 3 years were 76·3% (95%CI = 73·4 – 79·4) vs. 83·8% (95%CI = 81·4 – 86·3) for CRCs with CD8$^+$ cell density at the 10th and 90th centiles respectively. In multivariable analysis, CD8$^+$ density was a stronger predictor of CRC recurrence (HR for each two-fold increase = 0·92, 95%CI = 0·87–0·97, $P = 3{\cdot}2 \times 10^{-3}$) and overall survival (HR = 0·93; 95% CI = 0·87–0·99, $P = 0{\cdot}02$), than MMR-D/*POLE* mutation or CIN, which were not significantly associated with either endpoint after adjustment for CD8$^+$ infiltrate. **Conclusions:** Quantification of CD8$^+$ cell density holds promise to refine prognostication in CRC beyond current clinicopathological and molecular factors.

3516 Poster Discussion Session; Displayed in Poster Session (Board #9), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Serial circulating tumor DNA (ctDNA) analysis as a prognostic marker and a real-time indicator of adjuvant chemotherapy (CT) efficacy in stage III colon cancer (CC). *First Author: Jeanne Tie, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia*

Background: Adjuvant CT in stage III CC prevents recurrence by eradicating minimal residual disease (MRD) not visible on imaging. However, many patients (pts) will not have MRD and not all pts with MRD will benefit from standard CT. In this study, we determined (i) if the presence of ctDNA following surgery was predictive of recurrence following CT; (ii) if ctDNA could be used to determine the effectiveness of CT during treatment and (iii) if the presence of ctDNA following CT completion was predictive for later recurrence. **Methods:** Serial plasma samples from stage III CC pts planned for adjuvant CT were collected post-surgery, during CT and at treatment completion. Somatic mutations in individual tumors were identified via massively parallel sequencing of 15 genes commonly mutated in colorectal cancer. Personalized Safe-SeqS assays to quantify ctDNA in plasma samples were designed. Clinicians were blinded to ctDNA results. **Results:** 95 pts were enrolled from Nov-2014 to May-2017, median age was 64 years. All received adjuvant CT and 19 (20%) had recurred at a median follow-up of 21.1 months. We observed an inferior recurrence-free survival (RFS) in the 19 of 95 pts (20%) with positive ctDNA post-surgery (HR, 3.52; p = 0.004). ctDNA status changed from positive to negative in 10 of 17 pts (59%) after 2 months of CT; and 9 of 18 pts (50%) at CT completion. Superior RFS was observed when ctDNA became undetectable after CT (HR 5.11; p = 0.02). Conversely, ctDNA status changed from negative to positive after CT in 6 of 71 pts (8%) and was associated with an inferior RFS (HR 5.30; p = 0.006). Finally, inferior RFS was seen in the 15 of 89 (17%) with positive ctDNA after adjuvant CT completion (HR, 7.14; p < 0.001). **Conclusions:** ctDNA can reveal the presence of residual metastatic cancer cells not apparent on imaging in stage III CC patients. Serial analysis of ctDNA can define subsets of pts benefiting or not benefiting from CT and is therefore a real-time marker of adjuvant treatment efficacy in solid tumors. Further studies are needed to define how best to use ctDNA analysis to guide a personalized and risk adjusted approach to the initiation and modification of adjuvant CT in stage III CC.

3517 Poster Discussion Session; Displayed in Poster Session (Board #10), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Validation of neoadjuvant rectal cancer (NAR) score as a surrogate endpoint for overall survival in real-life practice settings. *First Author: Y. Nancy You, University of Texas MD Anderson Cancer Center, Houston, TX*

Validation Of Neoadjuvant Rectal Cancer (NAR) Score As A Surrogate Endpoint For Overall Survival In Real-life Practice Settings Background: Response to neoadjuvant therapy(NT) for rectal cancer(RC) correlates with long-term outcome. Pathologic complete response(pCR) has been used as an early endpoint in RC clinical trials, but is limited by its binary nature. NAR, a composite score available after resection, is a novel short-term surrogate endpoint. The association between overall survival(OS) and NAR has not been validated in clinical practice outside of clinical trials. **Methods:** The National Cancer Database (2004-2013) was queried for patients with non-metastatic RC and known staging and survival data (N = 47,833). Those who underwent neoadjuvant chemoradiation (45-54 Gy) and proctectomy formed the study cohort (N = 19,831). NAR was defined as [5 ypN - 3 (cT - ypT) + 12]^2/9.61. Patients were categorized by ypCR, pathologic stage, and NAR score (Table). OS was calculated by the Kaplan-Meier method and compared using log-rank tests. **Results:** Clinical stage was II (N = 9929, 50.0%) or III (N = 9932, 50.0%). After NT, 2490 patients (12.6%) achieved pCR (ypT0N0); another 5727 (28.9%) were downstaged (ypT1-2N0). The median NAR was 15.0 (Interquartile range: 8.4-26.6). After 4.2 years of follow-up, OS correlated with pCR, pathologic stage, and NAR categories (Table). **Conclusions:** Similar to data from clinical trials, NAR demonstrated predictive validity for OS in real-life practice. Nearly half of the RC patients nationwide had high NAR, and quartiling NAR offered best stratification of OS, highlighting the advantage of NAR as a versatile continuous measure of NT response.

Category	No. of patients (%)	5-year OS	p-value
Complete pathologic response (pCR)			< 0.001
Yes	2490 (12.6)	88.9	
No	17341 (87.4)	75.2	
Pathologic stage			< 0.001
ypT0N0	2490 (12.6)	88.9	
ypT1-2N0	5727 (28.9)	86.4	
ypT3,4 or N+	11614 (58.5)	69.8	
NAR risk (as defined from NSABP R04)			< 0.001
Low (< 8)	3629 (18.3)	88.0	
Intermediate (8-16)	9793 (49.4)	81.0	
High (> 16)	6409 (32.3)	64.6	
NAR quartiles			< 0.001
1st (< = 8.4)	3629 (25.0)	88.0	
2nd (8.5-15.0)	9793 (25.0)	81.0	
3rd (15.1-26.6)	1431 (25.0)	75.2	
4th (> 26.6)	1978 (25.0)	61.7	

3518 Poster Discussion Session; Displayed in Poster Session (Board #11), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

RIA: Randomized phase II study comparing induction (I) mFOLFOX6 with or without aflibercept followed by chemoradiation (CRT) and total mesorectal excision (TME) in high risk-rectal cancer. GEMCAD 14-02 trial. *First Author: Carlos Fernandez-Martos, Instituto Valenciano De Oncologia, Valencia, Spain*

Background: Preclinical studies suggest that VEGF blockade can have a role in the preoperative treatment of rectal cancer but how to combine it with chemotherapy (CT) and/or CRT remains controversial. Increased risk of postoperative morbidity has been reported with preop anti VEGF/CRT combination. Aflibercept (Afli) acts as a soluble receptor that binds to human VEGF-A, VEGF-B, PlGF. We hypothesized that administering Afli/FOLFOX followed by CRT would improve pathological complete response (pCR) without compromising wound healing. **Methods:** Between 1/2015-3/2017, pts selected with centrally reviewed magnetic resonance (mr) imaging with middle or distal third, mrT3/T4/N2 rectal adenocarcinoma were randomly assigned (2:1, stratified by mr extra-mural venous invasion and mrT4) to mFOLFOX6 with (arm 1) or without Afli (arm 2) prior to standard CRT (capecitabine with 50.4 Gy in 28 fractions) and TME. The study was designed to perform a hypothesis testing with an alpha = .2 and beta = .2. Due to two planned interim analyses (OáBrien), the threshold for statistical significance was p < 0.1984 in the final analysis. We present primary (pCR) and early secondary endpoints: acute toxicity and compliance. **Results:** 115/65 pts were assigned to arm 1/arm 2. The pCR rate (ypT0N0) in pts who underwent curative surgery was achieved in 25/103: 24.2%; (95% CI 16.36-33.71) in arm 1 and in 9/62: 14.5% (CI 6.86-25.78) in arm 2. p = 0.1335 Preoperative grade 3-4 toxicity occurred in 50% in arm 1 and 23% in arm 2 during the I period (difference mostly due to hypertension). Overall postoperative complications were similar between both arms (14.7% and 12.3%). Six cycles of I CT were administered in 92% and 95% and 90% and 96% completed CRT in arm 1 and 2 respectively. R0 resection rate was 87.3% and 88.7%. **Conclusions:** The addition of aflibercept to I mFOLFOX6 led to a significantly greater pCR rate compared with mFOLFOX6 alone in patients with high-risk rectal cancer. The experimental arm showed higher toxicity during the I phase, with similar toxicity afterwards and no increase in surgical complications. Funding: Sanofi Clinical trial information: NCT02340949.

3520 Poster Session (Board #13), Sun, 8:00 AM-11:30 AM

Genomic landscape, clinical characteristics and outcomes of early onset (EO) compared with average onset (AO) colorectal cancer (CRC). *First Author: Gustavo Dos Santos Fernandes, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The incidence of CRC in patients (pts) under the age of 50 has been rising over the past decade. Little is known about the biologic differences between early and AO (over the age of 50) CRC, but early reports suggest tumors in these EO patients are more aggressive and present with advanced disease. **Methods:** To better understand the differences in etiology and biology of these EO tumors, we retrospectively reviewed the charts of all pts with EO CRC (n = 384) treated at Memorial Sloan Kettering Cancer Center between 2014 and 2017 for pathology, radiology, and clinical characteristics and compared these to a cohort of AO CRC cases (n = 543). We also performed tumor sequencing using a targeted NGS panel (> 300 genes, MSK IMPACT). Pts with CRC related hereditary syndromes such as Lynch Syndrome and inflammatory bowel disease were excluded. **Results:** In the EO pts median age was 44 (17-50); 52% male and 48% female. Sixty-six % of patients had stage (St) IV disease at diagnosis, 24% had St III, 7% had St II, and 2.6% had St I. Twenty four % of pts wereBMI≥30 and 29% ever smoked. Family history of CRC in first or second degree relatives was present in 29%. The majority of pts had moderately differentiated (74%) and L sided tumors (78%). All EO and AO pts evaluated were MSS with a median mutational burden of 4.9 mut/Mb and 5.0 mut/Mb, respectively. The median age of AO pts was 61 (51-93). EO versus AO CRC identified enrichment of TP53 mutations (87v 78%, p = 0.001, q = .14) and 20q amplifications 5 vs 1% p = .006, q = 0.33). In metastatic pts median OS was higher in EO (73 vs 69, p = 0.022) months. In EO there was a trend towards no difference in outcomes between L vs R sided tumors (HR 1.53 p = 0.13). **Conclusions:** This is the largest cohort describing a broad range of clinical and genomic characteristics of the EO CRC population with comparison to AO CRC. In our initial analyses EO pts present with predominantly L sided tumors, with similar histology and few molecular differences when compared AO CRC. In contrast to prior reports, EO appears to be associated with better survival. Detailed clinical and molecular characterization and multivariate analysis of EO vs AO will be presented.

3521 Poster Session (Board #14), Sun, 8:00 AM-11:30 AM

Final overall survival (OS) analysis of first-line (1L) FOLFOX-4 ± cetuximab (cet) in patients (pts) with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 3 TAILOR trial. *First Author: Shukui Qin, Nanjing Bayi Hospital, Nanjing, China*

Background: The survival advantage conferred by the addition of cet to FOLFOX chemotherapy was verified in TAILOR, the first prospective, randomized, phase 3 study of the addition of cet to 1L FOLFOX in pts with *RAS* wt mCRC. We previously presented the primary analysis of the TAILOR trial, with fewer OS events. Here, we provide the final OS results for this trial. **Methods:** TAILOR was an open-label, randomized, multicenter, phase 3 trial with a modified intention-to-treat (mITT) population of 393 pts from China that evaluated FOLFOX-4 ± cet in *RAS* wt mCRC. The primary endpoint was progression-free survival (PFS) time; secondary endpoints include OS time, overall response rate (ORR), and safety/tolerability. **Results:** An updated analysis (performed after 84% of events occurred) verified the survival advantage of the addition of cet to FOLFOX-4 (Table). Additionally, > 77% of pts in the cet + FOLFOX-4 arm reached ≥ 80% dose intensity of cet, confirming that cet + FOLFOX-4 has high compliance. There were no new or unexpected safety findings. Finally, 59.6% and 56.0% of pts in the cet + FOLFOX-4 and FOLFOX-4 arms, respectively, received subsequent anticancer therapy after treatment discontinuation (54.4% and 49.5% received any chemotherapy, and 17.6% and 27.0% received any targeted therapy). Clinical trial information: NCT01228734. **Conclusions:** The TAILOR study met all its endpoints, confirming cet in combination with FOLFOX-4 as an effective standard-of-care 1L treatment regimen for pts with *RAS* wt mCRC. We acknowledge that OS findings for the mITT population are likely influenced by the low percentage of pts who received further lines of treatment after progression on their 1L regimen, suggesting regional differences in access to anticancer therapy.

Efficacy outcome	Cet + FOLFOX-4 (n = 193)	FOLFOX-4 (n = 200)
OS		
# events	156	174
Median, months	20.8	16.5
95% CI	16.3-23.5	14.8-19.5
HR (95% CI); p value	0.763 (0.614-0.949); p = .015	
PFS by investigator		
# events	165	142
Median, months	9.2	7.4
95% CI	8.8-10.9	5.8-7.5
HR (95% CI); p value	0.629 (0.498-0.794); p < .001	
Response rate by investigator, %		
ORR	66.3	40.5
95% CI	59.2-72.9	33.6-47.7
OR (95% CI); p value	2.893 (1.918-4.363); p < .001	

3522 Poster Session (Board #15), Sun, 8:00 AM-11:30 AM

Effect of matched therapy in metastatic colorectal cancer on progression free survival in the phase I setting. *First Author: Michael Lam, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The benefits of matching targeted treatments to aberrations identified by molecular profiling (MP) is unclear. Outcomes in phase 1 settings have been traditionally reported across tumor histologies. We report outcomes based on a metastatic colorectal cancer (mCRC) population. **Methods:** Patients (pts) with mCRC receiving at least one dose of treatment on a phase 1 study were annotated for variants detected by MP. A precision oncology decision support (PODS) team determined variant function and actionability. A matched therapy (MT) was defined as allocation to a novel agent that targeted the aberration or predicted pathway deemed actionable by PODS. Progression-free survival (PFS) was estimated using the Kaplan-Meier method. A Cox proportional hazards model was used to estimate hazard ratios (HR). **Results:** A total of 370 patients enrolled onto 467 phase 1 trials were identified from January 2012 to April 2017. 106 enrolments were assigned to MT. Pts with microsatellite instability-high (MSI-H), $BRAF^{V600E}$, PIK3CA mutation were more likely to be assigned a MT, while left-sided tumors and RAS mutant patients were less likely to be treated with a MT. Molecularly-targeted regimens (MTR) were utilized more frequently in MT while immune-targeting MTR was more common in non-MT. $BRAF^{V600E}$ mutations and HER2 amplification/overexpression made up 44.3% of MT. There was a significant difference in PFS between the MT vs non-MT group (HR 0.65, 95% CI 0.51-0.83, p = 0.016) in univariate analysis. The 6-month PFS probability was 31% (95% CI; 23-41%) versus 13% (95% CI; 10-17%) respectively. Other significant factors in univariate analysis associated with longer PFS were MSI-H, $BRAF^{V600E}$ and use of a regimen containing cytotoxic chemotherapy while RAS mutations were associated with shorter PFS. In multivariate analysis, after correcting for mutation status, allocation to a MT was associated with improved PFS (HR = 0.72, 95% CI 0.50-0.99, p = 0.043). **Conclusions:** Matching clinical trial enrollment to MP based on dedicated decision support is associated with improved outcomes in mCRC patients. The MT strategy is still hampered by a limited number of actionable variants, and is driven by a small number of active MTs.

3523 Poster Session (Board #16), Sun, 8:00 AM-11:30 AM

APOLLON: A phase I/II study of panitumumab combined with TAS-102 in patients (pts) with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC). *First Author: Yasutoshi Kuboki, Gastrointestinal Oncology Division, National Cancer Center Hospital East, Kashiwa, Japan*

Background: APOLLON is an open-label, single-arm phase I/II study investigating the efficacy and safety of panitumumab (Pmab) in combination with TAS-102 (trifluridine/tipiracil) in pts with *RAS* (*KRAS*/*NRAS*) wt mCRC refractory to standard chemotherapy. The recommended phase II dose (RP2D) of this combination was reported in ASCO-GI 2017 as Pmab at 6 mg/kg on Days 1 and 15, every 4 weeks (Q4W) and TAS-102 at 35 mg/m² BID on Days 1–5 and 8–12, Q4W, and was well tolerated without dose-limiting toxicities. Here, we present the efficacy and safety data for pts treated with Pmab with TAS-102 at the RP2D. **Methods:** Eligible pts were aged 20–74 years (y); ECOG PS 0–1; with *RAS* wt mCRC; refractory or intolerant to fluoropyrimidines, irinotecan, oxaliplatin or anti-angiogenesis therapy; and had no prior treatment with any anti-EGFR antibody, TAS-102 or regorafenib. Primary endpoint was investigator-assessed progression-free survival (PFS) at 6 months in RP2D-treated pts (including seven pts in phase I). Secondary endpoints included PFS, response rate (RR), disease control rate (DCR) and safety. Using an exact single-stage binomial design, 47 pts were required, with a 6-month PFS of 48% deemed promising and 29% unacceptable (one-sided $\alpha = 0.05$; $\beta = 0.2$). **Results:** From 2015 to 2017, 56 pts (30 male) with a median age of 64 y (range: 38–74 y) were enrolled. Median follow-up was 10.4 months. 6-month PFS rate (n = 54) was 33.3% (90% CI: 22.8–45.3; p = 0.2414). Median PFS, RR and DCR were 5.8 months (95% CI: 4.5–6.5), 37.0% and 81.4%, respectively (n = 54). The most common grade (G) 3/4 treatment-emergent adverse events (n = 55) included neutropenia (G3: 30.9%, G4: 16.4%), febrile neutropenia (G3: 10.9%), stomatitis (G3: 9.1%), dermatitis acneiform (G3: 9.1%), fatigue (G3: 3.6%) and hypomagnesemia (G3: 3.6%). There were no treatment-related deaths or unexpected safety signals. **Conclusions:** The first phase II study of Pmab with TAS-102 at the RP2D showed favorable antitumor activity with an acceptable safety profile for pretreated pts with *RAS* wt mCRC, although the primary endpoint of PFS at 6 months did not meet the prespecified threshold. Clinical trial information: NCT02613221.

3524 Poster Session (Board #17), Sun, 8:00 AM-11:30 AM

Optimizing treatment strategy for advanced rectal cancer in the West and Japan: International multicenter cohort study. *First Author: Akira Ouchi, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The treatment strategies for locally advanced rectal cancer in the West and Japan have evolved through divergent philosophies - preoperative chemoradiation (CRT) and total mesenteric excision (TME) in the West and upfront TME with lateral pelvic node dissection (LPND) in Japan. The purpose of this study was to compare these approaches. **Methods:** Consecutive patients with ≥cT3 rectal cancer located ≤12 cm from the anal verge and diagnosed between 1998 and 2013 at 3 tertiary cancer centers (1 US and 2 Japan) were identified. Only patients who received preoperative CRT+TME in the US and those who underwent TME+/-LPND based on tumor location in Japan were included. The primary outcome was cumulative rate of local recurrence (LR) and secondary outcomes included relapse free survival (RFS). **Results:** A total of 1597 patients (836 US and 761 Japan) met study criteria and were analyzed. Adjuvant chemotherapy was given to 88.4% in the US and 24.4% in Japan. Five-year cumulative risk for LR was 4.6% in the US and 6.7% in Japan ($HR_{adjusted}$ 0.58 [95% CI 0.30-1.13]). Overall RFS was longer in the US on univariate analysis (HR 2.09 [1.64-2.66], p < 0.001), but after adjustment for (y)p stage and relevant covariates, did not differ from Japan ($HR_{adjusted}$ 0.89 [0.66-1.19]). Following CRT and TME in the US or TME+/-LPND in Japan, 63.4% and 21.2% of stage cIII patients were downstaged, respectively. On stage stratified adjusted analysis, there were no differences in RFS for stage cII and (y)pII subgroups; meanwhile RFS in stage cIII subgroup was significantly longer in the US, but did not differ for stage (y)pIII subgroup (Table). **Conclusions:** This is the first comparison of a large cohort of patients treated by CRT+TME, and TME+/-LPND within dedicated cancer centers in the US and Japan. Overall the rates of local recurrence were lower than historically reported. These results suggest good outcomes can be achieved without CRT for some stage cII patients but that neoadjuvant CRT is associated with improve survival for stage cIII patients who are downstaged.

RFS	$HR_{adjusted}$ [95% CI]	p
Stage cII	1.40 [0.73-2.68]	0.30
Stage (y)pII	1.28 [0.53-3.11]	0.57
Stage cIII	2.54 [1.79-3.61]	< 0.001
Stage (y)pIII	0.86 [0.61-1.21]	0.41

3525 Poster Session (Board #18), Sun, 8:00 AM-11:30 AM

Change in CEA as an early predictor of progression to first-line systemic therapy in metastatic colorectal cancer. *First Author: Pat Gulhati, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Carcinoembryonic antigen (CEA) levels are used in conjunction with imaging to monitor response to systemic therapy in pts with metastatic colorectal cancer (mCRC). We sought to identify a threshold for change in CEA from baseline that can predict progressive disease (PD) at first restaging scan in mCRC pts receiving first-line therapy. **Methods:** Pts from trials collected in ARCAD database were included if baseline CEA was ≥10 ng/mL and repeat CEA was available within 14 days of first restaging scan. Optimal cutoffs for CEA change were identified by ROC analysis. Prediction performance of cutoffs was evaluated by sensitivity, specificity, and negative predictive value (NPV). Analyses were conducted by treatment class: chemotherapy alone (chemo) and chemotherapy plus anti-VEGF antibody (anti-VEGF). **Results:** 2828 pts from 7 trials [M/F: 60%/40%; median age: 61 yrs; ECOG PS 0-1: 97%] with mCRC [55% pts with ≥2 metastatic sites] treated with systemic therapy were included. In chemo group (n = 957), median percent change of CEA from baseline to first restaging was -53.1% and +23.6% for pts with CR/PR/SD and PD, respectively. In anti-VEGF group (n = 1355), median percent change of CEA was -71.7% and -45.3% for pts with CR/PR/SD and PD, respectively. Optimal cutoffs based on sensitivity and specificity (AUC cutoff) or 99% NPV are shown in the table. The optimal AUC cutoff for differentiating PD from CR/PR/SD on first restaging was -7.5% for chemotherapy and -62.0% for anti-VEGF group. A drop in CEA less than optimal AUC cutoff was significantly associated with higher risk of PD at 1st restaging; chemo, $OR^{adj} = 6.51$; anti-VEGF, $OR^{adj} = 3.45$. The use of a 99% NPV cutoff for prediction of CR/PR/SD would avoid a CT scan at first restaging in 21% of chemotherapy and 16% of anti-VEGF treated patients. **Conclusions:** Change in CEA from baseline to first restaging can accurately predict PD in pts receiving chemotherapy.

PD Prediction by CEA	Change in CEA	AUC	Sensitivity	Specificity	NPV	CT scans avoided
Cutoff by optimal AUC						
Chemo only	-7.5%	0.79	71.6%	76.2%	97.3%	72.8%
Chemo + Anti-VEGF	-62.0%	0.72	66.7%	63.6%	97.9%	62.4%
Cutoff by 99% NPV						
Chemo only	-79.4%	0.79	97.0%	22.4%	99%	21.0%
Chemo + Anti-VEGF	-88.7%	0.72	96.3%	16.7%	99%	16.0%

3526 Poster Session (Board #19), Sun, 8:00 AM-11:30 AM

A validation study of stratification by the 55-gene classifier for assessing recurrence risk in stage II colon cancer: The 55 STAR study (UMIN23879). *First Author: Shigeki Yamaguchi, Gastroenterological Surgery, Saitama Medical University International Medical Center, Hidaka-Shi, Japan*

Background: Cancer subtypes classified by DNA microarray data have shown excellent abilities in predicting patient prognosis; in particular, consensus molecular subtypes (CMSs) are regarded as the most robust classification system with clear biological interpretability. Recently, we performed unsupervised clustering analysis using a public database and selected the expression of 55 gene to construct a discriminant model with the aim of classifying colon cancer (CC) into three subtypes: "microsatellite instability (MSI)-like", "chromosomal instability (CIN)-like", and "stromal"; the recurrence rates of these subtypes were shown to be different (p = 0.001). In this study, we conducted a retrospective, multi-institutional study to validate the quality of a novel 55-gene classifier (55GC) for Stage II CC and compared 55GC subtypes with the CMS categories. **Methods:** We collected formalin-fixed, paraffin-embedded cancer specimens from 232 patients with Stage II CC who underwent curative surgery (R0) without adjuvant chemotherapy at 10 institutions between 2009 and 2012. Tissue sections were prepared from each specimen and subjected to DNA microarray measurement. **Results:** Using the 55GC, patients were classified as having the MSI-like subtype in 27%, CIN-like in 41%, and stromal in 32% of the cases. The 5-year recurrence-free survival (RFS) rate of patients with the MSI-like, CIN-like, and stromal subtype cancers was 88.5%, 83.3%, and 71.2%, respectively (stromal vs. others: p = 0.0049). Multivariate analysis by Cox's proportional hazard model revealed that stromal subtype (hazard ratio, 2.3; p = 0.0063), pT4, and the number of lymph nodes examined (< 12) were independent poor prognostic factors. The overall concordance rate between 55GC and CMS was 72%: 29% (18/62) of the MSI-like subtype, 79% (75/95) of the CIN-like subtype, and 98% (74/75) of the stromal subtype were judged as CMS1, CMS2/3 and CMS4, respectively. The 5-year RFS rate of patients with CMS1, CMS2/3 and CMS4 was 100%, 86.3%, and 73.0%, respectively (CMS4 vs. others: p = 0.005). **Conclusions:** 55GC is a useful and reproducible grading system for recurrence risk stratification of Stage II CC.

3527 Poster Session (Board #20), Sun, 8:00 AM-11:30 AM

Effect of PET-CT on disease recurrence and its management in patients with potentially resectable colorectal cancer liver metastases. The long-term results of a randomized controlled trial (PET-CT Imaging prior to liver resection for colorectal adenocarcinoma metastases). *First Author: Pablo Emilio Serrano Aybar, McMaster University, Hamilton, ON, Canada*

Background: The PETCAM randomized trial evaluated the effect of preoperative PET-CT (vs. no PET-CT) on surgical management in patients with colorectal cancer liver metastases. This trial resulted in 8% change in surgical management, including a higher proportion of major liver resections in the PET-CT arm. This study is the long-term follow up of the PETCAM trial and aims to compare the disease-free (DFS), overall survival (OS), and long-term clinical course of enrolled patients. **Methods:** Recruitment to the trial occurred between 2005-2010, with last follow-up in 2013. Data on recurrence, management and mortality from 2013-2017 was collected retrospectively. Cox proportional Hazard Models were used to calculate risk for recurrence and death. OS was calculated with Kaplan-Meir method and compared with log-rank test. **Results:** At 5 years, 172/404 (43%) patients were alive. There were no differences in DFS (HR: 1.13, 95%CI: 0.89-1.43) or OS (HR: 1.02, 95%CI: 0.78-1.32) between groups. Median DFS was 17 months, 95%CI: 14-19. Risks factors for recurrence were: extrahepatic disease, liver tumour size, nodal stage and disease-free duration. Median OS was 51 months, 95%CI: 44-64. During the follow-up period, 264/368, 72% patients recurred, mostly lung (51%) and liver (41%); 120/264 (46%) received chemotherapy and 112/264, 42% were re-resected, with a recurrence of 72% (81/112). Median OS following first recurrence was 28 months, 95%CI: 24-31. Most important risks factors for death following recurrence are node-positive disease, more than one recurrence site and disease-free duration < 5 months. **Conclusions:** PET-CT did not improve DFS or OS. Recurrence following liver resection is common. Prognosis following recurrence is worse compared to first recurrence. Patients with high risk factors should not undergo surgical resection. Clinical trial information: NCT00265356.

3528 Poster Session (Board #21), Sun, 8:00 AM-11:30 AM

A randomized phase II study of perioperative chemotherapy plus bevacizumab versus postoperative chemotherapy plus bevacizumab inpatients with upfront resectable hepatic colorectal metastases (APPROACH). *First Author: You Jin Chun, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Seoul, Korea, Republic of (South)*

Background: Whether patients with resectable colorectal cancer liver metastases (CRLM) gain a survival benefit or not from neoadjuvant chemotherapy remains controversial. The addition of bevacizumab to chemotherapy also remains unclear. **Methods:** 76 patients with CRLM were randomly assigned to either six cycles of FOLFOX or FOLFIRI with bevacizumab before and six cycles after surgery or to twelve cycles after surgery. The primary objective was to detect DFS. The primary analysis was by intention to treat and DFS were estimated by the Kaplan-Meier method and compared by the log-rank test. This trial was registered with ClinicalTrials.gov, number NCT01632722. **Results:** In patients with chemotherapy plus bevacizumab, the median DFS was 37.4 months at 5.4 years follow-up and the median overall survival (OS) was not reached. The DFS between the perioperative group and the postoperative group showed a better tendency in the perioperative group, but there was no statistical difference (HR 0.837 [95.0% CI 0.606-1.156], *p = 0.280).* The OS was statistically better in the perioperative group (*p = 0.049).* There was no difference in DFS between the two groups in patients with CEA≥5 or more than two liver metastases, but there was OS benefit in the perioperative group than in the postoperative group (CEA, HR 0.485 [95.0% CI 0.252-0.933], *p = 0.030;* number of liver metastases, HR 0.548 [95.0% CI 0.300-0.999], *p = 0.049).* BMI, the largest size of liver metastases, primary T or N stage, disease-free interval, and sidedness did not affect the difference in DFS and OS. There was no difference in postoperative complications of bevacizumab and adverse event during chemotherapy between the two groups. **Conclusions:** In patients with resectable CRLM, perioperative chemotherapy had no effect on DFS but improved OS. The perioperative chemotherapy plus bevacizumab do not increase the risk of complications in liver resection. Patients with high levels of CEA or the number of liver metastases may have benefited from perioperative chemotherapy. Clinical trial information: NCT01632722.

3529 Poster Session (Board #22), Sun, 8:00 AM-11:30 AM

Impact of the type and modalities of preoperative chemotherapy on the outcome of liver resection for colorectal liver metastases: A LiverMetSurvey study. *First Author: Yuichi Goto, Centre Hépato-Biliaire, AP-HP, Hôpital Paul Brousse, Villejuif, France*

Background: Prognostic factors of survival have been extensively reported after resection of colorectal liver metastases (CLM). However, a specific analysis of patients submitted to preoperative chemotherapy (PCT), with the real impact of type and modalities of PCT on patient outcome is lacking. **Methods:** The study population consisted of a multicentric cohort of patients who received PCT before resection of CLM within a 20-year period and whose data were prospectively collected in the LiverMetSurvey. Patients were analyzed in terms of intentions of PCT including neoadjuvant (N-CT) and conversion (C-CT) chemotherapy. Overall survival (OS) rates were analyzed by Kaplan-Meyer method and compared using the log-rank test. The distribution of potential prognostic factors for OS including age, sex, sidedness of primary tumor, timing of metastases, tumor number, diameter of largest CLM, CEA, bilaterality, and type and number of PCT cycles were analyzed by Cox regression model. **Results:** Of 7,202 eligible patients, N-CT was submitted in 4,422 (61.4%) for resectable and C-CT in 2,780 patients (38.6%) for unresectable CLM. In N-CT, 5-year OS of Irinotecan-based (Iri-) PCT was decreased compared to the oxaliplatin-based (Oxa-) PCT (40.9% vs. 47.8%, $p < 0.01$). The 5-year OS was not different with or without targeted therapy (41.1% vs. 47.0%, $p = 0.12$). As for C-CT, the 5-year OS was comparable between Iri- and Oxa-PCT (32.2% vs. 32.9%, $p = 0.32$), and also not different with regard to the use of targeted therapy ($p = 0.47$). On multivariate analysis, Iri-PCT was associated with worse OS in N-CT (HR = 1.46 [1.02-1.52], $p = 0.02$) but not in C-CT ($p = 0.89$). Use of targeted therapy was not associated with OS for both N-CT and C-CT ($p = 0.53$, $p = 0.06$, respectively). PCT > 6 cycles in N-CT (HR = 1.46 [1.23-1.76], $p = 0.04$) and > 8 cycles in C-CT (HR = 2.39 [1.73-3.30], $p < 0.01$) was associated with worse OS. **Conclusions:** For resectable CLM with N-CT, Oxa-PCT is associated with better survival compared to Iri-PCT. For unresectable CLM with C-CT, the type of PCT did not influence the outcome, provided that resection was achieved. For both, the shorter is the PCT, the best is the survival after surgery.

3530 Poster Session (Board #23), Sun, 8:00 AM-11:30 AM

Multicenter phase I/II trial of BBI608 and pembrolizumab combination in patients with metastatic colorectal cancer (SCOOP Study): EPOC1503. *First Author: Eiji Shinozaki, Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: The anti–PD-1 antibody pembrolizumab provided an objective response rate of 28-57% in patients (pts) with Microsatellite Instability–High (MSI-H) metastatic colorectal cancer (mCRC) vs 0% in pts with Non-MSI-H. The WNT/β-catenin signaling has been reported to prevent anti-tumor immunity and promote resistance of anti-PD-1/PD-L1 antibodies. Furthermore, STAT3 has been known to be a key driver of the immune evasion. This study investigates efficacy and safety of the combination of BBI608, which blocks phosphorylated STAT3 and downregulates WNT/β-catenin signaling, with pembrolizumab in pts with mCRC. BBI608 480mg BID with pembrolizumab was determined as RP2D in the phase I part (Kawazoe A, et al. ASCO-GI 2018). Here, we present the preliminary results of the ongoing phase II part. **Methods:** Phase II part was composed of Cohort A (MSI-H) and Cohort B (Non-MSI-H). The main eligibility criteria was pts with mCRC not responded or intolerant to standard chemotherapies. Primary endpoint was Immune-related objective response rate (irORR) determined by irRECIST. Sample size for Cohort A with 10 pts was determined in an exploratory manner. In Cohort B, according to a null hypothesis and alternative hypothesis; irORR = 5% and 20%, estimating required sample size was 40 pts with a one-sided alpha of 5% and power of 90%. **Results:** From Feb 2017 to January 2018, 10 pts were enrolled in Cohort A, and 37 pts in Cohort B. As of October 2017, tumor response was evaluated in 3 pts of Cohort A and 25 pts of Cohort B, respectively. Two out of the 3 pts in Cohort A showed confirmed partial response. Among 12pts with right-sided colon in Cohort B, one patient showed confirmed partial response with remarkable decline of CEA level, and two pts showed stable disease lasting more than 16 weeks. Immunohistochemistry before treatment demonstrated the high expressions of PD-L1, CD8, and MHC-class I in the tumor samples from the patient with partial response. No severe or unexpected adverse events occurred up to the present. **Conclusions:** BBI608 with pembrolizumab showed preliminary efficacy signals with acceptable toxicity for MSI-H as well as Non-MSI-H mCRC pts with right-sided primary. Clinical trial information: NCT02851004.

3531 Poster Session (Board #24), Sun, 8:00 AM-11:30 AM

Results of a randomized phase 3 study evaluating the potential benefit of a second-look surgery plus HIPEC in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP- NTC01226394). *First Author: Diane Goere, Institut Gustave Roussy, Villejuif, France*

Background: Complete cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) allow to prolong survival in patients with colorectal peritoneal metastases (CRPM), especially with a low tumor burden. The aim of the PROPHYLOCHIP multicentric randomized phase 3 study was to evaluate the potential survival benefit of a systematic second-look surgery plus HIPEC in patients at high risk of developing CRPM. **Methods:** Patients at high risk of developing CRPM defined as minimal CRPM resected with the primary, or history of ovarian metastases, or perforated primary tumor, were eligible. After 6 months of adjuvant chemotherapy, patients without sign of recurrence were randomized into 2 arms: (1) surveillance, (2) systematic second-look surgery plus HIPEC (intraperitoneal oxaliplatin). The primary end-point was the 3-year disease-free survival (DFS). Secondary end-points included overall survival (OS), peritoneal DFS and postoperative complications. **Results:** Between 2012 and 2015, 150 patients were randomized. During the second-look laparotomy (n = 71), CRPM was diagnosed in 52%, with a median peritoneal cancer index of 4 [0-26]. No patient died postoperatively and grade 3-4 complications occurred in 41%. After a median follow-up of 51 [47-55] months, the 3-year DFS of 44% [33-56] in the second-look group and of 51% [40-62] in the surveillance group did not differ ($p = 0.75$). In the surveillance group, a peritoneal relapse occurred in 25 (33%) patients, which was accessible to CRS-HIPEC in 16, whereas in the second-look group, 24 (32%) patients had a peritoneal relapse of whom 2 were treated with a new CRS-HIPEC. The 3-year OS was not significantly different, 80% [69-88] and 79% [68-87] in the surveillance and in the second-look groups, respectively. **Conclusions:** This study confirms that criteria for high risk of developing PM are strong, and strengthens the role of a peritoneal-centered surveillance in these patients. However, a pro-active strategy including a systematic second-look surgery plus HIPEC failed to improve survival, in comparison to an adequate surveillance. Clinical trial information: NCT01226394.

3532 Poster Session (Board #25), Sun, 8:00 AM-11:30 AM

High levels of cell-free DNA (cfDNA) at baseline (BL) and increase of at least one mutation at day 14 (D14) as independent prognostic biomarkers for patients (pts) with advanced colorectal cancer (aCRC) under regorafenib. *First Author: Pashalina Kehagias, Gastro-Oncology Translational Laboratory, Institut Jules Bordet - Université Libre de Bruxelles (ULB), Brussels, Belgium*

Background: BL-cfDNA combined with plasmatic changes in tumor-specific mutations after 14 days of therapy are explored as independent determinants of outcome in pts with aCRC. **Methods:** Archival tumor tissue and plasma samples at BL and D14 after regorafenib initiation were prospectively collected in aCRC pts (n=141) in a multicentric trial (NCT01929616). Tumor-specific mutations, selected on their allelic frequency on CRC-oriented targeted sequencing of tumor tissue, were analyzed for circulating tumor DNA (ctDNA) at BL and D14 via droplet digital PCR (Bio-Rad QX200 ddPCR system) using a 12 % cutoff to assess changes in ctDNA levels. **Results:** The cfDNA's optimal cutoff at BL (Contal & O'Quigley method) is 1 μg/ml in 134/141 evaluable pts. Hazard ratio (HR) of cfDNA ≥1 vs <1 is 2.50 (95% CI, 1.73-3.63) $P<0.001$ for progression-free survival (mPFS) and 3.83 (95% CI, 2.57-5.71) $P<001$ for overall survival (mOS). The most common mutated genes (96 evaluable pts for ctDNA) are *APC* (73%), *TP53* (72%), *KRAS* (66%), and *PI3KCA* (23%). On average 2 (1-4) mutations are followed per pt. An increase of ≥1 tumor-specific mutation as compared to none is associated with a significantly worse outcome: mPFS 1.3 vs 3.0 months (mo) (HR 1.88, $P=0.002$, 95% CI 1.24-2.85) and mOS 3.9 vs 8.5 mo (HR 2.04, $P<0.001$, 95% CI 1.33-3.12). BL cfDNA level and ctDNA changes between BL & D14 are not statistically correlated ($P=0.23$), and combined, define 4 subgroups with different prognosis. (Table 1) **Conclusions:** BL cfDNA and early (D14) changes in ctDNA during treatment with regorafenib are independent predictive markers for pts' outcome and appear as potential robust tools for treatment personalization. Clinical trial information: NCT01929616.

	mPFS (mo)		mOS (mo)	
	0 mut increase	≥ 1 mut increase	0 mut increase	≥ 1 mut increase
BL cfDNA ≥1	1.3 (95% CI, 1.1 - 3.0) n=19	1.1 (95% CI, 0.4 - 1.3) n=30	6.1 (95% CI, 2.1 - 8.1) n=19	2.3 (95% CI, 1.3 - 3.0) n=30
HR	*1.79 (95% CI, 0.99-3.23) P 0.05*		*2.43 (95% CI, 1.29-4.59) P 0.006*	
BL cfDNA<1	4.8 (95% CI, 1.6 - 5.1) n=24	2.2 (95%CI, 1.3 - 3.1) n=23	13.8 (95% CI, 8.2 - 19.1) n=24	6.6 (95% CI, 5.9 - 10.9) n=23
HR	*1.85 (95% CI, 1.02 - 3.35) P 0.04*		*1.83 (95% CI, 0.99 - 3.37) P 0.05*	

3533 Poster Session (Board #26), Sun, 8:00 AM-11:30 AM

Circulating tumor DNA (ctDNA) as an early marker to monitor clinical benefit of regorafenib and TAS-102 in patients with metastatic colorectal cancer (mCRC). *First Author: Allan Andresson Lima Pereira, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Utilization of ctDNA has been rapidly adopted as a predictive diagnostic in advanced Non-Small Cell Lung Cancer and indications in GI cancers may be emerging. We aimed to evaluate ctDNA as an early biomarker of efficacy of new therapies for mCRC. **Methods:** mCRC patients (pts) who consented to a genomic matching protocol and had started a new line treatment with regorafenib or TAS-102 were eligible. Droplet digital PCR (ddPCR) assays were performed using 3 mL of plasma samples from pts with tumors harboring *RAS* mutations (BioRad). Serial plasma samples also underwent retrotransposable element (RE) based multiplexed qPCR assay using 300 μL of plasma; a DNA Integrity Index (DII) was calculated using a ratio of long to short DNA fragment size concentrations (Innogenomics). Progressive disease (PD) by ctDNA, defined as any increase in allele frequency (AF) by ddPCR and any decrease in DII by RE-qPCR, was compared to RECIST at first restaging. **Results:** 40 mCRC pts were included. 16 pts were treated with regorafenib and 31 with TAS-102 (7 pts received both drugs). Therefore, 47 treatment regimens were included in this study with serial monitoring completed in 22 treatments with ≥ 2 serial plasma samples. At baseline, the median AF by ddPCR was 18.1% and the median DII was 0.112. A moderate correlation was seen between baselines CEA and AF by ddPCR ($r = 0.43$; $p = 0.056$). The sensitivity and specificity of ddPCR in detecting PD by RECIST was 61.5% (95%CI: 32% - 86%) and 100%, respectively. RE-qPCR had a sensitivity of 47.4% (95%CI: 24% - 71%) and specificity of 100%. Unlike ddPCR which was limited to monitoring patients with common mutations in *KRAS* and *NRAS*, the DII was successfully obtained in all patients. There was no false-positive in either assays. Serial change in CEA was more sensitive (77.8%), but less specific (16.8%). **Conclusions:** Our findings suggest that pts with ctDNA predicted PD may be safely switched to another treatment before radiologic restaging. ctDNA by both ddPCR and RE-qPCR can predict later radiological progression with high specificity, with RE-qPCR providing benefits of a universal assay and limited sample requirements.

3534 Poster Session (Board #27), Sun, 8:00 AM-11:30 AM

Impact of primary tumor side on outcomes of every-2-weeks (q2w) cetuximab + first-line FOLFOX or FOLFIRI in patients with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC) in the phase 2 APEC trial. *First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Woodville, Australia*

Background: In the *RAS* wt population of APEC, q2w cetuximab combined with first-line FOLFOX or FOLFIRI achieved an overall response rate (ORR), median progression-free survival (PFS), and median overall survival (OS) similar to those reported in prior first-line pivotal studies involving weekly cetuximab. In this subgroup analysis, we evaluated the impact of tumor side in the APEC study population with *RAS* wt mCRC. **Methods:** APEC was a nonrandomized phase 2 trial conducted in the Asia-Pacific region, with ORR as the primary endpoint. Patients with *KRAS* exon 2 wt tumors received q2w cetuximab + investigator's choice of FOLFOX or FOLFIRI. Tumor side was categorized in evaluable patients with *RAS* wt tumors (left [L]-sided = splenic flexure, descending colon, sigmoid colon, and rectum; right [R]-sided = appendix, cecum, ascending colon, hepatic flexure, and transverse colon). **Results:** Among 167 patients with *RAS* wt mCRC, 159 were evaluable for tumor side; 130 (81.8%) had L-sided and 29 (18.2%) had R-sided mCRC. Baseline characteristics in the tumor side subgroups reflected the known differences between L- and R-sided mCRC; indeed, 95.4% and 75.9% of patients had *BRAF* wt disease, respectively. Efficacy data are summarized in the Table. **Conclusions:** Consistent with prior first-line pivotal studies with weekly cetuximab, a prognostic effect of tumor side in patients receiving first-line q2w cetuximab was confirmed in APEC. In patients with R-sided mCRC, ORR remained ≥ 50%, and resection rate was comparable to that of L-sided patients, in line with prior evidence showing that use of cetuximab may be appropriate when rapid tumor shrinkage is the goal. These hypothesis-generating data raise the possibility of a synergy between cetuximab and irinotecan in patients with R-sided tumors, although numbers are small. Clinical trial information: NCT00778830.

	L-side			R-side		
	Cetuximab + FOLFIRI	Cetuximab + FOLFOX	Total	Cetuximab + FOLFIRI	Cetuximab + FOLFOX	Total
n	43	87	130	10	19	29
ORR, %	74.4	65.5	68.5	50.0	52.6	51.7
Median PFS, months	12.8	14.2	14.0	15.4	8.3	8.9
Median OS, months	31.7	30.6	30.6	32.1	21.8	24.6
Resection rate, %	2.3	14.9	10.8	10.0	10.5	10.3

3535 Poster Session (Board #28), Sun, 8:00 AM-11:30 AM

Induction chemotherapy (CT) with FOLFIRINOX or FOLFOX/FOLFIRI, plus cetuximab (CET) or bevacizumab (BEV) (by RAS status), in patients (pts) with primarily unresectable colorectal liver metastases (CRLM): Results of the randomized UNICANCER PRODIGE 14-ACCORD 21 (METHEP-2) trial. *First Author: Marc Ychou, Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France*

Background: pts with unresectable CRLM who respond to induction CT allowing curative-intent liver surgery have longer overall survival (OS) than pts who do not. Triplet (3-) or doublets (2-) CT, combined with CET or BEV, are often used in this setting. However, the best CT regimen remains to be determined. **Methods:** METHEP2 assessed whether 3-CT (FOLFIRINOX) compared to 2-CT (FOLFOX or FOLFIRI), combined with CET or BEV (by KRAS/RAS status), would increase R0/R1 liver-resection rate in pts with initially unresectable CRLM. Randomization was stratified by KRAS (amended to RAS) status, meta- vs. synchronous CRLM, and reason for non-resectability (technical vs. oncological). It was designed to demonstrate a 20% increase in the R0/R1 liver-resection rate (2-CT arm, 50% vs. 3-CT arm, 70%; bilateral α-test, 5%; β, 10%). **Results:** 256 pts were included, 126 in the 2-CT arm (FOLFIRI, 56; FOLFOX4, 70) and 130 in the 3-CT arm. KRAS and RAS were mutated in 91 pts (35.5%) and in 109 pts (42.6%), respectively. After a median follow-up of 45.6 months (mo), R0/R1 liver resection was achieved in 74/130 pts (56.9%; 95%CI, 48-66) in the 3-CT arm vs. 61/126 pts (48.4%; 95%CI, 39-57) in the 2-CT arm ($p = 0.17$). The odds for R0/R1 resection were higher in the 3-CT than in the 2-CT arm (OR, 1.8; 95%CI, 1.1-2.7; $p < 0.02$) when using a logistic regression model adjusted on stratification factors. Median OS was 42.9 mo in the 3-CT arm vs. 37.6 mo in the 2-CT arm (HR = 0.80; 95%CI, 0.56-1.16). Efficacy by targeted agent was as follows: R0/R1 resection 86/153 (56.2%; 95%CI, 48-64) and 49/103 (47.6%; 95%CI, 38-58), objective response: 120/153 (78.4%; 95%CI, 71-85) and 58/103 (56.3%; 95CI, 46-66), mPFS: 12.8 mo (95%CI, 11.6-13.1) and 10.7 mo (95%CI, 9.7-13.1), OS: 43.6 mo (95%CI, 40.0-51.8) and 34.2 mo (95%CI, 27.8-40.4), for CET- and BEV-treated pts, respectively. **Conclusions:** Despite not reaching our primary objective, FOLFIRINOX tends to be superior to FOLFIRI/FOLFOX, combined with CET or BEV, in terms of R0/R1 liver-resection rate in pts with initially unresectable CRLM. Clinical trial information: NCT01442935.

3536 Poster Session (Board #29), Sun, 8:00 AM-11:30 AM

Safety analysis of a phase III randomized trial comparing FOLFOX + Bevacizumab vs FOLFOXIRI + Bevacizumab as 1st line treatment in patients with metastatic colorectal cancer (mCRC) with ≥3 circulating tumor cells (CTCs) (VISNÚ-1 TTD TRIAL). *First Author: A. Gomez, Reina Sofia Hospital, University of Cordoba, Maimonides Institute of Biomedical Research, Spanish Cancer Network, Instituto de Salud Carlos III, Cordoba, Spain*

Background: FOLFOXIRI plus bevacizumab has demonstrated a survival benefit compared with FOLFIRI plus bevacizumab (TRIBE Lancet Oncol 2015) in first-line mCRC. This schedule is not routinely recommended in all patient groups due to toxicity. VISNÚ-1 trial compared FOLFOX + Bevacizumab (arm A) vs FOLFOXIRI + Bevacizumab (arm B) in non-elderly patients(p) with ≥ 3CTCs at baseline as a poor prognostic factor. Preliminary safety analysis is presented here. **Methods:** This is an open, multicentric, randomized phase III trial. Patients aged ≤ 70 years, ECOG 0-1 were randomized to arm A or arm B, stratified per *KRAS* mutation. The data presented here were generated from a snapshot of the database from Oct-31st-2017. **Results:** 350 p have been included in the study, 347 p were available for safety analysis. General characteristics in arms A and B: Median age (59 vs 60.5 years), gender (Male/Female: 67.2/32.8 vs 69.4/30.1%), ECOG 0/1 (48/52 vs 47/53%), primary tumor unresected (32.2 vs 37.1%), previous adjuvant chemotherapy (4.0 vs 5.3%). Most common grade ≥3 toxicities and treatment modifications are shown in table 1. Only neutropenia, asthenia, diarrhea and mucositis were more frequent in arm B. Fourteen patients dead due to treatment-related adverse events (6 in the FOLFOX- BEV arm and 8 in the FOLFOXIRI-BEV arm): 7 sepsis, 5 bowel perforation, 2 pulmonary toxicity). **Conclusions:** In our study, the use of FOLFOXIRI + Bev in mCRC did not result in an increase in treatment delays, dose reductions or treatment interruptions as compared with FOLFOX+Bev despite an increased incidence of neutropenia, diarrhea, asthenia and mucositis. Clinical trial information: NCT01640405.

	FOLFOX+BEV (N=177)	FOLFOXIRI+BEV (N=173)
Treatment	N (%)	N (%)
Delayed		
No	29 (16.4)	23 (13.5)
Yes	148 (83.6)	147 (86.5)
Dose Reductions		
No	83 (46.9)	62 (36.5)
Yes	94 (53.1)	108 (63.5)
Interrupted		
No	75 (42.4)	74 (43.5)
Yes	102 (57.6)	96 (56.5)
Adverse Events related to treatment (%)	%	%
Grade ≥3	62.2	76.5
Neutropenia	24.3	34.7
Asthenia	6.2	14.7
Diarrhea	5.1	20
Neurotoxicity	21.5	18.8
Mucositis	3.4	8.8
Hypertension	3.4	3.6
Bowel perforation	4.5	2.35

3537 Poster Session (Board #30), Sun, 8:00 AM-11:30 AM

Subgroup analysis by prior anti-VEGF or anti-EGFR target therapy in FRESCO, a randomized, double-blind, phase 3 trial comparing fruquintinib versus placebo plus best supportive care in Chinese patients with metastatic colorectal cancer (mCRC). *First Author: Ruihua Xu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Patients with mCRC are typically offered chemotherapy and might also receive target therapy-drugs targeting VEGF or EGFR. In phase 3 FRESCO trial, fruquintinib demonstrated a statistically significant and clinically meaningful overall survival benefit in third-line mCRC patients in China. To explore possible effects of prior target therapy on fruquintinib, we conducted subgroup analysis of patients with prior target therapy (PTT) and those without (non-PTT). **Methods:** Overall survival (OS) and progression-free survival (PFS) were evaluated by Kaplan-Meier method. Hazard ratio (HR) was estimated through Cox proportional hazards model. P-value was generated from log rank test. **Results:** Among a total of 278 fruquintinib-treated patients, 111 received prior target therapy (84 with anti-VEGF;40 with anti-EGFR and 13 with both). In PTT subgroup, fruquintinib significantly prolonged OS (Median OS: 7.69 months (m) vs 5.98 m;HR = 0.63; p = 0.023) and PFS (Median PFS:3.65m vs 1.84m;HR = 0.24;p $<$ 0.001) compared to placebo. Patients who received prior anti-VEGF treatment (N = 84) also benefited from fruquintinib in OS (HR = 0.68,95%CI: 0.45-1.03) and PFS (HR = 0.24,95%CI: 0.15-0.38). In non-PTT subgroup, the median OS was 10.35 m for fruquintinib vs 6.93 m for placebo (HR = 0.63,p = 0.01) and the median PFS for fruquintinib was 3.81 m vs 1.84 m for placebo (HR = 0.28, p $<$ 0.001). There were no observed accumulative Grade$\geq$3 treatment-emergent adverse events (TEAEs) in PTT subgroup. Grade$\geq$3 TEAEs rates of fruquintinib were similar in PTT and non-PTT subgroup (61.3% and 61.1%). The most common drug-related Grade $\geq$3 TEAEs of fruquintinib in PTT and non-PTT subgroup were hypertension (20.7% and 21.6%), hand-foot-skin reaction (7.2% and 13.2%) and proteinuria (5.4% and 1.8%). **Conclusions:** This subgroup analysis result is consistent with previously reported FRESCO intent-to-treatment population result. Fruquintinib showed clinically meaningful benefits in third-line mCRC patients regardless of prior target therapy without observed accumulative toxicity. Clinical trial information: NCT02314819.

3538 Poster Session (Board #31), Sun, 8:00 AM-11:30 AM

Outcomes of oxaliplatin-based (Ox) chemotherapy (CT) on R0 resection of colonic liver metastases (CLM). *First Author: Nicholas Adam Bosma, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: In resected CLM, randomized studies of Ox CT have not demonstrated improvements in overall survival (OS) and Ox CT has not been compared to non-Ox CT. The aim of this study was to assess the impact of Ox CT regimens on OS in patients that have undergone resection of CLM in a real world setting. **Methods:** Patients who underwent resection of CLM in the provinces of Alberta and British Columbia, Canada were identified from 1996-2016. Perioperative (pre and/or post) CT regimens were reviewed and categorized as Ox CT, non-Ox CT or no CT. OS was measured from the time of metastatic diagnosis to death or last follow-up using the Kaplan-Meier method. CT regimens were compared using the log-rank test and a Cox regression model, adjusting for possible confounders including age, gender, primary tumor sidedness and the presence of synchronous metastatic disease. **Results:** 516 patients were identified who underwent R0 resection of CLM for mCRC, including 205 that received Ox CT, 129 non-Ox CT and 182 with no CT. Of these patients, 24% and 56% received pre-operative and post-operative CT, respectively. 70% of these patients received a fluoropyrimidine (5-FU or capecitabine), 40% oxaliplatin, 13% irinotecan, 7% received bevacizumab and 1% panitumumab. Median age of these patients was 64, with 60% male and 57% demonstrating synchronous metastatic disease and 38% right-sided primary. The median OS for patients receiving Ox CT was 98 months, for non-Ox CT 60 months and no CT 56 months, p = 0.01. After adjusting for potential confounders with a Cox-proportional hazard model, patients who received Ox CT had a lower risk of death HR of 0.65 (95% CI 0.48-0.87, p $<$ 0.01), while the non-OX CT group did not, HR 0.84 (95% CI 0.62-1.13, p = 0.25) compared to no CT. **Conclusions:** Perioperative Ox CT appears to improve OS in conjunction with R0 resection of CLM in this multicenter population based study. This observation remained significant even after controlling for potential confounders. Ox CT should be considered in patients that undergo R0 resection of CLM, in favor of non-Ox CT. The addition of biologic agents to CT remains limited. Further studies should evaluate the optimal timing and duration of perioperative CT.

3540 Poster Session (Board #33), Sun, 8:00 AM-11:30 AM

First-in-human dose escalation of monalizumab plus durvalumab, with expansion in patients with metastatic microsatellite-stable colorectal cancer. *First Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Monalizumab (IPH2201) is a humanized IgG4 antibody targeting CD94/NKG2a to suppress inhibitory signaling by tumors on NK cells. The combination of monalizumab and durvalumab (anti-PD-L1) may promote antitumor immunity via complementary mechanisms targeting both innate and adaptive immune systems. This is a first-in-human, phase 1 dose escalation and expansion study to evaluate monalizumab plus durvalumab in patients with select advanced solid tumors. **Methods:** Patients received durvalumab 1500 mg every 4 weeks in combination with monalizumab at increasing doses. Escalation was determined using a modified toxicity probability interval. Antitumor activity was based on RECIST v1.1. Following initial efficacy in escalation, an expansion cohort of metastatic microsatellite-stable colorectal cancer (MSS-CRC) was enrolled. **Results:** We report the experience of 55 patients treated with monalizumab plus durvalumab, including 15 patients in escalation and 40 in MSS-CRC expansion. In escalation, there were no treatment-related adverse events (TRAEs) that led to discontinuations, no grade 3/4 TRAEs, no DLTs, and no deaths; MTD was not reached. Any grade TRAEs were observed in 12 patients (80%); most frequent was diarrhea (n = 4). Safety in expansion was similar to escalation: 19 patients (48%) had any grade TRAEs, 1 patient had a grade 3/4 TRAE (sepsis). PK of both drugs in combination showed no interactions. Monalizumab PK approached linearity at the highest dose level, which was thus chosen for expansion. In MSS-CRC expansion (58% with 3+ lines of prior therapy, n = 37 evaluable for efficacy), there were 3 confirmed PR and 11 SD, including 3 patients with tumor reduction who continued therapy for $>$ 200 days; DCR at 16 weeks was 24%. Updated clinical and biomarker data will be presented. **Conclusions:** Dose escalation of this first-in-human combination of monalizumab plus durvalumab has been completed, demonstrating a manageable toxicity profile. Preliminary data indicate that the combination has promising activity in patients with MSS-CRC, a population historically nonresponsive to PD-1/PD-L1 blockade. Clinical trial information: 02671435.

3541 Poster Session (Board #34), Sun, 8:00 AM-11:30 AM

Effect of time to resection of colorectal liver metastases on recurrence risk. *First Author: Emerson Yu-sheng Chen, Oregon Health and Sciences University, Portland, OR*

Background: Resection of colorectal liver metastases (CRLM) with perioperative chemotherapy is curative in only 20-30% of patients. There are no biomarkers or robust clinical predictors that can effectively select patients curable by resection. The time interval from diagnosis of liver metastasis to hepatic resection (time to resection, or TTR) has not been studied to risk-stratify patients who would benefit. **Methods:** A retrospective analysis of patients who underwent resection for CRLM from 2003 to 2017 was conducted at our institution. Patients were categorized as: 1) no evidence of disease (NED) or 2) disease relapse or death. NED patients with $<$ 1 year follow-up were excluded. Factors including TTR (short = $<$ 3 months; intermediate = 3-6 months; and long = $>$ 6 months) were compared between the two groups (all p $<$ 0.05 unless noted). Logistic regression was used to identify factors associated with NED. **Results:** We identified 264 patients with a median follow-up of 30 months. Of these, 60% presented with synchronous liver metastases, 42% had bilateral liver disease, and 76% received preoperative chemotherapy. Preoperative MRI was performed in 19% of patients. R0 resection was achieved in 88%. Overall, 27% of patients were NED at one year. Patients with intermediate TTR had a higher proportion of NED compared to short TTR and long TTR (45% vs. 27% vs. 28%). Primary tumor location, grade, metachronous CRLM, and response to chemotherapy were not associated with NED. Long TTR was associated with synchronous CRLM, bilateral disease, and more liver lesions compared to intermediate and short TTR. On multivariate analysis, patients with long TTR (OR: 0.65), older age (OR: 0.97), more liver lesions (OR: 0.80), and positive resection margin (OR: 0.08) were less likely to achieve NED. Preoperative MRI use was predictive of NED (OR: 2.6). **Conclusions:** Intermediate TTR is associated with NED status at $>$ 1 year when compared to short TTR. This suggests liver resection should wait 3-6 months to assess for more indolent tumor biology. Lack of benefit seen with long TTR was likely due to high tumor burden in our dataset. Use of preoperative MRI may better quantify extent of liver involvement to help select patients who will benefit from resection. Analysis is ongoing.

3542 Poster Session (Board #35), Sun, 8:00 AM-11:30 AM

Bevacizumab (B) + bi-weekly capecitabine (C) and oxaliplatin (O) (XELOX2) or FOLFOX4 in first-line treatment of metastatic colorectal cancer (mCRC): Final results of a multicenter randomized phase II trial of the Gruppo Oncologico dell'Italia Meridionale (GOIM protocol 2802). *First Author: Evaristo Maiello, U.O. Oncologia, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy*

Background: B plus bi-weekly FOLFOX4 or three-weekly XELOX represents a standard 1-line therapy for mCRC pts. In our previous phase II study (Fedele P et al, ASCO 2009) we demonstrated a similar efficacy of a bi-weekly schedule of C combined with O (XELOX2). In this randomized phase II trial, pts with mCRC, previously untreated, ECOG PS 0-1, age 18-75, were randomized to receive, in a 2:1 ratio, XELOX2 + B (experimental arm) vs. FOLFOX4 + B (calibration arm). Primary endpoint was ORR; secondary endpoints were PFS, OS and toxicity. **Methods:** B (5 mg/kg on d1 of a 2-week cycle) was administered before O, with FOLFOX4 (Arm A) or XELOX-2 (Arm B; O 100 mg/m2 on d1 followed by oral C 1,000 mg/m2 twice daily on d1 through 7 of a 14-day cycle). After a maximum of 12 cycles (induction phase), pts in CR,PR and SD were randomized to maintenance with B alone or B+Fluoropyrimidine (C or FU). Sample size of experimental arm was calculated according to Simon's two-stage design, with a type I error rate 0.05 and 0.90 power. With null hypothesis ORR 32% and alternative hypothesis ORR 48%, 46 pts had to be accrued in the first stage, for a final number of 80 pts. Study design was formally non comparative, but exploratory comparison between arms was performed. **Results:** One-hundred thirty-two pts were randomized (45 arm A; 87 arm B). The main characteristics of the entered pts were well balanced. ORR (Arm A vs B) was 55.6% vs 48.3% (p = 0.43). With a median follow-up of 47.2 months, PFS was 10.0 vs 9.9 months (HR 0.96, 95%CI 0.65-1.41; p = 0.84) and OS was 29.8 vs 25.0 months (HR 1.21, 95%CI 0.77-1.92; p = 0.41). Main G3-4 toxicity rate (A vs B) were as follows: thrombocytopenia 2/2, anemia 4/3, neutropenia 15/3, nausea 9/5. vomiting 2/3, diarrhea 7/7, neurotoxicity 2/2 and hypertension 2/1. **Conclusions:** GOIM study 2802 showed that the XELOX2+B regimen is active as FOLFOX4+B in pts with mCRC. Given the extreme tolerability and convenience of administration of therapy, XELOX2 + B appears to be indicated even in frail or elderly patients. Clinical trial information: 2010-022091-31.

3543 Poster Session (Board #36), Sun, 8:00 AM-11:30 AM

Phase 2 study of veliparib plus FOLFIRI ± bevacizumab versus placebo plus FOLFIRI ± bevacizumab in metastatic colorectal cancer. *First Author: Vera Gorbunova, N. N. Blokhin Cancer Research Center, Moscow, Russian Federation*

Background: Survival rates for patients with metastatic colorectal cancer (mCRC) are low. Current front-line therapy includes a combination of irinotecan/5-fluorouracil/leucovorin (FOLFIRI) ± bevacizumab. Veliparib (Vel) is a potent, competitive poly (ADP-ribose) polymerase (PARP)-1/2 inhibitor that enhances the activity of irinotecan in pre-clinical models. This study assessed if addition of oral Vel concurrent to FOLFIRI, with the goal to potentiate irinotecan activity, improves survival in patients with previously untreated mCRC. **Methods:** This is a randomized, blinded, phase 2 study (NCT02305758) comparing Vel (200 mg BID administered for 7 days of each 14-day cycle) to placebo (PBO), each in combination with FOLFIRI. Bevacizumab was allowed in both arms. Endpoints were progression-free survival (PFS), overall survival (OS), objective response rate (ORR) by RECIST 1.1, duration of overall response (DOR), safety and tolerability. **Results:** As of October 31, 2017, 130 patients were randomized to receive either Vel (n= 65) or PBO (n= 65). Median PFS was 12 vs 11 months (Vel vs PBO) [HR = 0.94 (95% CI: 0.60, 1.48)]. Median OS was 25 vs 27 months (Vel vs PBO) [HR = 1.26 (95% CI: 0.74, 2.16)]. There were 27 OS events each in the Vel and PBO arms. ORR was 56.9% (Vel) and 61.5% (PBO). Median DOR was 11.1 vs 9.4 months (Vel vs PBO) [HR = 0.73 (95% CI: 0.38, 1.40)]. Common adverse events (AE) (in ≥20% patients) assessed as related to Vel that did not differ from Vel to PBO arm were nausea, fatigue, and vomiting. Grade 3/4 AE (in ≥5% patients) assessed as related to Vel (for Vel vs PBO) include neutropenia (22% vs 11%), diarrhea (5% vs 9%), nausea (8% vs 2%), and asthenia (6% vs 0%). SAE assessed as related to Vel (for Vel vs PBO) include febrile neutropenia (3% vs 3%) and diarrhea (2% vs 3%). All grade hematopoietic cytopenias were more common with Vel than PBO (79% vs 52%, p= 0.003). Two treatment-emergent AE deaths occurred in each Vel and PBO arm. 14% of patients in Vel arm and 15% in PBO arm prematurely discontinued treatment due to AEs. **Conclusions:** Vel added on to FOLFIRI ± bevacizumab demonstrated similar efficacy as FOLFIRI ± bevacizumab in frontline mCRC patients. Overall, there were no unexpected safety concerns. Clinical trial information: NCT02305758.

3544 Poster Session (Board #37), Sun, 8:00 AM-11:30 AM

Quality-adjusted time without symptoms or toxicity (Q-TWiST) of patients with metastatic colorectal cancer (mCRC) treated with fruquintinib in the randomized phase III FRESCO trial. *First Author: Yu-Xian Bai, Harbin Medical University Cancer Hospital, Department of Medical Oncology, Harbin, China*

Background: The FRESCO Study is a randomized, double-blind, phase III trial comparing fruquintinib + best supportive care (BSC), to placebo + BSC in the treatment of metastatic colorectal cancer (mCRC). This ad-hoc analysis aims to compare the quality-adjusted survival between the two arms using quality-adjusted time without symptoms or toxicity (Q-TWiST) methodology, and to investigate the Q-TWiST benefit of fruquintinib treatment among sub-groups. **Methods:** The survival time for each patient was divided into 3 portions: TOX (time with ≥ grade 3 toxicity before progression), TWiST (time without symptoms or ≥ grade 3 toxicity), and REL (time from progression or relapse until death or end of follow-up). Q-TWiST was calculated as the sum of the utility-weighted mean durations for each health state. Threshold analyses were conducted to understand Q-TWiST gains associated with utility weight and subgroup analyses were performed according to baseline clinical characteristics. **Results:** Of 416 patients randomized, 278 received fruquintinib treatment. Survival benefit was seen in Q-TWiST in patients in the fruquintinib arm when compared to those in the placebo arm (mean: 7.0 vs. 4.8 months, difference [95% CI]: 2.2[1.4, 3.0]) in the base case scenario (TOX = 0.5 and REL = 0.5). Threshold analyses suggested that Q-TWiST gains ranged from 16.7% to 39.9% and favored fruquintinib across all possible utility weight combinations. The differences in Q-TWiST favored patients in the fruquintinib arm across pre-specified subgroups. Patients benefited from fruquintinib treatment in terms of Q-TWiST gain regardless of prior targeted treatment (32.3% and 22.9% of those with and without prior targeted treatment, respectively). **Conclusions:** In mCRC patients who failed 2 lines of standard therapy, fruquintinib treatment resulted in more quality-adjusted survival benefits when compared to placebo arm. The benefits seen may have been achieved by good disease control and safety profile. Both patients with and without prior targeted therapy can benefit from fruquintinib treatment.

3545 Poster Session (Board #38), Sun, 8:00 AM-11:30 AM

Correlation of measurements of tumor heterogeneity based on next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) with clinical outcomes in STEAM, a prospective, randomized, multicenter study in metastatic colorectal cancer (mCRC). *First Author: Stephanie Yaung, Roche Sequencing Solutions, Pleasanton, CA*

Background: STEAM (clinical trial NCT01765582) assessed efficacy and safety of concurrent and sequential FOLFOXIRI-bevacizumab (BEV) vs FOLFOX-BEV for first-line treatment of mCRC. The AVENIO ctDNA Expanded and Surveillance Kits (Research Use Only) were used to detect somatic mutations by NGS in tissue, and pre- and post-induction plasma samples. **Methods:** Plasma-based molecular measures of tumor heterogeneity were defined as: 1) Plasma Recovery Rate (PRR), a ratio of shared plasma and matched tissue variants to total plasma variants; 2) Mutant-Allele Tumor Heterogeneity (MATH), a measure of variant allelic frequency dispersion, applied here to plasma; and 3) Multi-Variant Gene Count (MVGC), a count of genes harboring > 1 somatic mutations in plasma. **Results:** Overall, greater pre-induction tissue-plasma discordance correlated with shorter OS, and subjects with complete tissue-plasma concordance (defined as PRR = 1, suggesting monoclonality) had longer PFS (18.3 vs 9.5 mo, HR 0.43, 95% CI 0.2 - 0.91, logrank p = 0.023). High plasma allele frequency dispersion, assessed as MATH in the top quartile, correlated with shorter PFS in pre-induction plasma (8.1 vs 11.7 mo, HR 1.8, 95% CI 1.1 - 3.1, logrank p = 0.026) and in post-induction plasma (7.4 vs 12.2 mo, HR 2.9, 95% CI 1.7 - 5.2, logrank p = 0.00012). Similar trends were seen for OS. Subjects with > 1 somatic mutation in a gene, classified as MVGC > 0, in post-induction plasma had shorter OS. An increase in MVGC from pre- to post-induction correlated with shorter OS (14.8 vs 26.4 mo, HR 4.6, 95% CI 1.9 - 10.9, logrank p = 0.00029). **Conclusions:** Analyses with AVENIO ctDNA Kits on STEAM reveal the potential prognostic value of measuring plasma-based tumor heterogeneity, with higher heterogeneity correlating strongly with poor outcomes. Pre-induction, a lower rate of recovery of plasma variants in tissue and high plasma dispersion correlated with shorter survival. Post-induction, high plasma dispersion and intragenic heterogeneity correlated with shorter survival. These hypothesis-generating results require further validation.

3546 Poster Session (Board #39), Sun, 8:00 AM-11:30 AM

A phase I expansion study of trifluridine and tipiracil (FTD/TPI) in combination with irinotecan (IRI) and bevacizumab (BEV) in patients with metastatic colorectal cancer (mCRC). *First Author: Anna M. Varghese, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: FTD/TPI is an oral antineoplastic agent that was developed to overcome resistance to fluoropyrimidines. FTD/TPI is approved for use in previously treated patients with mCRC. This Phase I expansion study investigated the safety, pharmacokinetics (PK), and preliminary efficacy of FTD/TPI and IRI with BEV. The dose-escalation phase determined the maximum tolerated dose of FTD/TPI and IRI to be FTD/TPI 25 mg/m^2 and IRI 180 mg/m^2. **Methods:** Patients aged ≥18 years with mCRC with disease progression following ≥1 line of chemotherapy were included. Patients who had required any prior IRI dose reductions, dose delay, or growth factor support in the first 8 weeks of treatment with IRI were excluded. FTD/TPI was administered at 25 mg/m^2 twice daily on days 1-5 of 14-day cycles with IRI 180 mg/m^2 preceded by BEV 5 mg/kg on day 1 of each 14-day cycle. PK samples were collected on days 1-3 of cycle 1. **Results:** Twenty-four patients with mCRC were enrolled; 67% were female and the median age was 55.5 years (range 19-73). The median number of prior regimens was 4; all patients had received prior fluoropyrimidine and oxaliplatin treatment, 3 patients were IRI-naïve, and 5 patients were BEV-naïve. Grade ≥3 adverse events were reported in 20 patients (83%); the most common were neutropenia (33%), leukopenia (25%), diarrhea (13%), and hypertension (13%). Based on RECIST v1.1 of the 24 evaluable patients, 3 had a partial response and 17 experienced stable disease. Median progression-free survival was 7.9 months (95% CI 5.1, 13.4). PK analysis did not show any significant correlation between the plasma concentrations of FTD/TPI and IRI or their metabolites. **Conclusions:** No new safety findings or cumulative adverse events were reported with the addition of BEV to FTD/TPI and IRI. Preliminary efficacy results indicate promising anti-tumor activity using FTD/TPI and IRI with BEV for patients who had failed a median of 4 prior regimens with most having had prior IRI. This triple chemotherapy combination warrants further evaluation in patients with mCRC. Clinical trial information: NCT01916447.

3547 Poster Session (Board #40), Sun, 8:00 AM-11:30 AM

A meta-analysis exploring the role of PET and PET-CT in the management of potentially resectable colorectal cancer liver metastasis. *First Author: Julian Daza Vargas, McMaster University, Hamilton, ON, Canada*

Background: It has been proposed that PET alone or combined with CT imaging improves detection of extra-hepatic disease in colorectal cancer liver metastasis (CRCLM). The objective of this study was to determine whether PET/PET-CT has a role in the preoperative workup of patients with potentially resectable CRCLM. **Methods:** From 2000 to April 2017, MEDLINE, EMBASE, and CENTRAL were searched for randomized and non-randomized studies investigating the use of PET and/or PET-CT in CRCLM. Screening and data collection were performed in duplicate. The primary outcome was overall survival (OS). Secondary outcomes included disease-free survival (DFS), change in surgical management, and futile laparotomy. The quality of the evidence was assessed using GRADE. Random effect models were used to pool treatment effects. Moderate to high heterogeneity was explored via subgroup analyses established *a priori*. **Results:** Of 4034 reviewed articles, 22 were included for subsequent analysis. PET/PET-CT did not improve OS (HR 0.94, 95% CI 0.69 – 1.26, I^2 = 0%) or DFS (HR 1.01, 95% CI 0.82 – 1.26, I^2 = 0%) when used preoperatively to determine surgical candidacy. In subgroup analyses, PET/PET-CT changed surgical management in 8% of cases (95% CI 5 – 11%, I^2= 0), and did not reduce futile laparotomies (RR 0.59, 95% CI 0.24 – 1.47, I^2= 47%) in randomized studies. In contrast, PET/PET-CT changed surgical management in 20% of cases (95% CI 17 – 22%, I^2 = 0) and resulted in fewer futile laparotomies (OR 0.51, 95% CI 0.32 – 0.81, I^2 = 0%) in non-randomized studies. **Conclusions:** The use of pre-operative PET/PET-CT does not improve OS or DFS in CRCLM. In addition, there is moderate to high quality evidence demonstrating it has a minimal impact on planning surgical management, and does not prevent unnecessary surgeries.

3548 Poster Session (Board #41), Sun, 8:00 AM-11:30 AM

FOLFIRINOX plus cetuximab (CET) or bevacizumab (BEV) in patients (pts) with initially unresectable colorectal liver metastases (CRLM) with BRAF mutated (mut) tumors: A subgroup analysis of the UNICANCER PRODIGE 14-ACCORD 21 (METHEP2) trial. *First Author: Evelyne Lopez-Crapez, Institut régional du Cancer de Montpellier ICM, Montpellier, France*

Background: The treatment of metastatic colorectal cancer (mCRC) pts with BRAF-mut tumors is a major challenge for physicians. They account for < 10% of mCRC, correlate with poor prognosis, and respond poorly to standard first-line regimens including chemotherapy doublets (2-CT) plus a targeted agent. Guidelines suggest treating BRAF-mut mCRC with a triplet CT regimen (3-CT; fluorouracil, irinotecan, and oxaliplatin combination) plus BEV, based on a subgroup analysis of the TRIBE study. In this analysis of 16 mCRC pts with BRAF-mut tumors, median PFS (mPFS) and OS (mOS) were 7.5 and 19 months (mo), respectively. Since the impact of 3-CT plus CET on outcomes in pts with BRAF-mut tumors is largely unexplored, we aimed to assess this subpopulation in the METHEP2 trial. **Methods:** This trial assessed whether 3-CT (FOLFIRINOX) compared to 2-CT (FOLFOX or FOLFIRI), combined with CET or BEV (by KRAS exon 2/RAS status), would increase R0/R1 liver resection rates in pts with initially CRLM. As an exploratory analysis, we assessed the outcome of the subset of BRAF-mut mCRC pts. **Results:** 256 pts were included. KRAS exon 2 and RAS (KRAS/NRAS: exon 2, exon 3, exon 4) were mutated in 91/256 pts (35.5%) and in 109/218 pts (50%), respectively. The R0/R1 liver resection rate was 57% in the 3-CT arm vs. 48% in the 2-CT arm. mPFS was 12.8 mo in the 3-CT arm vs. 11.5 mo in the 2-CT arm (HR, 1.05; 95%CI, 0.79-1.39). mOS was 42.9 mo in the 3-CT arm vs. 37.6 mo in the 2-CT arm (HR, 0.80; 95%CI, 0.56-1.16). Nine out of 230 (3.9%) mCRC pts were BRAF-mut: 8/9 pts received CET and 1 (in the 2-CT arm) received BEV as the targeted agent. Efficacy results in the 2-CT (n = 4) vs. the 3-CT (n = 5) arms were as follows: objective tumor response, 0/4 vs. 4/5; R0/R1 resection, 0/4 vs. 2/5; mPFS, 1.8 vs. 6.1 mo; and mOS, 6.6 vs. 21.3 mo. **Conclusions:** In this small series, pts with BRAF-mut tumors treated with 3-CT plus a targeted agent had better PFS and OS than those treated with 2-CT plus a targeted agent. Moreover, intent-to-treat survival outcomes with 3-CT plus CET are in the same range than those with 3-CT plus BEV from TRIBE. Clinical trial information: NCT01442935.

3549 Poster Session (Board #42), Sun, 8:00 AM-11:30 AM

Proteomic profiling of phosphatidylinositol 3-kinase (PI3K) altered metastatic colorectal cancer (mCRC) after protein kinase B (Akt) inhibition: Insulin like growth factor 1 receptor (IGF1R) mediates adaptive resistance. *First Author: Maliha Nusrat, Cancer Medicine Fellowship Program, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We have reported earlier that Akt inhibition is clinically ineffective as monotherapy in PI3K altered (PIK3CA mutant or PTEN loss) mCRC patients (pts). The reasons for this are unknown yet vital for developing effective treatments. We hypothesized that mCRC evades Akt inhibition via adaptive signaling activation. **Methods:** KRAS^{wt} BRAF^{wt} PI3K altered mCRC pts were treated with single agent oral Akt inhibitor, MK2206 (200 mg/week), on a CTEP-sponsored clinical trial (n = 18). Metastases were biopsied at baseline and on day 15. Pt derived xenografts (PDXs) were established for a co-clinical trial with either MK2206 or carrier (30% Captisol) for 3 weeks. Signaling pathways were profiled by reverse phase protein array (RPPA) on tumors from pts and PDXs, as well as on 2 CRC cell lines (KM12L4 and SW480) treated with MK2206. Protein levels from treated and untreated samples were compared by paired or student's t-test, or ANOVA as applicable. **Results:** Out of 18 pts, 16 progressed and 2 had stable disease. Similarly, all treated PDXs progressed after a brief response. RPPA data was available for 15 paired biopsies, 9 treated PDXs and 10 control PDXs. MK2206 adequately inhibited pharmacodynamic (PD) markers (including pAkt T308 and pAkt S473) in PDXs, with a similar but nonsignificant trend in pAkt in pts' biopsies. In cell lines, IGF1R rose after 24 hours and was maintained up to 7 days ($P < 0.01$). Similarly, treated PDXs had increased IGF1R, insulin receptor beta (INSRB) and HER3 levels ($P < 0.001$ for all) with a nonsignificant rise in platelet-derived growth factor receptor (PDGFR). In pts' biopsies, IGF1R, PDGFR and STAT3 increased after two weeks of MK2206 treatment ($P < 0.05$ for all). MK2206 did not affect MAPK signaling. **Conclusions:** Akt inhibition with MK2206 in mCRC induces adaptive upregulation of receptor tyrosine kinases, namely IGF1R but also HER3 and PDGFR, resulting in reactivation of the Akt pathway. Combined analysis of cell lines, PDXs and pts' samples allows in-depth interrogation of adaptive resistance and identifies rational combination therapies worthy of further investigation.

3550 Poster Session (Board #43), Sun, 8:00 AM-11:30 AM

Folate gene prediction of treatment response to 5-FU and leucovorin in advanced colorectal cancer. *First Author: Bengt Gustavsson, Surgical Oncology Laboratories at Sahlgrenska University Hospital, Gothenburg, Sweden*

Background: 5-fluorouracil (5-FU) with the folate pro-drug leucovorin (LV) has long been backbone of chemotherapy for colorectal cancer (CRC). Low expression of folate-related genes may lead to poor response to 5-FU + LV (FLV) since poor transport and metabolization of LV yield insufficient co-factor ([6R]-5,10-methylenetetrahydrofolate) and weak inhibition of the target gene thymidylate synthase (TYMS). We have previously found a positive correlation between survival and expression of folate pathway genes in stage III CRC treated with adjuvant FLV. The aim of the present study was to relate progression-free survival (PFS) with gene expression in tumors from patients with metastasizing CRC (mCRC). **Methods:** Tissue samples of primary tumors were obtained at surgery from patients with mCRC (n = 143) prior to FLV-based chemotherapy. Outcome data were extracted from the Sahlgrenska University Hospital data base. Gene expression was determined with qPCR. **Results:** Significant positive correlations between PFS and expression of several folate relevant genes were found. After adjustment in a multiple Cox analysis of all analyzed genes, only ABCC3 remained significant ($p < 0.0002$). The ABCC3 protein is involved in outward transport of folates, and has preference for 10-formyltetrahydrofolate. This folate inhibits the first conversion step of LV to active co-factor. High expression of ABCC3 may therefore cause a high conversion rate of LV to co-factor, and enhanced inhibition of TYMS. After Cox analysis, ABCC3 expression levels were divided into tertiles; the low, intermediate and high levels. The intermediate and low tertiles had near identical outcomes and were combined. The high expression group had a median PFS of 10.1 months compared to 6.5 months among patients in the low expression group. **Conclusions:** Folate-related genes predict response to treatment with FLV in stage III and IV CRC. Outcome study after direct treatment with the direct co-factor diastereoisomer is warranted.

3551 Poster Session (Board #44), Sun, 8:00 AM-11:30 AM

Real-world data on overall survival (OS) impact of anti-EGFR sequence in patients (pts) with microsatellite stable (MSS) all-RAS and *BRAF*^{V600E} wild-type metastatic (met) colorectal cancer (CRC). *First Author: Elena Elez, Medical Oncology Department, Vall d'Hebron University Hospital; Vall d'Hebron Institute of Oncology (VHIO)., Barcelona, Spain*

Background: Pts with MSS all-RAS and *BRAF*^{V600E} wild-type met CRC are more likely to respond to anti-EGFR drugs, irrespective of treatment (tx) line, particularly if left-sided primaries (prim). The best sequence of targeted agents is still under investigation in molecularly-selected pts. **Methods:** From a prospective clinical-molecular cohort of CRC pts, the subset with all-RAS and *BRAF*^{V600E} wild-type tumors (2010-2016) plus MSS status (2015-2016) was used to investigate the impact of anti-EGFR sequence (1st vs. 2nd/3rd lines) in OS after met diagnosis. A propensity-score-weighted (PSW) Cox proportional hazard model was built to adjust for tx selection bias based on stage at diagnosis (dx), number and site of met, type of first-line chemotherapy (chem), and curative resection of met. **Results:** In total, 913 pts were registered in the database and 416 (45%) fulfilled the molecular criteria. From these pts, 98% received two chem regimens, 70% anti-EGFR tx, 60% anti-angiogenic tx and 45% had surgery of met. Clinical variables associated with no administration of anti-EGFR tx were older age at dx, single met site and surgery of met ($p < .05$). The only factor linked to preference for anti-EGFR tx as 1st line was year: 30% from 2010-2014 and 56% from 2015-2016 ($p < .01$). In anti-EGFR treated pts not eligible to curative surgery of met (n = 152), OS in pts with left-sided prim (splenic flexure-rectum, 85% of all cases) was 47.5 months and in those with right-sided prim (cecum to transverse, 15%) it was 33.6 months (HR 1.58; CI95% 1.03-2.41; p = .04). In a PSW Cox model with molecularly-selected pts (n = 275), offering an anti-EGFR regimen at 1st line in pts with left-sided prim did not impact on OS (HR = 0.96, CI95% 0.8-1.2, p = .72). The same was true for right-sided prim (HR = 1.26, CI95% 0.8-2.1, p = .36; interaction p = .32). **Conclusions:** In a real-world cohort before the "sidedness" era we found that anti-EGFR sequence did not affect OS of pts with left-sided prim, but 1st line therapy was preferred setting in more recent years. Only 15% of molecularly-selected pts have poor outcome right-sided prim, limiting subgroup analysis.

3552 Poster Session (Board #45), Sun, 8:00 AM-11:30 AM

A phase I/II study of nintedanib and capecitabine in refractory metastatic colorectal cancer. *First Author: Patrick McKay Boland, Roswell Park Cancer Institute, Buffalo, NY*

Background: Refractory metastatic colorectal cancer patients (mCRC) have a median survival of 4-6 months. Nintedanib is a TKI which inhibits VEGFR, PDGFR, and FGFR with preclinical efficacy in bevacizumab resistant CRC. This phase I/II study sought to evaluate the recommended phase II dose (RP2D) and efficacy of nintedanib and capecitabine in refractory mCRC patients. **Methods:** Key eligibility criteria included histologically proven mCRC, ECOG PS of 0 or 1, progression/intolerance to a fluoropyrimidine, oxaliplatin, irinotecan, and anti-EGFR therapy for RAS wt patients. Prior regorafenib was exclusionary. The primary endpoint was 18-week progression free survival (PFS). A one-sided binomial test (at $\alpha = 0.1$) compared the observed 18-week PFS to a historic control of 0.25. Secondary endpoints included median PFS, median OS, ORR, and AE profile. **Results:** 40 patients were enrolled across 2 dose levels. Nintedanib 200 mg po bid and Capecitabine 1000 mg/m2 po bid was established to be the RP2D. 36 patients were treated at the RP2D and evaluable for efficacy. The 18 week progression free survival (PFS) was 36% (13/36 patients), p = 0.0922, indicating a statistically significant increase in PFS over historic control. No responses were observed; 19 (53%) patients experienced SD. Median PFS was 3.3 mos. Median OS was 7 mo. 16 (44%) patients experienced a grade 3/4 AE, with the most common evens being fatigue (8%), palmoplantar erythrodysesthesia (8%), AST elevation (6%), asthenia (6%), pulmonary embolus (6%), and dehydration. PK/PD and plasma biomarker data will be presented. **Conclusions:** The combination of Capecitabine and Nintedanib was well tolerated. Efficacy compares favorably to historic data with regorafenib or TAS-102 monotherapy and is similar to results from other investigations of multi-kinase TKIs and flouropyrimidines in the refractory setting. Further investigation is warranted. *This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by Boehringer Ingelheim Pharmaceuticals, Inc.* Clinical trial information: NCT02393755.

3553 Poster Session (Board #46), Sun, 8:00 AM-11:30 AM

Association between genotypes, clinical scores and survival outcome in metastatic colorectal cancer. *First Author: Moreno Reinaldo, Hospital Clínic Barcelona, Barcelona, Spain*

Background: Several prognostic clinical scores for metastatic colorectal cancer (mCRC) GEMCAD (Ann Oncol 25 (Supp 4)), 2014; GERCOR (Oncologist 16, 2011); Köhne (Ann Oncol 13, 2002) are useful for treatment guidance. Next generation sequencing (NGS) allows the evaluation of multiple deregulated pathways (WNT, TGFB, PI3K-RTK-RAS and p53 signaling) (Nature, 2012). We hypothesize that complex vs simple genotypes evaluated by NGS, could be distributed differently according sidedness and clinical scores and would provide independent prognostic value.**Methods:** NGS by Ion Torrent in 22 CRC significant genes was employed to process samples from 141 consecutive mCRC patients (pts) diagnoses from February 2016 to November 2017 in a single institution. Genotype was defined as Complex:1) BRAF mutant 2) RTK-RAS-PI3K+/-p53+FBXW7 mutant 3) RTK-RAS-PI3K+/-p53+SMAD4 mutant; Simple: 1) RTK-RAS-PI3K mutant alone 2) p53 mutant alone 3) RTK-RAS-PI3K mutant+p53 mutant 4) no mutations. Associations were analyzed with Fisher-t test. Cox proportional hazard models and interaction analyses were used to explored the effect of genotype, primary sidedness and clinical scores with overall survival (OS). **Results:** Informative cases (128/141); 91%. Complex genotype; 29%; *p53* (67%), *KRAS* (45%), *BRAF* (14%), *SMAD4* (13%), *PI3K* (12%), *FBXW7* (8%), *NRAS* (3%), other (< 3%). Complex genotype was not associated with sidedness (p = 0.997) but was associated with high-risk GEMCAD score (p = 0.03). In the Cox model, genotypes by NGS remain significant for OS independently of clinical scores (see Table). **Conclusions:** NGS genotype provides independent prognostic information beyond clinical scores. The combination of both variables should allow optimal prognostic stratification in mCRC.

Prognostic value for overall survival (cox proportional hazard model).

	GEMCAD		GERCOR		Köhne	
	HR (95% IC)	p	HR (95% IC)	p	HR (95% IC)	p
Genotype						
Simple	1		1		1	
Complex	1.82 (1.04 – 3.20)	0.037	2.13 (1.22 – 3.73)	0.008	2.31 (1.31 – 4.08)	0.004
Score						
Low	1		1		1	
Intermediate	2.96 (0.67 – 12.94)	0.149	5.32 (0.72 – 39.39)	0.101	2.13 (0.94 – 4.78)	0.067
High	7.83 (1.84 – 33.34)	0.005	14.81 (2.01 –109.40)	0.008	7.78 (3.69 – 16.40)	0.0001

3554 Poster Session (Board #47), Sun, 8:00 AM-11:30 AM

What is the prognostic impact of *BRAF* mutation in patients undergoing resection of colorectal liver metastases? Results of nationwide intergroup (ACHBT, FRENCH, AGEO) cohort of 249 patients. *First Author: Jean-Baptiste Bachet, Hospital Pitié-Salpêtrière, Paris, France*

Background: *BRAF* mutation is associated with poor prognosis in patients with metastatic colorectal cancer. In patients with resectable colorectal liver metastases (CRLM), the prognostic impact of *BRAF* mutation is unknown and the benefit of surgery is debated. This study aims to evaluate oncologic outcome of patients undergoing liver resection for *BRAF*-mutated CRLM. **Methods:** From 2012 to 2016, 66 patients underwent resection for *BRAF*-mutated LM in 24 centers. Case-matched comparison was made with 183 patients who underwent resection for *BRAF* wild-type CRLM during the same period. The matching criteria were: synchronous or metachronous CRLM, initially resectable or unresectable CRLM, uni- or bilobar distribution, and number ($\leq$ or $>$ 4) of CRLM. Patients with extra-hepatic disease were excluded. **Results:** Mean follow up was 28.7 $\pm$ 19.8 months after surgery. The 1- and 3-year disease-free survival (DFS) rates were 46.1% and 19.3% in *BRAF*-mutated and 55.4% and 27.8% in *BRAF* wild-type patients (p = 0.430). In multivariate analysis, *BRAF* mutation was not a predictor of worse DFS (p = 0.574, OR: 1.12 95%CI: 0.74-1.71). The 1- and 3-year overall survival rates after surgery were 93.5% and 54.3% in *BRAF*-mutated and 95.8% and 82.9% in *BRAF* wild-type patients (p = 0.004). The median survival after disease progression was 23.0 months (11-34.9) in *BRAF*-mutated and 44.3 months (35.9-52.6) in *BRAF* wild-type patients (p = 0.049). Multisite disease progression was more common in *BRAF*-mutated than in *BRAF* wild-type patients (48 vs 30%, p = 0.034) and was less likely to be surgically treated with curative intent (27% vs 42%, p = 0.085). **Conclusions:** Our results support the interest of surgical therapy of *BRAF*-mutated resectable CRLM as *BRAF* mutation by itself does not increase the risk of relapse after surgery. By analogy to non-metastatic CRC, *BRAF* mutation has a negative impact on survival in patients who relapse after resection of LM.

3555 Poster Session (Board #48), Sun, 8:00 AM-11:30 AM

A phase I/II trial of cabozantinib (C) with or without panitumumab (P) in patients (pts) with RAS wild-type (WT) metastatic colorectal cancer (mCRC): Clinical outcomes in pts with *MET* amplification (amp) detected in blood. *First Author: Jingquan Jia, Duke University Medical Center, Durham, NC*

Background: *MET* amp is a well described driver of acquired EGFR antibody (Ab) resistance. Blood-based genomic profiling of cell free (cf)DNA is a safe and efficient means to identify pts with acquired *MET* amp. To determine whether a MET targeting strategy is feasible and clinically active in pts with *MET* amp RAS WT mCRC, we studied pts treated with an anti-c-MET multi-kinase inhibitor (C) combined with an anti-EGFR Ab (P) or (C) alone. **Methods:** Pts with RAS WT mCRC were enrolled in 2 cohorts: 1) C+P combination (C+P); or 2) C monotherapy (C) (NCT02008383). Peripheral blood was sequenced for up to 73 single nucleotide variants, insertions/deletions, fusions, and amps, including *MET* amp (Guardant360, Guardant Health). Pts enrolled in the C+P cohort received retrospective cfDNA profiling for *MET* amp. Pts enrolled in the C cohort were prospectively screened for *MET* amp; only those pts with *MET* amp in blood were treated in the C cohort. **Results:** 64/65 pts (98%) had detectable cfDNA (C+P = 13; C = 51). *MET* amp was identified in 12 pts (18%) (C+P = 4; C = 8). Among pts with *MET* amp detected in blood the median copy number was 2.6 (range 2.3-6.4). 8 pts with *MET* amp received treatment (C+P = 4; C = 4); 7 pts were evaluable for efficacy (C+P = 4; C = 3). 1 pt (C+P cohort) had a RECIST PR, and this pt had low grade *EGFR* and *MET* co-amp (*MET*= 2.3 copies; *EGFR*= 2.2 copies). 4/7 pts (57%) had a reduction of measurable RECIST target lesions, 3 of whom received C+P (PR = 1; SD = 1; PD = 1) and 1 (SD; 27% reduction) received C. 3/4 pts in the C+P cohort had *EGFR* and *MET* co-amp, 2 of these pts had a reduction in RECIST lesions (PR = 1; PD = 1). No evaluable pts in the C cohort had *EGFR* and *MET* co-amp. **Conclusions:** This study demonstrates the feasibility of utilizing cfDNA to identify *MET* amp in pts with RAS WT mCRC. Although there are signals of clinical activity for the C+P combination and C alone in this limited sample, further study is needed. The ideal *MET* amp copy number threshold, the role of EGFR co-amp, and the additive value of combined EGFR blockade remain to be determined. Clinical trials utilizing cfDNA to identify and treat *MET* amp mCRC are ongoing. Clinical trial information: NCT02008383.

3556 Poster Session (Board #49), Sun, 8:00 AM-11:30 AM

Apatinib as a salvage treatment for refractory metastatic colorectal cancer. *First Author: Xiaofeng Chen, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*

Background: Apatinib, an oral VEGFR2 inhibitor, has been approved as third line treatment for metastatic gastric cancer in China. The aim of this study was to evaluate the efficacy and safety of apatinib, in the treatment of refractory metastatic colorectal cancer patients who failed from two or more lines of chemotherapy. **Methods:** In this open-label, single-arm, phase II study, patients were treated with apatinib in daily dose of 500 mg, po, in the third - or more line setting. Capture sequencing was dynamically performed to identify somatic variants in circulating tumor DNA (ctDNA) with a panel of 1021 cancer related genes.The primary endpoint was progression-free-survival (PFS) and the tumor response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Interim analyses was applied as predefined. **Results:** From June 01, 2016 to December 31, 2017, 26 patients were enrolled. The median PFS of the whole group was 3.9m (95% CI: 2.1-5.4). Patients with PS 0-1 had longer PFS than those with PS 2 (4.17m vs 1.93m, p = 0.0014). Patients without iver metastasis also had longer PFS than those who had live metastasis (5.87m vs 3.33m, p = 0.0274). Median overall survival was not reached. 10-month survival rate was 55%. The common side effects of apatinib were hypertension, hand-foot syndrome, proteinuria and diarrhea. The incidence for grade 3-4 hypertension, hand-foot syndrome, proteinuria and diarrhea were 76.92%, 11.54%, 73.08%, and23.08%, respectively. All of the patients received dose reduction due to adverse effect. Results of capture sequencing showed APC, TP53 and KRAS were most frequently mutant genes.Patients with high tumor mutation burden (TMB) in baseline blood had a trend of prolonged overall survival than those with low TMB (p = 0.077). The molecular tumor burden from ctDNA increased before the radiographic assessment in 10 patients. **Conclusions:** Apatinib monotherapy showed promising efficiency for refractory colorectal cancer patients, especially in patients with PS 0-1 or no liver metastasis. TMB is a potential prognostic biomarker. In addition, tumor molecular burden may be a predictor in serial monitoring of tumor load. Clinical trial information: NCT03190616.

3557 Poster Session (Board #50), Sun, 8:00 AM-11:30 AM

ENCORE 601: A phase 2 study of entinostat in combination with pembrolizumab in patients with microsatellite stable metastatic colorectal cancer. *First Author: Nilofer Saba Azad, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: In studies reported to date, no objective responses have been observed with PD-1 inhibitors in advanced/metastatic CRC (mCRC) pts with microsatellite stable (MSS)/mismatch repair proficient (pMMR) tumors. About 95% of mCRC pts have this phenotype; additional strategies are needed to improve effectiveness of immunotherapies in these pts. Entinostat (ENT), an oral, class I-selective histone deacetylase inhibitor, enhances anti-PD-1 activity by downregulation of immunosuppressive cell types in the tumor microenvironment *in vivo* and has shown promising activity with pembrolizumab (PEMBRO) in pts with melanoma and lung cancer. This study evaluates the safety and efficacy of ENT + PEMBRO in MSS/pMMR CRC pts. **Methods:** This study is a multi-cohort, Simon 2-stage, phase II trial. Main eligibility criteria for pts in the CRC cohort are: documented MSS/pMMR status, $\geq$1 prior regimen in the metastatic setting, and no prior anti-PD-(L)1 therapy. All pts received ENT 5 mg PO QW + PEMBRO 200 mg IV Q3W. The primary endpoint is objective response rate (ORR) as assessed by irRECIST. Results of the first stage are reported. **Results:** 16 pts were enrolled in Stage I with a median age of 58 (range 36-68) and 4 lines of prior therapy. Median follow up is 4.7 mos. To date, 2 pts had documented pseudoprogression (1 subsequently became a confirmed PR). As of data cutoff, 6 pts (1 PR, 5 SD) remain on study (median time on treatment of 18 wks). Common ($>$ 15%) treatment-related AEs include fatigue (37.5%), arthralgia (18.8%), and increased alkaline phosphatase (18.8%). Grade 3/4 related AEs were observed in 3 patients, and two deaths occurred on study – one due to sepsis secondary to cholangitis and the other due to progression. Serial blood and pre-treatment biopsies were obtained in all pts, with paired post-treatment biopsies in a subset of pts. Evaluation of PD-L1 expression, gene expression, myeloid and lymphoid compartments in biospecimens is in progress. **Conclusions:** ENT + PEMBRO demonstrates acceptable safety and encouraging preliminary activity in a small cohort of MSS/pMMR CRC pts, a patient population in which objective responses have not been reported with PD-(L)1 monotherapy. Clinical trial information: NCT02437136.

3558 Poster Session (Board #51), Sun, 8:00 AM-11:30 AM

EORTC-ESSO 1409 GITCG: A prospective colorectal liver metastasis database with an integrated quality assurance program (CLIMB). *First Author: Carmela Aves Caballero, EORTC, Brussels, Belgium*

Background: The European Organization for Research & Treatment of Cancer & European Society of Surgical Oncology joined forces to build an infrastructure for surgical quality assurance (QA) in clinical trials (SURCARE) and advance the surgical research agenda in Europe. Benchmarking is a critical step to achieve this. Their first project is CLIMB, a prospective study to evaluate complications and identify indicators for improvement in surgery for unresectable or borderline resectable colorectal liver metastasis (CRLM). **Methods:** CLIMB (NCT02218801) opened in 2015 in 9 countries and 14 specialised centers for liver surgery. Eligible patients were registered after multidisciplinary evaluation and before surgery. Primary endpoint was 30 and 90 day surgical complication rate. On-site visits and central review ensured prospective data inclusion of the following: biomarker, imaging, chemotherapy, surgery, complications graded by Clavien-Dindo classification and survival. Data until post op day 90 were analysed but long term outcome will be reported after all patients were followed for two years after registration. **Results:** Among 210 patients registered, 126 (60%) who had at least one liver surgery were analysed. 73% had left-sided or rectal primary tumor, 95.2% had synchronous primary and liver metastasis, 19.8% had extra-hepatic lesions and CRLM. Most patients (N = 95, 75.4%) had one stage liver surgery while 30 (23.8%) had two stage liver surgery, 10 of whom had ALPSS. Over-all complication rates for one stage was 53.7% (95% CI [43%, 64%]), 17.9% (95% CI [11%, 27%]) with grade≥3 and 93.3% (95% CI [78%, 99%]) for two stage, 46.7% (95% CI [28%, 66%]) with grade≥3 including two deaths. Intra-abdominal, wound and urinary tract infections, bile leak and post hepatectomy liver failure grade A were most commonly reported over-all. **Conclusions:** CLIMB prospectively collected data from complex surgery for unresectable CRLM. Two stage surgery had more grade≥3 complications. Harmonizing standards in multidisciplinary evaluation, biomarker testing and imaging may improve this outcome. SURCARE will use these indicators to develop trials with enhanced QA methods to improve cancer surgery. Clinical trial information: NCT02218801.

3559 Poster Session (Board #52), Sun, 8:00 AM-11:30 AM

Surgical quality and the impact of liver resection on outcome in the New EPOC study. *First Author: Sian Alexandra Pugh, University of Southampton, Southampton, United Kingdom*

Background: The New EPOC study demonstrated a shorter overall survival (OS) with the addition of cetuximab to chemotherapy for operable colorectal liver metastasis. The combination of a liver resection with EGFR inhibition is unique to this study. Consequently this analysis explores both surgical quality and the impact of volume of liver resected on outcome. **Methods:** Data is presented for 257/271 patients (early study withdrawals excluded). Details of surgery were completed by the operating or lead surgeon in 19 UK specialist centres. The report of no residual tumour in the pathological specimen was queried in each case. Volume of liver resected was estimated and patients divided into tertiles (tertile 1: ≤20.5%, tertile 2 20.6-50.0%, tertile 3: > 50.0%) to investigate association with OS. **Results:** Operations were performed on 221/257 patients (113 chemo alone CT, 108 chemo and cetuximab CTX) of which 207 (108 CT, 99 CTX) underwent a resection. A further 15 had surgery that included ablation (5 CT, 10 CTX). 159 had major resections (88 CT, 71 CTX) and the median estimated volume of total liver volume resected was the same in both groups (CT 30.6% IQR 17.4-63.4, CTX 28.1% 17.0-63.4). Those with a small volume (tertile 1, ≤20.5%) of liver resected appeared to have a shorter OS with cetuximab (median OS for CT: not reached, CTX: 55.3 months, HR: 2.45 (95% CI: 1.14-5.24), p = 0.021). By contrast those with a larger volume of liver resected (tertiles 2 & 3) had similar outcomes irrespective of the use of cetuximab (median OS for CT: 81.0 months, CTX: 79.0 months, HR: 1.18 (95% CI: 0.72-1.95), p = 0.509). Examination of the pathological specimen revealed no residual tumour (complete pathological response) in 17 patients (10 CT, 7 CTX) of whom 5 subsequenly died (3 CT, 2 CTX). Other surgical data, including the number of R1 resections (13 CT, 19 CTX), was similar between the study arms. **Conclusions:** These exploratory analyses suggest the technical aspects of surgery are similar between the treatment groups and that those patients having smaller volume resections may be disadvantaged by the addition of cetuximab. Clinical trial information: 2006-003121-82.

3560 Poster Session (Board #53), Sun, 8:00 AM-11:30 AM

Screening and stepped care targeting psychological distress in patients with metastatic colorectal cancer: The TES cluster randomized trial. *First Author: Claudia Schuurhuizen, Department of Medical Oncology, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Psychological distress occurs frequently in patients with cancer. Effective management requires targeted selection of patients (T), followed by enhanced care (E), and the application of stepped care for psychological distress (S). This study aimed to evaluate the effectiveness of a screening and stepped care program (the TES program) compared to usual care in reducing psychological distress in patients with metastatic colorectal cancer (mCRC) starting with first line systemic treatment. **Methods:** In this cluster randomized trial, 16 hospitals were assigned to either the TES program or care as usual (CAU). Patients in the TES arm were screened for psychological distress with the Hospital Anxiety and Depression Scale (HADS) and Distress Thermometer/Problem List (at baseline, 10 and 18 weeks). Stepped care was offered to those with distress, as well as to patients expressing the need for psychosocial care. Stepped care consisted of watchful waiting, guided self-help, face-to-face problem-solving therapy, or referral to specialized mental health care. The primary outcome was change in psychological distress over time (HADS); secondary outcomes were quality of life (QOL), satisfaction with care and recognition and referral of distressed patients by clinicians. Measures were assessed at baseline, after 3, 10, 24 and 48 weeks of follow-up. Linear mixed models were used to evaluate the outcome. **Results:** A total of 349 patients were included; 184 to the TES program and 165 to CAU. In the TES arm, 60.3% of the patients screened positive for psychological distress; 26.1% of patients entered the stepped care program (14.7% only used watchful waiting, and 11.4% used at least one of the following steps).There was no difference in the course of psychological distress over time between treatment groups ($p > 0.05$). The TES group reported higher satisfaction with the received treatment over time and better cognitive QOL (all p-values < 0.05). **Conclusions:** Screening and subsequent treatment for psychological distress does not improve psychological distress. Our results suggest that enhanced discussion of psychosocial concerns may improve aspects of patient's well-being. Clinical trial information: NTR4034.

3561 Poster Session (Board #54), Sun, 8:00 AM-11:30 AM

Avelumab and cetuximab in combination with FOLFOX in patients with previously untreated metastatic colorectal cancer (MCRC): Results of the safety run-in phase of the phase II AVETUX trial (AIO-KRK-0216). *First Author: Alexander Stein, Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany*

Background: Single agent PD-1/L1 inhibition is efficacious in mismatch repair deficient tumours - about 5% of MCRC patients (pts). For the remaining MCRC pts the role of immunotherapy still needs to be determined. FOLFOX and cetuximab in combination with avelumab (AVETUX regimen) in 1st line RAS/BRAF wildtype MCRC is currently evaluated in a phase II trial independent of mismatch repair status (NCT03174405). **Methods:** This is a single arm exploratory investigator-initiated trial planned to include 43 pts to receive mFOLFOX6 and cetuximab in combination with avelumab (AVE) (10mg/kg day 1 from cycle 2 onwards). Primary endpoint is 12 months progression-free survival rate. Secondary endpoints are response rate, tolerability and translational research evaluating tissue and serial ctDNA. A safety analysis was planned after the 15th patient has passed 2 months to inform about tolerability. **Results:** As of 1st of February 2018 24 of 43 pts were enrolled and treated with the AVETUX regimen at 8 German sites. The safety analysis of the run-in phase was conducted on the 1st of February after a median of 3.2 months of treatment. The following adverse events were noted: 19/5 grade 3/4 (CTC AE 4.03) in 9 patients, including neutropenia (n = 11/4), nausea (n = 3), and infection (n = 3/1), mostly related to chemotherapy with only two grade 3 AE related to AVE. In 7 out of 15 patients 9 SAEs (one related to AVE), were noted including one case of grade 3 hepatitis, which resolved quickly with steroid treatment, 4 infections/fever, one diarrhea and three nausea (in one patient). Despite the relatively high absolute rate of G3/4 toxicity and SAEs, adverse events were manageable and did not relevantly impact on treatment feasibility. Two pts developed uncomplicated fever the day after the first infusion of AVE, both among the highest T cell infiltrated tumors. The IDMC recommended trial continuation based on these safety data. Updated safety and translational data and efficacy results will be presented at the meeting. **Conclusions:** The interim safety analysis has supported the feasibility of the AVETUX regimen in 1st line MCRC. The trial is ongoing. Clinical trial information: NCT03174405.

3562 Poster Session (Board #55), Sun, 8:00 AM-11:30 AM

Update survival analysis from a multicenter, randomized phase 3 study on the optimization of the combination of bevacizumab with FOLFOX/OXXEL in patients with metastatic colorectal cancer (mCRC). *First Author: Antonio Avallone, Istituto Nazionale Tumori Fondazione G.Pascale, Naples, Italy*

Background: Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody, approved in combination with chemotherapy in the treatment of mCRC. It has been hypothesized that the schedule of administration might be critical and that anticipating bevacizumab to chemotherapy might improve treatment efficacy. Present analysis updates 2016 findings **Methods:** mCRC pts, ≤ 75 years, ECOG PS ≤1, were randomized (1:1) to receive standard (S) administration of bevacizumab (5mg/kg d1 Q14) with chemotherapy (mFOLFOX/OXXEL regimen for 12 cycles) *vs* experimental (E) bevacizumab given whenever 4 days before chemotherapy (same dose and cycles number). Pts could receive maintenance bevacizumab with fluoropyrimidines until disease progression or unacceptable toxicity. Primary end point was the objective response rate (ORR). With 80% power and 2-tailed alpha 0.05, an expected 20% increase in response rate, 230 pts were planned. Analyses were based on the intention to treat. Correlative studies on biomarkers and FDG-PET were also planned. **Results:** From May 2012 to Dec 2015, 230 pts were randomised to E (n = 115) and S (n = 115) arm. Median age was 62 years (IQ range 53-68), 79% were PS 0, 93% were not pretreated, 53% had a single metastatic site, 71% had a left primary site (71% and 74% in S and E, respectively), 54% were RAS-mutant (47% and 62% in the S and E arm, respectively). ORR was 54% in both arms (p = 0.89). With a median follow-up of 42 months, 209 PFS events and 150 deaths were reported. Median PFS was 10.5 and 11.7 months (HR 0.80, 95% CI: 0.61-1.06; multivariate adjusted p = 0.12) and median OS was 23.8 and 29.1 months (HR 0.70, 95% CI: 0.51-0.97; multivariate adjusted p = 0.03), in the S and E arm, respectively. Distribution of patients receiving treatment after progression was similar across the arms. **Conclusions:** Anticipating bevacizumab to chemotherapy does not improve ORR and PFS, but results associated with a significantly longer OS. Further studies are required to confirm whether this schedule might improve treatment efficacy in mCRC patients. Supported by the Italian Ministry of Health. Clinical trial information: NCT01718873..

3563 Poster Session (Board #56), Sun, 8:00 AM-11:30 AM

Comparison of mismatch repair status between primary and matched metastatic sites in patients with colorectal cancer. *First Author: Wen-Zhuo He, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Mismatch repair (MMR) status is crucial in the management of patients with metastatic colorectal cancer (mCRC) to predict responses to anti-PD-1 therapy. This study compares the MMR status between primary and matched metastatic tumors in patients with mCRC. **Methods:** 331 patients were analyzed in this study. The expression of four most common MMR proteins, MLH1, MSH2, MSH6 and PMS2 were tested by immunohistochemistry. Polymerase chain reaction (PCR) analysis was performed to test microsatellite instability (MSI) when MMR status was inconsistent between primary and metastatic sites. **Results:** A total of 331 patients were included; 23 patients had dMMR primary tumors. Among these, 17 (73.9%) and 6 (26.1%) patients showed dMMR and pMMR metastatic tumors, respectively. The remaining 308 patients showed pMMR primary tumors:11 (3.6%) dMMR and 297 (96.4%) pMMR metastatic tumors were observed. For patients who had inconsistent MMR status between primary and metastatic sites, the detailed results were shown in the table, including PCR results. **Conclusions:** Our study suggests a notable discrepancy in mismatch repair status between primary and matched metastatic tumors in patients with mCRC.

						Primary tumor					Metastatic tumor				
Case	Age	Sex	Primary	Metastatic	Synchronous /metachronous	MLH1	MSH2	MSH6	PMS	Microsatellite	MLH1	MSH2	MSH6	PMS	Microsatellite
1	64	M	Rectal	Liver	S	+	+	-	+	MSI-L	+	+	+	+	MSI-L
2	35	F	Rectal	Peritoneum	S	-	+	+	+	MSI-H	+	+	+	+	MSI-H
3	44	F	Descending colon	Ovarian	S	-	+	+	+	MSI-H	+	+	+	+	MSS
4	51	M	Descending colon	Distant lymph node	S	+	+	+	-	MSI-H	+	+	+	+	MSI-H
5	35	M	Rectal	Peritoneum	M	+	-	-	+	MSI-L	+	+	+	+	MSS
6	62	F	Ascending colon	Ovarian	M	-	+	+	-	MSI-H	+	+	+	+	MSS
7	24	F	Rectal	Distant lymph node	M	+	+	+	+	MSI-L	-	+	+	-	MSI-L
8	61	M	Ascending colon	Lung	M	+	+	+	+	MSI-L	-	+	+	+	MSI-L
9	46	F	Ascending colon	Uterus	S	+	+	+	+	MSS	+	+	+	-	MSS
10	63	F	Sigmoid colon	Peritoneum	S	+	+	+	+	MSI-H	-	+	+	+	MSI-H
11	56	M	Rectal	Peritoneum	S	+	+	+	+	MSI-H	-	+	-	+	MSI-H
12	28	F	Sigmoid colon	Liver	S	+	+	+	+	MSI-L	-	+	+	+	MSI-H
13	43	M	Rectal	Distant lymph node	M	+	+	+	+	MSI-H	+	+	+	-	MSI-H
14	75	F	Ascending colon	Peritoneum	S	+	+	+	+	MSS	+	+	+	-	MSS
15	65	F	Sigmoid colon	Peritoneum	S	+	+	+	+	MSS	+	+	-	+	MSI-H
16	60	F	Sigmoid colon	Uterus	S	+	+	+	+	MSS	-	+	+	+	MSI-L
17	70	M	Sigmoid colon	Peritoneum	S	+	+	+	+	MSS	-	+	+	+	MSS

3564 Poster Session (Board #57), Sun, 8:00 AM-11:30 AM

Health related quality of life in elderly or frail patients with advanced colorectal cancer treated with dose reduced capecitabine. *First Author: Daniel Adam Breadner, Schulich School of Medicine and Dentistry, London, ON, Canada*

Background: Palliative chemotherapy's role is to prolong survival while minimizing treatment toxicities to preserve or improve quality of life. We have recently published a phase 2 trial of dose reduced capecitabine in elderly or frail patients with advanced colorectal cancer (aCRC). We herein provide a robust analysis of the HRQoL data from our trial. **Methods:** A single arm multi-centered phase II trial of dose reduced capecitabine in elderly or frail patients. Capecitabine was given at 2000 mg/m^2 days 1-14 q21 days; or 1500 mg/m^2 for patients with prior pelvic RT, as determined in the phase I portion of the study. Phase II participants (182 patients) were asked to complete FACT-G questionnaires at enrollment, after each cycle of capecitabine and once after cessation of the study drug, if possible. **Results:** 157 patients completed a baseline questionnaire (86%), and 137 patients (75%) completed at least one subsequent questionnaire. The mean baseline score was 81.6, out of a possible 108. The mean score peaked at 92 after cycle 10. The mean change from baseline was always positive. Patients achieving the minimal clinically important difference (MCID) ranged from 30% to 45% during treatment cycles. Higher baseline FACT-G score and Physical Well-being score were independently prognostic for improved survival (p = 0.006 and p < 0.0001, respectively). Time until definitive deterioration (TUDD) was longer, but not significant, in patients with a higher baseline FACT-G (p = 0.18). **Conclusions:** Baseline HRQoL scores were independently prognostic for survival, supporting their importance in clinical trials. Compared to full dose, reduced dose capecitabine has previously demonstrated equivocal efficacy and reduced toxicity. We have reported dose reduced capecitabine improves quality of life in elderly or frail patients with aCRC while on treatment, further supporting its use in the management of aCRC.

3565 Poster Session (Board #58), Sun, 8:00 AM-11:30 AM

Prognostic impact of residual HPV ctDNA detection after chemoradiotherapy for anal canal carcinoma. *First Author: Luc Cabel, Institut Curie, Paris, France*

Background: Chemoradiotherapy (CRT) is the current standard of care for patients diagnosed with locally advanced anal squamous cell carcinoma (ASCC), but some patients will present a local and/or a distant relapse during follow-up. We previously reported the analytical validity of HPV circulating tumor DNA (HPV-ctDNA) detection by droplet digital PCR in HPV-related cancers. The current study aimed at monitoring HPV ctDNA levels during CRT in locally advanced ASCC. **Methods:** We analyzed prospectively collected samples from patients with HPV16 or HPV18-positive locally advanced ASCC. Plasma samples collected at diagnosis (before CRT initiation) and at the end of CRT. Cell-free DNA from serum or plasma was extracted, quantified and subjected to HPV16 or HPV18 ctDNA detection as previously published with droplet digital PCR. **Results:** 36 stage II-IV ASCC patients were included. HPV-ctDNA detection had a sensitivity of 89% (n = 32/36). All 4 patients with no ctDNA detected had a stage II ASCC (detection rate 33% versus 100% for higher stage, p = 0.001). In patients with detectable ctDNA before CRT, median ctDNA levels were significantly associated with lymph node(s) status: the median ctDNA level was 102 copies/ml (range 8.7-9333) in N+ ASCC vs 32 copies/ml (range 3-1350) in N- ASCC (p = 0.026). Among 18 patients with available paired samples (before and after RCT), only 3 (17%) displayed residual detectable HPV-ctDNA at the end of CRT. Residual ctDNA detection was correlated with the patients' outcome, such as these 3 patients were the only patients to experience a metastatic relapse (Fisher exact test, p = 0.001). Residual HPV-ctDNA after CRT was strongly associated with relapse-free survival (p < 0.0001). **Conclusions:** This is to our knowledge the first proof of concept study assessing the prognostic value of ctDNA after CRT in locally advanced ASCC. In most patients, HPV-ctDNA can be detected before CRT but drops below detection limits during CRT. We show here that residual ctDNA levels at the end of CRT are associated with a very poor outcome, suggesting the use of HPV-ctDNA as tool to select high-risk patients that may be eligible for further systemic treatments

3566 Poster Session (Board #59), Sun, 8:00 AM-11:30 AM

Phase II study of panitumumab, 5-fluorouracil, mitomycin-c and radiotherapy treatment in patients with non-metastatic squamous cell carcinoma of the anal canal: safety and efficacy results (VITAL study)—GEMCAD 09-02. *First Author: Jaime Feliu, Hospital Universitario La Paz, Madrid, Spain*

Background: More than 80% of squamous cell carcinoma of the anal canal (SCCAC) express epidermal growth factor receptor protein (EGFR). VITAL was a phase II, multicentre, single arm study, which aimed to evaluate efficacy and safety of the addition of panitumumab (Pmab) to fluorouracil (5-FU), mitomycin C (M) and radiotherapy (RT) standard treatment in patients with SCCAC (NCT01285778). **Methods:** Treatment naïve patients $\geq$ 18 years old, with SCCAC (Stage T2-T4, any N, M0 defined by MRI) with $\leq$ 2 ECOG performance status, received Pmab (6 mg/kg, day 1 and q2w during 8 weeks), 5-FU (1000 mg/m2/day; IV infusion, days 1-4 and 29-32) and M (10mg/m2, days 1 and 29) plus RT 45 Gy (1.8 Gy/fraction) to the primary tumour and mesorectal, iliac and inguinal lymph nodes, plus boost dose of 10-15 Gy to primary tumour and affected lymph nodes. The primary objective was disease free survival (DFS) at 3 years (anticipated DFS: 73.7% $\pm$ 12%) estimated by Kaplan-Meier. Multivariable analysis of efficacy variables adjusting for key baseline covariates will be presented. **Results:** A total of 58 patients (31 women; median age: 59 years; ECOG performance status: 0 [41%] / 1 [57%] / 2 [2%]; TNM II [29%] / IIIA [21%] / IIIB [47%]/ non-evaluable [NE] [4%]) were evaluated. The 3-year DFS rate was 61.1% (95% CI 47.1 - 72.4). The median follow-up was 45 months. The 3-year overall survival rate and progression free survival rate were 78.4% (95%CI 65.1-87.1) and 57.5% (95%CI 43.6 - 69.2) respectively. Eighteen patients (31.0%) had a colostomy within the first 2 years post-treatment. Grade 3-4 toxicities were experienced by 53 (91%) patients. Radiation skin injury (19%), diarrhoea (10%), neutropenia (9%) and leukopenia (19%) were the most common ($>$ 10%) grade 3-4 adverse events associated with Pmab. There were no toxic deaths. Potential predictive efficacy and safety biomarkers are currently being assessed. **Conclusions:** The overall 3-year DFS rate does not reach the anticipated level for the main objective of the study. The multivariable analysis will determine if any subgroup of patients may benefit from this treatment scheme. Financed by Amgen S.A. Clinical trial information: NCT01285778.

3567 Poster Session (Board #60), Sun, 8:00 AM-11:30 AM

FOLFCIS regimen for treatment of cancer of the anal canal. *First Author: Sebastián Mondaca, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The combination of cisplatin and 5-fluorouracil (5-FU) is a standard chemotherapy regimen for advanced anal squamous cell cancer (AC) and is associated with significant toxicity. We examined the efficacy of a modified schedule, FOLFCIS, and performed an integrated clinical and genomic analysis of advanced AC. **Methods:** We reviewed all patients with metastatic or recurrent locally advanced AC treated with first line FOLFCIS chemotherapy at Memorial Sloan Kettering Cancer Center (MSK) between January 2007 and July 2017. FOLFCIS, which is essentially FOLFOX with cisplatin substituted for oxaliplatin, consisted of cisplatin 40 mg/m^2 day 1, leucovorin 400 mg/m^2 day 1, 5-FU 400 mg/m^2 day 1, 5-FU 1000 mg/m^2/d days 1 and 2 in a 14-day cycle. Forty-one advanced AC patients underwent targeted next generation tumor sequencing of $>$ 300 genes (MSK-IMPACT), including 23 of the patients treated with FOLFCIS. **Results:** Fifty-three AC patients (48 metastatic; 5 unresectable, locally advanced) received first line FOLFCIS during this period; all were platinum naive. Median age was 59 years, and 32% had metastatic disease at diagnosis. Thirteen patients (25%) received multimodal treatment for metastatic disease. Administered dose intensity of both cisplatin and 5-FU was $>$ 70%. Response rate was 48% (95% CI, 32.6 - 63). With a median follow up of 41.6 months, progression free survival (PFS) and overall survival (OS) were 7.1 months (95% CI, 4.4 - 8.6) and 22.1 months (95% CI, 16.9 - 28.1), respectively. Among all advanced AC, most frequent genomic alterations consisted of chromosome 3q amplification (17%) and mutations in PIK3CA (24%) and KMT2D (24%). Genomic alterations affecting the phosphatidylinositol 3-kinase pathway in PIK3CA, PTEN, or AKT2 were detected in 54% of cases. TP53 mutation, YAP1 amplification, and TERT promoter mutations appeared enriched in HPV-negative AC. No genomic alteration correlated with response to platinum-containing treatment. **Conclusions:** FOLFCIS is effective and safe as first line chemotherapy in advanced AC patients and represents an alternative treatment option for patients with AC.

3568 Poster Session (Board #61), Sun, 8:00 AM-11:30 AM

Association of postoperative carcinoembryonic antigen (CEA) levels with survival in stage III colon cancer (CC): Post hoc analysis of the MOSAIC and PETACC-8 studies. *First Author: Edouard Auclin, Gastrointestinal Oncology Department, European Georges Pompidou Hospital, Paris, France*

Background: CEA is a CC biological marker that correlates with tumor stage. Its measurement is recommended for follow up after surgery. CEA above 5 ng/mL is of poor prognosis, however this cutoff is debated. Thus, we explored the prognostic value of postoperative CEA, in its continuous form. **Methods:** Eligible patients (pts) in MOSAIC and PETACC-8 studies had postoperative CEA available. The association between CEA and overall (OS) and disease free survival (DFS) was explored in the MOSAIC discovery cohort. It was assessed in 3 groups of pts (group 1: 0 to 1.30 ng/ml, n = 630; group 2: 1.30 to 5 ng/ml, n = 613; group 3: $>$ 5 ng/ml, n = 49) by the Kaplan Meier method. Then relation of CEA and outcomes was continuously modelled with the restricting cubic splines (RCS) and multiple polynomial fractional (MFP) methods. Cox uni- and multivariate models were constructed. Findings were confirmed in a PETACC-8 validation cohort. **Results:** CEA was available in 1292 (96%) and 2477 (97%) pts in the discovery and validation cohorts, respectively with 96.2% and 95.9% of pts having a CEA below 5 ng/ml. In the discovery cohort, 5y OS were 79% (95%CI: 76-82), 70% (95%CI: 66-74) and 47% (95% CI: 35-64) in groups 1, 2 and 3, $p < 0.001$. Five-year DFS rate were 68% (95%CI: 65-72), 58% (95%CI: 54-62) and 42% (95%CI: 31-61), in groups 1, 2 and 3, $p < 0.001$. RCS and MFP showed that relation between CEA and survival was following a square root function, suggesting that values over 1.3 ng/ml were associated with prognosis. CEA over 1.3 ng/ml was an independent prognostic factor for OS and DFS (Table 1). All those results were confirmed in the validation cohort (Table 1). **Conclusions:** In 2 cohorts from large phase III trials, we showed that postoperative CEA was highly prognostic for OS and DFS. This was true for CEA levels above and below 5 ng/ml, suggesting that this single cutoff is not sufficient and that CEA should be used more precisely as stratification factors in future adjuvant trials.

Hr (95%ci) from multivariate cox models.

	Discovery		Validation	
	OS	DFS	OS	DFS
Group 1	1	1	1	1
2	1.7 (1.3-2.3)	1.7 (1.3-2.2)	1.5 (1.2-1.8)	1.4 (1.2-1.7)
3	2.3 (1.3-4.4)	2.7 (1.5-4.7)	2.6 (1.7-3.8)	2.7 (1.9-3.8)

All p-values < 0.001

3569 Poster Session (Board #62), Sun, 8:00 AM-11:30 AM

SATB2 loss and the immune milieu of colorectal cancer (CRC). *First Author: Darran O'Connor, Department of Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland*

Background: SATB2 orchestrates gene expression by regulating higher-order chromatin structure. Antibody screening of 48 normal human tissues and 20 cancers, showed SATB2 as almost exclusively expressed in gastrointestinal tissue. We confirmed this in 10,533 further samples. **Methods:** Tissue microarray (TMA) analysis was used to determine SATB2 expression in CRC, Kaplan-Meier analysis and the log rank test were used to illustrate differences between disease-specific survival (DSS) according to SATB2 expression. Cox regression proportional hazards models were used to estimate the relationship between outcome and SATB2 expression, grade, age, stage, differentiation and gender. Gene set enrichment analysis (GSEA) was used to identified pathways associated with loss of SATB2 expression and RNAi was used to modulate SATB2 in cell lines. **Results:** Differential SATB2 expression was observed in CRC, with loss occurring along the adenoma-carcinoma sequence (n = 320, p = 0.023). SATB2 expression was decreased in metastatic SW620 cells and knockdown of SATB2 in SW480 cells increased their growth and migratory capacity. By automated image analysis of SATB2 expression in CRC (n = 309), SATB2 was found to be an independent predictor of DSS (HR = 0.52, 95% CI 0.32-0.83, p = 0.006). SATB2 was examined in a second cohort (n = 290) and again, found to be an independent predictor of DSS (HR = 0.40, 95% CI 0.18-0.92, p = 0.031). SATB2 significantly correlated with CD3+ infiltrates (p = 0.006) and inversely correlated with COX2 expression (p = 0.019). In two independent CRC cohorts (n = 467), SATB2-low tumours were found to be significantly enriched in the CMS1 (immune-related) subtype ($p < 0.001$). GSEA revealed that SATB2-low tumours demonstrated altered immune signalling with significant increases in IFNγ (p = 0.001), IL6 (p = 0.001), IL8 ($p < 0.001$) TFGβ ($p < 0.001$), which was mirrored by manipulation of SATB2 in CRC cells. Furthermore, in a longitudinal cohort of ulcerative colitis patients, we found a significant correlation between loss of SATB2 and occurrence of future cancers (p = 0.013). **Conclusions:** We postulate that SATB2 acts as a master regulator of inflammation in the gut and loss of expression is significantly associated with the progression of colorectal cancer.

3570 Poster Session (Board #63), Sun, 8:00 AM-11:30 AM

Causal modeling of CALGB 80405 (Alliance) to identify network drivers of metastatic colorectal cancer (CRC). *First Author: Rahul K Das, GNS Healthcare, Cambridge, MA*

Background: CALGB 80405 is a phase III clinical trial of FOLFOX/ FOLFIRI with randomly assigned cetuximab/ bevacizumab. Novel causal machine learning approaches to the study dataset may lead to valuable insights into CRC prognosis and management of CRC progression. **Methods:** Using a Bayesian causal machine learning and simulation platform, we built an ensemble of network models for overall survival (OS). We used 78 baseline clinical and demographic variables for 947 patients with wild-type KRAS tumors. Causal modeling identifies the set of conditional dependencies between variables leading to outcomes. Building an ensemble of causal models estimates model uncertainty and identifies key drivers by model consensus as measured by ensemble frequency (*f*). Counterfactual simulations were performed on this ensemble to identify causal drivers of disease. **Results:** Key causal variables of OS ($f > 50\%$) include primary tumor side ($f =$ 85%), aspartate aminotransferase (AST) and hemoglobin (HGB) concentrations (f = 100%, 91%), and tumor sites: local primary and intra-abdominal metastases (f = 85%, 89%). Counterfactual simulations, controlling for confounders, suggested a significant causal effect of the following variables on driving OS: AST (median hazard ratio (HR) = 1.3, 75^{th} vs. 25^{th} percentile value; 10^{th} - 90^{th} percentile interval: 1.2-1.4), HGB (0.8, 0.7-0.9), primary side (1.5, 1.0-1.7; right vs. left), and tumor sites (present vs. absent): local primary (1.3, 1.0-1.5), intra-abdominal (1.4, 1.1-1.6) and liver (1.1, 1.04-1.14) metastases. AST was a stronger biomarker of OS in patients with liver metastases (1.6, n = 705) than without (1.2, n = 242). **Conclusions:** Primary side, AST, HGB, and tumor sites (local primary, intra-abdominal, and liver) play a central role as independent drivers/biomarkers of OS. Availability of these measures at baseline will allow better risk stratification at initiation of treatment. Clinical trial information: U10CA180821, U10CA180882.

3571 Poster Session (Board #64), Sun, 8:00 AM-11:30 AM

Night shift work duration and risk of colorectal cancer according to IRS1 and IRS2 expression. *First Author: Yan Shi, Chinese PLA General Hospital, Beijing, China*

Background: Although accumulating evidence supports an association between night shift work and an increased risk of colorectal cancer (CRC), the mechanism remains elusive. Notably, metabolic disorders, including insulin resistance, play an important role in both CRC development and other chronic diseases caused by circadian disruption. IRS1 (insulin receptor substrate 1) and IRS2 are the primary mediators of insulin-dependent mitogenesis and could respond to the metabolic microenvironment. We therefore hypothesized that the risk of CRC in night shift workers might be different according to IRSs expression level. **Methods:** Among 77,470 eligible women with available night work data in the Nurses' Health Study, we documented a total of 1,397 physician-confirmed CRCs during 24 years of follow-up, of which 304 and 308 had available data on IRS1 and IRS2, respectively. We used duplication method Cox proportional hazards regression analysis for competing risks data to calculate age-adjusted and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for each CRC subtype. We measured tumor IRS1 or IRS2 protein expression by immunohistochemistry. **Results:** Compared with women who never worked night shifts, those working a rotating night shift for 15 years or more had a trend of increased overall risk of CRC [P_{trend}= 0.06, multivariable HR = 1.20, 95%CI, 0.99 to 1.45]. For the same comparison, longer of night shift duration was associated with a higher risk of IRS1-positive tumors (multivariable HR = 1.81, 95%CI 0.94 to 3.48, P_{trend}= 0.06) but not with IRS1-negative tumors (multivariable HR = 1.13, 95%CI 0.71 to 1.80, P_{trend}= 0.56, $P_{heterogeneity}$ for IRS1 subtypes = 0.02). The corresponding multivariable HRs were 2.69 for IRS2-positive tumors (95%CI 1.48 to 4.89, P_{trend}= 0.001) and 0.90 for IRS2-negative tumors (95%CI 0.54 to 1.51, P_{trend}= 0.72, $P_{heterogeneity}$ for IRS2 subtypes = 0.008). **Conclusions:** Working 15 years or more of rotating night shift was associated with higher risk of CRC with IRS1-positive or IRS2-positive, but not negative tumors. This molecular pathological epidemiology data suggest a potential role of insulin receptor substrate in mediating carcinogenesis induced by night shifts.

3572 Poster Session (Board #65), Sun, 8:00 AM-11:30 AM

Impact of MLH1, PMS2, MSH2, and MSH6 alterations on tumor mutation burden (TMB) and PD-L1 expression in 1,057 microsatellite instability-high (MSI-H) tumors. *First Author: Mohamed E. Salem, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC*

Background: MSI-H tumors are associated with higher TMB. We examined the yet uncharacterized relationship between TMB and individual MMR gene alterations in MSI-H tumors. **Methods:** MSI-H was determined by examining altered microsatellite (MS) loci using NextGen sequencing (cutoff: $> = 46$) on a 592-gene panel. TMB was calculated by enumerating somatic missense mutations. MMR protein expression was evaluated by IHC. ANOVA and chi-square tests were used for comparisons. **Results:** A total of 1057 MSI-H tumors (283 colorectal cancer [CRC]; 449 endometrial cancer [EC]; and 325 others from 29 cancer types) were examined. High TMB ($\geq$ 17 mutations/megabase [mt/MB]) was seen in 74% of tumors. MSI-H CRC had the highest TMB compared to MSI-H EC and "all others" (mean TMB: 39 vs. 23 vs. 31 mt/MB, respectively; $p < 0.0001$). There was no difference in TMB between *BRAF* V600 mutant and wild type MSI-H CRC (38.7 vs. 39 mt/MB). In general the most frequently altered (IHC loss or mutation) MMR genes were MLH1 and PMS2 (72% and 83%, CRC; 90% and 95%, EC). MSH2 and MSH6 were more frequently altered in CRC than EC (21% vs. 5% and 49% vs. 28%, respectively; $p < 0.0001$). In CRC, MSH2 and MSH6 were more frequently altered in left than right sided MSI-H tumors (45% vs. 12% and 67% vs. 40%; $p = 0.01$). Overall MSH2 or MSH6 alterations were associated with higher TMB (48.5 and 40 mt/MB, respectively) than MLH1 or PMS2 (27 mt/MB for both); $P < 0.0001$. Tumors with MSH2/6 co-alterations (4%) had a higher TMB compared to those with MLH1/PMS2 (39%) co-alteration (50 vs. 24 mt/MB; $p < 0.0001$). PD-L1 overexpression was seen at a higher frequency in tumors with MSH2 (23%) than MSH6 (16%), MLH1 (16%), or PMS (14%); $P = 0.01$. MSH2/6 alterations in EC were associated with higher MS alterations (MSH2, 88; MSH6, 73; MLH1, 68; PMS2, 68; $p < 0.0001$), while all genes were equal in CRC. MSH2 alterations were associated with higher frameshift mutation rates in 36 genes in EC, and in different 10 genes in CRC. **Conclusions:** TMB varies significantly across MSI-H tumors. MSH2/MSH6 alterations were associated with a significantly higher TMB than MLH1/PMS2 across several cancer types. The MS alterations associated with MSH2/6 were tumor-type specific.

3573 Poster Session (Board #66), Sun, 8:00 AM-11:30 AM

Association between density of tumor infiltrating lymphocytes and disease-free survival (DFS) in patients with resected stage I-III colorectal cancer in the FACS randomized trial. *First Author: Sian Alexandra Pugh, University of Southampton, Southampton, United Kingdom*

Background: Accumulating evidence demonstrates an association between density of tumor infiltrating lymphocytes and outcome in colorectal cancer (CRC). This study sought to assess the prognostic utility using an accurately staged cohort of patients followed up in a clinical trial. **Methods:** Observational analysis of data from the FACS (follow-up after CRC surgery) trial after 5 years of follow-up. All patients had undergone treatment with curative intent for stage I-III primary CRC, with microscopically clear margins, no evidence of metastases on axial imaging and CEA $< 10\mu g/l$ following completion of treatment. Immune cell densities were quantified in the centre (CT) and invasive margin (IM) of all tumors for both CD3 and CD45RO. For each tumor region high (Hi) and low (Lo) CD3 and CD45RO densities were determined according to the median of the cohort to investigate association with disease free survival (DFS). **Results:** Tumor samples have been analyzed from 297 patients to date for which the combined 5 year DFS is 83% (left sided CRC 81%, right sided CRC 85%). High densities of CD3 and CD45RO positive cells in both tumor regions were associated with a superior outcome: $CD3^{Hi}_{CTIM}CD45RO^{Hi}_{CTIM}$ 94% 5yr DFS vs $CD3^{Lo}_{CTIM}CD45RO^{Lo}_{CTIM}$ 81%, HR 0.36 95% CI 0.15-0.89 p = 0.04. This difference was most notable in left sided CRC: $CD3^{Hi}_{CTIM}CD45RO^{Hi}_{CTIM}$ 96% 5yr DFS vs $CD3^{Lo}_{CTIM}CD45RO^{Lo}_{CTIM}$ 78%, HR 0.13 95%CI 0.04-0.41 p = 0.02. In right sided CRC the difference was not significant: $CD3^{Hi}_{CTIM}CD45RO^{Hi}_{CTIM}$ 91% 5yr DFS vs $CD3^{Lo}_{CTIM}CD45RO^{Lo}_{CTIM}$ 83%, HR 0.70 95%CI 0.17-2.89 p = 0.62. **Conclusions:** In a well characterized and followed up cohort of CRC patients within a clinical trial we have demonstrated that $CD3^{Hi}_{CTIM}CD45RO^{Hi}_{CTIM}$ left sided tumors have a significantly better outlook. The potential for these data to impact on the need for clinical follow up in patients with left sided CRC should be examined in a prospective study. Clinical trial information: 61091474.

3574 Poster Session (Board #67), Sun, 8:00 AM-11:30 AM

MSI-high and MSI-stable colorectal carcinomas (CRC): A comprehensive genomic profiling (CGP) study. *First Author: Siraj Mahamed Ali, Foundation Medicine, Inc., Cambridge, MA*

Background: High levels of microsatellite instability (MSI-H) is an approved biomarker for the selection of immunotherapy across solid tumor types. Given the high prevalence of MSI high in CRC, we used CGP to uncover additional therapy targets associated with MSI status. **Methods:** Hybrid capture-based CGP was performed on 8,004 clinically advanced CRC. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability status (MSI-H or MS-Stable, MSS) was determined by principal components analysis of optimal homopolymer loci. **Results:** Of the 8,004 mCRC, 402 (5%) MSI-H and 7,602 (95%) MSS. Patient age and gender distribution did not differ between the 2 groups. Significant GA differences were found: MSS mCRC featured more *KRAS*, *TP53* and *APC* GA, whereas MSI-H mCRC had more *BRAF*, *PIK3CA*, *BRCA2* and *ALK* GA (Table). As expected, GA in the 4 genes associated with heritable CRC (HNPCC) were significantly enriched in MSI-H tumors. In addition, *RNF43* correlated with MSI-H status. Median TMB was markedly higher in the MSI-H samples, 96% of which featured ≥20 mutations/Mb, compared to only 1% of MSS mCRC. Mutation frequencies and false discovery rate corrected p values from chi-squared analysis are presented below. **Conclusions:** MSI-H mCRC feature GA in *RNF43*, *BRAF*, *PIK3CA*, *ALK* and *BRCA2* and near universal high TMB, impacting potential responses to both targeted and immunotherapies. MSS mCRC is characterized by more *KRAS* and *TP53* GA frequencies and low TMB. GA in receptor kinases such as in *ERBB2* and *ALK* are more often found in MSI-H mCRC, but are present in both types and represent additional potential targets for treatment strategies.

	MSI-High CRC (402)	MSI-Stable CRC (7,602)	Significance
Median Age and (range) in years	62 (8-201)	58 (13-88)	
Gender	50% female	46% female	
Mean GA/tumor	18.5	5.8	P < < 0.0001
KRAS	30%	52%	P < 0.0001
TP53	34%	78%	P < < 0.0001
BRAF	36%	8%	P < < 0.0001
PIK3CA	33%	18%	P < 0.0001
ERBB2	7%	5%	NS
MSH6	29%	1%	P < < 0.0001
MLH1	17%	< 1%	P < < 0.0001
MSH2	15%	< 1%	P < < 0.0001
PMS2	6%	< 1%	P < < 0.0001
RNF43	55%	3%	P < < 0.0001
BRCA2	21%	2%	P < 0.02
APC	44%	80%	P < < 0.0001
ALK	3%	1%	P < 0.0001
Median TMB (mut/Mb)	47	4	P < 0.0001
TMB ≥10 mut/Mb	99%	5%	P < 0.0001
TMB ≥20 mut/Mb	96%	1%	P < 0.0001

3575 Poster Session (Board #68), Sun, 8:00 AM-11:30 AM

Genetic variation in TET3 and survival in metastatic colorectal cancer (mCRC) from FIRE-3, TRIBE, and MAVERICC clinical trials. *First Author: Stephen B. Gruber, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: Patients enrolled in FIRE-3, TRIBE, and MAVERICC clinical trials for mCRC were genotyped using Illumina Oncoarray to identify predictive and prognostic biomarkers. Here we report results of a genome-wide association study (GWAS) of overall survival (OS) and progression-free survival (PFS) in 790 patients from 3 clinical trials. **Methods:** DNA samples from patients of European descent (≥80% estimated European ancestry) treated on all arms of FIRE-3, TRIBE, and MAVERICC were genotyped on the Infinium OncoArray through the Colorectal Transdisciplinary (COLORECT) Study. We performed a GWAS of directly genotyped markers with a minor allele frequency ≥ 1% (403,467 SNPs) in 790 patients with mCRC from three trials (FIRE-3 n = 235, TRIBE n = 320, MAVERICC n = 235). Cox proportional hazards regression adjusted for age, sex, principal components for global ancestry, and trial was performed in R using GenABEL to identify associations between genetic variants and OS and PFS. Subgroup analysis by study arm, sex, and primary location was performed. Bonferroni correction for the number of independent genetic markers was applied to minimize false positives. **Results:** Males were 514 (65.1%) and females were 276 (34.9%) of the patients meeting eligibility criteria and genotype data passing QC. The median OS was 21.0 months and median PFS was 9.2 months. Genomic control lambda values for OS = 1.03 and PFS = 1.03 showed minimal population stratification. One SNP, rs7597070 on 2p13.1 within an intron of *TET3*, was significantly associated with OS and exceeded the Bonferroni correction threshold for genome-wide significance < 1.67E-07. The A allele (MAF = 0.016) was associated with increased OS versus the T allele (HR = 0.29; 95% CI, 0.19-0.45; P-value = 5.9E-08). Suggestive evidence also supported an association with PFS (HR = 0.53 (A allele); 95% CI, 0.34-0.81; p = 3.4E-03). The frequency of the A allele was 1.6% in our European patients, 10% in East Asians and 42% in Africans in the 1000 Genomes data. **Conclusions:** Our data identify a new promising prognostic biomarker for OS and PFS among patients with mCRC, and population genetic differences may contribute to disparities in survival by ancestry.

3576 Poster Session (Board #69), Sun, 8:00 AM-11:30 AM

Polymorphism in the circadian clock pathway to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from TRIBE and FIRE-3 phase III trials. *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: The clock machinery comprises a complex network of transcription-translation feedback loops which regulates the circadian expression of target genes involved in key cellular functions. The disruption of the circadian clock has been associated with increased CRC risk, and the expression levels of core clock genes with clinicopathological features, survival and treatment response. We therefore hypothesized that genetic variants in clock genes may predict first-line treatment outcome in mCRC pts. **Methods:** Genomic DNA from blood samples of pts enrolled in two independent randomized phase III trials, TRIBE and FIRE-3, was genotyped through the OncoArray, a custom array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of 22 selected SNPs in 11 genes of the clock pathway (*CLOCK*, *BMAL1*, *NPAS2*, *PER 1-2-3*, *CRY 1-2*, *RORa*, *hTIM*, *SIRT1*) was analyzed. **Results:** A total of 451 pts were included in the analysis. TRIBE FOLFIRI/bevacizumab (bev) arm served as discovery cohort (n = 215, median PFS/OS: 9.7/26.2 mo), FIRE-3 FOLFIRI/bev arm as validation (n = 107, mPFS/OS: 11.5/31.4 mo) and FOLFIRI/cetuximab arm as control (n = 129, mPFS/OS: 12.8/49.8 mo). In the discovery cohort, the overall population carrying the 3'UTR CLOCKrs3749474 T/T variant showed a shorter mPFS (8.8 vs 10.4 mo) compared to pts with any C allele both in univariate (HR = 1.69; 95%CI 1.11-2.59; p = 0.012) and in multivariable analysis (HR = 2.06; 95%CI 1.26-3.37; p = 0.004). This effect was stronger in female pts (p < 0.001), and left-sided CRCs (p = 0.002). Significant interaction was found with gender (p = 0.005); however, no interaction was found with tumor location or *RAS* status. Findings were validated in overall pts in FIRE-3 bev cohort both in univariate (HR = 1.99; p = 0.027) and in multivariable analysis (HR = 2.45; p = 0.013). No significant association was observed in the control arm. **Conclusions:** Our results provide the first evidence that CLOCKrs3749474 polymorphism may have a predictive value in mCRC pts treated with first-line FOLFIRI/bev. This finding supports a possible role of clock genes in contributing to resistance to anti-VEGF treatment.

3577 Poster Session (Board #70), Sun, 8:00 AM-11:30 AM

Molecular analyses of left- and right-sided tumors in adolescents and young adults (AYA) with colorectal cancer (CRC). *First Author: Megan Jagosky, Levine Cancer Institute, Charlotte, NC, US*

Background: The incidence of CRC, particularly left sided tumors, in AYA is rising. Epigenetic events appear to play an important role in tumorigenesis and cancer progression, especially in AYA. We compared molecular features of left-sided colorectal tumors (LT) in AYA to right-sided tumors (RT) in AYA and to LT in older patients. **Methods:** Primary tumors annotated by site of origin were examined by NextGen Sequencing (592 genes), protein expression, and gene amplification. Tumor mutation load (TML) was calculated by enumerating somatic missense mutations. Chi-square testing was used for comparisons. **Results:** In total, 1,064 primary CRCs were examined. Comparing LT (n = 220) with RT (n = 47) in AYA (≤ 40 years; see table), RT had higher mutation rates in *RNF43* (33.3% vs. 3.4%, *P* < 0.001), *PIK3CA* (31% vs. 11.1%, *P* = 0.005), *KMT2D* (29.6% vs. 4.1%, P < 0.001), *MSH6* (14.8% vs. 2%, *P* = 0.002), *PTEN* (13.8% vs. 2%, *P* = 0.003), *BRCA2* (13.3% vs. 3.9%, P = 0.038), *MLH1* (10.3% vs. 2%, *P* = 0.022) and *MSH2* (10% vs. 1.3%, *P* = 0.009). MSI-H was seen in 25% of RT compared to 5.5% of LT (*P* = 0.001). RT had a higher frequency of TML-high compared to LT (32% vs. 6.9%, *P* < 0.001). When we compared LT from AYA (≤ 40 years; n = 220) with LT from older pts (≥ 65 years; n = 589), AYA exhibited higher mutation rates of *BRCA2* (3.9% vs. 0.8%, *P* = 0.014), *MSH2* (1.3% vs. 0%, *P* = 0.031), and *TSC2* (1.4% vs. 0%, *P* = 0.031). Genes responsible for histone modification were significantly more frequently mutated in AYA than older pts: *KMT2A* (1.5% vs. 0%, P = 0.027), *KMT2C* (4.5% vs. 0%, P = 0.003), and *KMT2D* (4.1% vs. 0.4%, P = 0.004). High TML was seen more frequently in AYA (6.9% vs. 2.8%, P = 0.031) **Conclusions:** LT in AYA carry genetic alterations that are different from RT in AYA, as well as LT in older pts. Our data suggest that histone modification warrants further exploration and may be a promising target in treatment of CRC in AYA.

Molecular differences between lt and rt in aya.

Gene	RT %	LT %	*P*-value
APC	50	75.7	0.006
TP53	50	77	0.002
ARID1A	54.5	22.2	0.04
POLE	7.7	0.7	0.01
BRCA1	6.9	0	0.01
EGFR	3.3	0	0.02
NOTCH1	3.7	0	0.02
NF2	3.4	0	0.02
MEN1	3.4	0	0.02
RAD50	20	1.3	0.002
HNF1A	11.1	2.1	0.01
CDH1	4.3	0	0.02
AMER1	7.1	0.7	0.0
PALB2	6.7	0	0.02
BMPR1A	6.9	0	0.00
PRKDC	3.7	0	0.02
SMAD2	3.7	13.3	0.01

3578 Poster Session (Board #71), Sun, 8:00 AM-11:30 AM

Results from a phase I study of andecaliximab in combination with FOLFIRI and bevacizumab in patients with second line metastatic colorectal cancer. *First Author: Zev A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Matrix metalloproteinase 9 is highly expressed in several malignancies, including metastatic colorectal cancer (mCRC) and is an adverse prognostic feature. In preclinical colorectal cancer models, inhibition of MMP-9 was associated with tumor growth inhibition. Andecaliximab (ADX) is a chimeric antibody directed against MMP-9 engineered to remove T cell epitopes and reduce risk of immunogenicity. In this phase I multi-cohort study, we combined ADX with standard of care chemotherapy in patients with 2nd line mCRC. (Clinicaltrials.gov NCT# 01803282) **Methods:** Patients were eligible if they progressed on a front line chemotherapy backbone of a fluoropyrimidine and a platinum with or without bevacizumab. All patients received ADX 800 mg IV every two weeks in combination with standard dose FOLFIRI + bevacizumab. The primary endpoints of this study were safety and tolerability. Exploratory endpoints were investigator assessed objective response rate (ORR), progression free survival (PFS) and overall survival (OS). **Results:** We enrolled 44 patients (25 female) with measurable disease who had received prior treatment for metastatic colorectal cancer. The median age was 58 years (range 23-81). As of September 22, 2017, the median ADX treatment duration for this study was 5.9 months. The most common adverse events (AEs) were diarrhea (57%), fatigue (57%), nausea (57%), stomatitis (34%), and vomiting (32%). Serious AEs were reported in 25% of pts. The most common serious AE was pulmonary embolism, which occurred in 2 patients. Median PFS was 9.2 months (90% CI 7.4-10.2 months) and the ORR was 21% (90% CI 11-33%). The median OS was not reached at the time. Study treatment continues in 27% of patients. **Conclusions:** The combination of ADX with FOLFIRI and bevacizumab was safe and effective. The activity of the combination appears encouraging in 2nd line treatment of metastatic colorectal cancer. Updated data will be presented at the time of the presentation. Clinical trial information: NCT01803282.

LBA3579 Poster Session (Board #72), Sun, 8:00 AM-11:30 AM

Comparison of chemotherapy use, cost, and survival in patients with metastatic colorectal cancer in Western Washington and British Columbia. *First Author: Todd Yezefski, University of Washington School of Medicine, Seattle, WA*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

3580 Poster Session (Board #73), Sun, 8:00 AM-11:30 AM

Prognostic value of tumour infiltrating lymphocytes in stage II colon cancer. A nationwide population-based study. *First Author: Ann Christina Eriksen, Danish Colorectal Cancer Center South, Vejle Hospital, Vejle, Denmark*

Background: Patients with high-risk stage II colon cancer (CC) may benefit from adjuvant chemotherapy, but additional prognostic markers are needed for better treatment stratification. We investigated the prognostic value of tumour infiltrating lymphocytes (TILs) in a true population-based cohort of patients with stage II CC. **Methods:** A total of 573 patients were included, representing all patients operated for stage II colon cancer in Denmark in 2002. Tumour blocks representing the deepest invasive part of the primary tumour were used for analysis. CD3+ and CD8+ TILs at the invasive front were evaluated by immunohistochemistry on whole tumour sections. The invasive area was manually outlined, and Visiopharm Integrator System software was used for quantification. Data were dichotomized for comparison with clinical data. The prognostic value was investigated in Cox proportional hazard models for recurrence-free survival (RFS) and overall survival (OS). **Results:** Low CD3+ or CD8+ TILs were significantly associated with poor RFS and OS, ($p = 0.0021$ and $p \leq 0.0009$, respectively, log-rank test). In multiple Cox regression analysis low CD3+ and CD8+ TILs were associated with reduced RFS with hazard ratio (HR) 1.386 (95% CI 1.039-1.850), $p = 0.026$, and HR 1.394 (95% CI 1.029-1.890), $p = 0.032$, respectively, independent of age, T-stage, localization, perforation, and microsatellite instability (MSI). In the subgroups of patients with low CD3+ or CD8+ TILs, there were no differences in survival between patients with MSI and microsatellite stable tumours, ($p = 0.821$ and $p = 0.907$, respectively). **Conclusions:** Low CD3+ and CD8+ TILs in the invasive area are both related to inferior prognosis in patients with stage II CC, and we recommend either of these parameters to be considered as an additional high-risk factor.

3581 Poster Session (Board #74), Sun, 8:00 AM-11:30 AM

Early response metrics for predicting trial outcomes: A report from volumetric CT for precision analysis of clinical trials (Vol-PACT). *First Author: Patrick Hilden, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The high frequency of negative phase III oncology trials following positive phase II results indicates a need for improved metrics which assess treatment effect. Vol-PACT is an ongoing private-public partnership launched to collect source imaging data from phase III trials with a goal of developing improved methods of assessing therapies in randomized clinical trials. With 8 phase III industry sponsored datasets received and more expected, Vol-PACT is among the largest collective cancer imaging databases with fully annotated measurements of target, non-target, and new lesions. **Methods:** Images from 4 phase III trials in metastatic colorectal cancer (mCRC) were evaluated and benchmarked against 4 phase III trials in other solid tumors. Lesions were measured directly on CT images using semi-automated algorithms. Four metrics quantifying change from baseline through 2 cycles (week 8-16) were evaluated: RECIST response rate, percent change over time, absolute change over time, and log change over time. One thousand phase II trials were simulated by resampling without replacement (50 pts/arm). The average standardized difference between arms was determined across simulations. The weighted linear correlation was estimated between average standardized difference and hazard ratios estimating progression-free survival benefit (PFS HR). **Results:** With sample sizes of 289 to 921 patients per trial ($n = 4,074$ across the 8 trials), PFS HR values ranged from 0.4 to 1.2 (6 significant, $p < 0.05$). For mCRC trials, correlations with PFS HR were 0.87 for RECIST response rate, 0.86 for percent change over time, 0.96 for absolute change over time, and 0.73 for log change over time. For other trials they were 0.80, 0.94, 0.94, and 0.95, respectively. Across the full set of 8 trials, observed correlations were 0.64, 0.90, 0.93, and 0.87. **Conclusions:** Continuous response metrics derived from original CT images correlated strongly with PFS HR across mCRC and other trials, and may be more informative than RECIST response categories. Development of metrics based on volumetric measurements are ongoing, as is the analysis of data from emerging immunotherapy trials.

3582 Poster Session (Board #75), Sun, 8:00 AM-11:30 AM

Genome-wide association with survival in stage II-III colon cancer clinical trials (NCCTG N0147, Alliance for Clinical Trials in Oncology; NSABP C-08, NRG Oncology). *First Author: Kathryn Penney, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: Many genetic variants have been identified as associated with colorectal cancer (CRC) risk; few have been associated with CRC survival. Identification of variants associated with survival may further explain the biology of disease progression and aid in outcome prediction. We performed a genome-wide association study (GWAS) in 2 CC clinical trials to identify genetic variants associated with overall survival (OS). **Methods:** We included patients from N0147, a phase III adjuvant trial in stage III CC patients, and C-08, a phase III trial comparing adjuvant therapy regimens for patients with stage II/III CC. 4974 samples were genotyped with the Illumina HumanOmniExpress + Exome array, consisting of 964,193 SNPs. Genotypes were imputed using 1000 Genomes Project data. We calculated OS as time from randomization to death from any cause and used Cox proportional hazards regression to evaluate association of each SNP with OS, adjusting for age, sex, treatment arm and principal components. Analysis was performed in N0147 and C-08 separately; results were combined in a fixed-effects meta-analysis. **Results:** Follow-up after diagnosis was similar for the 2 trials; median OS for N0147 and C-08 was 1678 days (IQR = 1238-2071) and 2224 days (IQR = 1901-2494), respectively. A locus on chromosome 7p15.2 was significantly associated with improved OS. The most significant variant at this locus, rs76766811 (p = 1.59e-8), is exceedingly rare in this primarily European American population but much more common in African Americans (AAs) (~19%). When the analysis is stratified by self-reported ancestry, the signal is only present in AAs (n = 359) (HR = 0.30, 95% CI: 0.21-0.43, p = 1.81e-10). **Conclusions:** This GWAS nested within 2 CC trials identified rs76766811 on 7p15.2 as significantly associated with OS among AA patients. This finding should be confirmed in additional study populations, particularly focusing on identifying variants associated with survival in AAs. Support: NIH R01 CA176272, U10CA-180868, -180821, -180822, UG1CA-189867, U24CA-196067, PA DoH (which disclaims certain responsibilities), Genentech, Inc., Sanofi-Synthelabo Inc.

3583 Poster Session (Board #76), Sun, 8:00 AM-11:30 AM

Validation of tumor infiltrating lymphocytes (TIL) and tumor budding as predictors of prognosis in patients with stage III colon cancers treated in a FOLFOX-based adjuvant trial: NCCTG N0147 (Alliance). *First Author: Frank A. Sinicrope, Mayo Clinic, Rochester, MN*

Background: TIL density reflects the anti-tumor immune response; tumor budding indicates an epithelial to mesenchymal transition (EMT). We determined if these features are prognostic in a single colon cancer (CC) stage with known DNA mismatch repair (MMR) status. **Methods:** TIL densities (per HPF) and tumor buds (per .785 mm^2 field) were quantified at light microscopy in 1,532 CC. Tumor budding at invasive margin was defined as single or cluster of $\leq$ 4 tumor cells. We divided the cohort into training and validation sets. Optimal cutpoints were identified; associations with 3-year disease-free survival (DFS) were evaluated by multivariable Cox regression. **Results:** TIL and tumor budding cutpoints identified in training set were confirmed in validation set for prognosis. Patients whose tumors had low ($\leq$ 3) *vs* high TILs were significantly more likely to have higher T, N stage, low histologic grade, left sidedness, worse performance status, non mutated *BRAF*, and proficient (p) MMR. Tumors with high budding ($>$ 3) had higher T, N stage; most had pMMR. Overall, significantly shorter DFS was found for tumors with low TILs [HR_{adj}= 1.74 (95% CI 1.35, 2.24), p $<$ .0001], or with high budding [HR_{adj}= 1.37 (1.13, 1.67), p = .0011]. When combined, low TILs plus high budding showed poor DFS [HR_{adj}= 2.07 (1.50, 2.88), p $<$ .0001]. Similar results were found for pMMR tumors (Table). Within dMMR, patients whose tumors had low ($\leq$ 3) *vs* high TILs had significantly shorter DFS (HR_{adj}= 2.14; p = .0173); budding was not prognostic (Table). **Conclusions:** Low TILs and high budding were each validated as markers of poor prognosis in FOLFOX-treated stage III CC, indicating that reduced anti-tumor immunity and an EMT phenotype increase tumor aggressiveness. Whereas TILs and budding each stratified pMMR tumors by DFS, only TILs were prognostic in dMMR tumors and identified the subset with poorest survival.

	pMMR (n = 1357)			dMMR (n = 153)		
	HR_{adj}	3-year DFS	P_{adj}	HR_{adj}	3-year DFS	P_{adj}
TILs						
High	Ref	81%	**P = .0002**	Ref	78%	**P = .0173**
Low	1.65 (1.25, 2.16)	71%		2.14 (1.14, 4.01)	53%	
Tumor Budding	Ref		**P = .0009**	Ref		**P = .8577**
High	1.41 (1.15, 1.73)	69%		1.06 (0.56, 2.02)	67%	
Low	Ref	79%		Ref	71%	

3584 Poster Session (Board #77), Sun, 8:00 AM-11:30 AM

Prognostic value of CD73 expression in resected colorectal cancer liver metastasis. *First Author: Nouredin Messaoudi, Research Centre of the Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada*

Background: As approximately 80% of patients recur and die of their cancer after undergoing curative-intent resection of colorectal cancer liver metastasis (CRLM) combined with systemic chemotherapy, novel prognostic biomarkers and therapeutic targets are needed to improve outcomes. We investigated in CRLMs whether the expression of the cell-surface enzyme CD73, rate limiting for the degradation of extracellular AMP into immune-suppressive adenosine, could define a subset of patients with distinct prognosis. **Methods:** A tissue microarray-based analysis of 391 CRLMs resected in 214 patients (2011-2014) and followed prospectively until 10/2017. Each CRLM was arrayed with six 0.6 mm intratumoral punch biopsies, with automated quantification of CD73, cytokeratins 8/18 (CK) and DAPI expression measured by multiplex immunofluorescence. We tested associations between CD73 and pathological variables, time to recurrence (TTR) and disease specific survival (DSS). **Results:** The mean patient age was 62.7 years, 78.5% received pre-operative chemotherapy (mean of 6 cycles), and a median of 2 CRLMs/patient were resected. The median TTR and DSS of patients was 15.4 and 56.7 months, respectively. CD73 expression was similar whether patients received or not pre-operative chemotherapy, but was higher in patients with larger CRLMs ($>$ 5cm vs. $\leq$5cm, p = 0.01), poor pathologic response to pre-operative chemotherapy (Rubbia-Brandt TRG score 4-5 vs. 1-2-3, p = 0.01), and more necrosis ($>$ 25% vs. $\leq$25% surface necrosis, p = 0.004). In patients who received pre-operative chemotherapy, those with $CD73^{high}$ CRLMs (n = 62, 38.3%) had significantly shorter median TTR (11 vs. 18 months, p $<$ 0.001) and DSS (47 vs. 58 months, p = 0.007) than $CD73^{low}$ patients. Pathologic response to chemotherapy was only associated with TTR, not DSS. By multivariate analysis, $CD73^{high}$ CRLMs was a poor prognostic factor independent of clinicopathological features for both TTR and DSS. **Conclusions:** Our results support that CD73 expression in CRLMs may identify a subset of patients with poor prognosis after exposure to systemic chemotherapy, providing insights to guide now-designed trials targeting CD73 with antibodies or the adenosine A2A receptor with inhibitors.

3585 Poster Session (Board #78), Sun, 8:00 AM-11:30 AM

The impact of skeletal muscle and adipose tissue on long-term survival in patients with resectable colorectal cancer. *First Author: Michael B. Sawyer, Cross Cancer Institute, Edmonton, AB, Canada*

Background: Computed tomography-derived body composition parameters are emerging prognostic factors in colorectal cancer. This study aimed to determine the roles of sarcopenia, myosteatosis and adiposity as independent and overlapping parameters in resectable colorectal cancer patients. **Methods:** This was a retrospective cohort study from a prospectively collected database. It included all adult patients with early-stage colorectal cancer, who underwent curative resection from 2007-09. All patients were seen in a tertiary care cancer center in Northern Alberta. Computed tomography-derived quantification of skeletal muscle and adipose tissues were used to determine cohort-specific cut-offs for sarcopenia, myosteatosis and total adiposity using an optimal stratification analysis. Multivariate cox proportional hazards models were performed to assess for associations between body composition parameters and overall, disease-free and cancer-specific survival. **Results:** In the 968 patients included, there were a total of 254 disease recurrences and 350 deaths. Body mass index and computed tomography-derived measures of adiposity did not result in worse survival outcomes. Sarcopenia was independently predictive of worse overall (HR 1.45; 95% CI 1.16, 1.84), recurrence-free (HR 1.32, 95% CI 1.00, 1.75) and cancer-specific survival (HR 1.46, 95% CI 1.09, 1.94) in a multivariate model. Myosteatosis was also independently predictive of overall survival (HR 1.53, 95% CI 1.19, 1.97). In a multivariate model considering joint effects of sarcopenia and myosteatosis, the presence of both parameters predicted the worst overall (HR 2.23, 95% CI 1.62, 3.06), recurrence-free (HR 1.53, 95% CI 1.06, 2.21) and cancer-specific survival (HR 2.40, 95% CI 1.69, 3.42). **Conclusions:** Sarcopenia and myosteatosis are independent predictors of worse survival in early-stage colorectal cancer. Their joint effect is highly predictive of reduced overall, recurrence-free and cancer specific survival. Sarcopenia and myosteatosis represent prognostic factors that may be easily integrated into clinical practice.

3586 Poster Session (Board #79), Sun, 8:00 AM-11:30 AM

Prognostic immune scoring of colorectal cancer liver metastasis with MHC class-I expression combined to T cell quantification. *First Author: David Henault, Research Centre of the Centre hospitalier de l'Université de Montréal (CRCHUM), Montreal, QC, Canada*

Background: Approximately 80% of patients recur after curative-intent resection of colorectal cancer liver metastasis (CRLM) and systemic chemotherapy. Immune profiling may help prognostication to individualize follow-up and lead to novel therapeutic strategies. We tested whether adding major histocompatibility class I (MHC-I) expression to T cell immune scoring in CRLMs could group patients with distinct prognosis. **Methods:** Tissue microarray analysis of 391 CRLMs resected in 214 patients (2011-2014) followed prospectively until 10/2017. Each CRLM arrayed with twelve 0.6 mm punch biopsies, 6 at the interface (IF) with normal liver and 6 intratumoral (IT). Automated quantification of $CD3^+$ cells and MHC-I^+ surface area stained by immunohistochemistry. We tested associations between immune, clinicopathological, and time to recurrence (TTR) and disease specific survival (DSS) outcome variables. **Results:** The mean patient age was 62.7 years, 78.5% received pre-operative chemotherapy (mean of 6 cycles), and a median of 2 CRLMs/patient were resected. The median TTR and DSS were 15.4 and 56.7 months, respectively. Pre-operative chemotherapy was associated with higher CD3 infiltration and lower MHC-I expression at IF and IT. Good pathological response to chemotherapy (Rubbia-Brandt TRG score 1-2-3) compared to lack of response (TRG 4-5) was associated with higher CD3 infiltration but no significant difference in MHC-I expression. CD3 immune scoring integrating the IF and IT areas had no prognostic value. MHC-I expression prognostically stratified patients with $CD3^{low}$ but not $CD3^{high}$ CRCLMs. Compared to the rest of the cohort, patients with at least one $CD3^{low}$MHC-I^{hi} CRLM (n = 35, 16.4 %) had significantly shorter median TTR (8.3 vs. 17.1 months, $p < 0.001$) and DSS (42.6 vs. 61.5 months, $p < 0.001$). $CD3^{low}$MHC-I^{hi} CRLMs were found in 41.2% of recurrent CRLMs in patients without this type of metastasis at first resection. $CD3^{low}$MHC-I^{hi} CRLM was an independent predictor of poor outcomes by multivariate analysis. **Conclusions:** $CD3^{low}$$MHC^{hi}$ CRLMs may identify patients with poorly immunogenic tumors associated with worst outcome and suboptimal response to systemic chemotherapy.

3587 Poster Session (Board #80), Sun, 8:00 AM-11:30 AM

Prognostic significance of number versus location of positive mesenteric nodes in node positive colon cancer. *First Author: Kozo Kataoka, Department of gastrointestinal surgery, Kanagawa Cancer Center, Yokohama, Japan*

Background: Metastasis to locoregional lymph nodes (LN) is one of the most powerful predictors of recurrence free survival (RFS) in colon cancer (CC). Debate persists on the prognostic value of the location of positive LN in addition to the positive lymph node ratio (LNR) or the number of invaded LN (LN+). The recently introduced technique of complete mesocolic excision (CME) presupposes a prognostic role of removal of high level (apical) LN. We analyzed the prognostic significance of positive LN location in a cohort of CC patients who underwent extensive (D3) lymphadenectomy. **Methods:** Colon cancer patients from Kanagawa Cancer Center, Japan, who underwent extensive (D3) lymphadenectomy from 2000 to 2016 were analyzed. Lymph nodes were classified according to anatomical location as paracolic (L1), intermediate (L2), or along the main vascular trunk (L3). RFS hazards were evaluated with their trends over the groups. Univariate and multivariate Cox proportional hazards models were used to evaluate the association of LN count and L level (L1, L2 and L3) with RFS. **Results:** 843 patients were included and 446 were node positive of whom only 25 (5.6%) had positive L3 nodes. The mean number of examined/positive nodes per patient was 42.5/2.6 in L1 (n = 310), 40.9/4.8 in L2 (n = 111), and 44.0/9.8 in L3 (n = 25). In univariate analysis, RFS was significantly lower for L3 vs. L2 positive patients (HR: 2.00, 95%CI [1.05-3.75], p = .034) and L3 vs. L1 (HR: 2.62 [1.45-4.71], p = 0.001) but the difference between L1 and L2 was not nominally significant (HR: 1.32 [0.89-1.95], P = 0.17). A multivariate Cox model built with T stage, tumor location (right vs. left), LNR, LN+ and L level identified T stage ($p < 0.001$) and LNR (p = 0.001) as prognostic factors with no significant contribution from the L level (p = 0.42). **Conclusions:** In this cohort of patients who underwent standard extensive (D3) lymphadenectomy for CC, apical (L3) nodes are infrequently invaded and confer a significantly worse RFS. The anatomical location of invaded nodes adds no prognostic information to T-stage and LNR. These findings question the value of standard extensive lymphadenectomy in CC.

3588 Poster Session (Board #81), Sun, 8:00 AM-11:30 AM

Prognostic evaluation of a new class of liquid biopsy biomarkers in patients with metastatic colorectal cancer: Using the tumor microenvironment as a source of protein biomarkers. *First Author: Stephanie Nina Kehlet, Technical University of Denmark, Kgs. Lyngby, Denmark*

Background: The local microenvironment of a tumor plays an important role in colorectal cancer (CRC) progression. A desmoplastic stroma surrounding the tumor, characterized by excessive collagen deposition, can result in reduced drug delivery into the tumor, leading to poor prognosis and lack of therapy response. Here we present a new class of liquid biopsy proteins, reflecting collagen formation (desmoplasia) and evaluate their prognostic use in CRC. **Methods:** Pro-peptides from collagen type III (PRO-C3) and collagen type VI (PRO-C6) were measured with ELISAs in pre-treatment (standard of care chemotherapy) serum from 40 patients with metastatic CRC (mCRC) and 40 healthy donors. Biomarker levels in patients and healthy donors were compared using unpaired, two-tailed Mann-Whitney test. The biomarkers were further evaluated by univariate Cox-regression analysis for their association with overall survival (OS) and progression-free-survival (PFS). **Results:** Serum levels of PRO-C3 and PRO-C6 were significantly elevated in patients with mCRC compared to healthy donors (PRO-C3: 11.5 ng/mL vs. 6.8 ng/mL, $p < 0.0001$, PRO-C6: 8.0 ng/mL vs. 5.9 ng/mL, $p < 0.0001$). The median OS was 266 or 213 days in biomarker high patients (75^{th} percentile) vs. 1330 or 979 days in biomarker low patients (25^{th} percentile) for PRO-C3 (HR 8.7, 95%CI 2.7-28.2) and PRO-C6 (HR 6.8, 95%CI 2.3-20.3), respectively. The median PFS was 251 or 267 days in biomarker high patients (75^{th} percentile) vs. 329 or 496 days in biomarker low patients (25^{th} percentile) for PRO-C3 (HR 2.3, 95%CI 0.7-7.1) and PRO-C6 (HR 2.6, 95%CI 0.8-9.0), respectively. **Conclusions:** This study evaluated the prognostic use of a new class of liquid biopsy biomarkers, namely small peptides originating from the tumor microenvironment that are released into the circulation as a consequence of tumorigenesis. High serum levels of PRO-C3 and PRO-C6 (collagen formation) were significantly associated with poor OS and shorter PFS in patients with mCRC. This may suggests that increased collagen deposition around the tumor, limits cancer therapy delivery into the tumor, resulting in a lack of response to therapy.

3589 Poster Session (Board #82), Sun, 8:00 AM-11:30 AM

Adjuvant chemotherapy and survival outcomes in diabetic patients with colon cancer: A population-based analysis. *First Author: Shiru Lucy Liu, BC Cancer Agency, Vancouver, BC, Canada*

Background: Diabetes can pose challenges when using adjuvant chemotherapy (AC), as specific cytotoxic drugs, including oxaliplatin, may potentiate certain diabetic complications, such as neuropathy. We performed a provincial analysis of resected colon cancer patients to evaluate the prevalence of diabetes, type of chemotherapy used, and survival outcomes. **Methods:** We examined 5,440 patients with resected stage 2 or 3 colon cancer who were diagnosed from 2004 to 2015 in Alberta. Baseline patient, tumor, and treatment characteristics were compared between those with and without diabetes. Survival analysis was conducted based on Kaplan-Meier methods. **Results:** 608 patients (11%) had uncomplicated diabetes (UDM) and 436 (8%) patients had diabetes with complications (CDM), defined as neuropathy or other micro/macrovascular end-organ damage. CDM patients were older and had worse Charlson comorbidity index ($p < 0.001$). While 34% of UDM patients and 35% of non-diabetic patients received AC, only 15% of CDM patients received AC ($p < 0.001$). Among those who received AC (N = 1574), an oxaliplatin-based regimen was given to 45% and 52% of UDM and non-diabetic patients, respectively, but only 35% of CDM patients ($p < 0.001$). Kaplan-Meier analysis revealed significantly worse overall survival (OS) in the CDM group when compared to the UDM or non-diabetic groups ($p < 0.001$). Of those treated with AC however, there were no statistical differences in OS (p = 0.188) or cancer-specific survival (CSS) (p = 0.461) across all groups regardless of diabetes or complication status (see Table). Receipt of oxaliplatin was associated with improved OS among patients with stage 3 disease compared to monotherapy (p = 0.006). **Conclusions:** Patients with CDM are less likely to receive AC; however, patients treated with oxaliplatin-AC appear to have similar survival outcomes as their UDM and non-diabetic counterparts.

N = 1574	5-year OS	5-year CSS
Non-Diabetic (N = 1345)		
Monotherapy	75%	80%
Oxaliplatin	80%	82%
UDM (N = 175)		
Monotherapy	72%	78%
Oxaliplatin	75%	79%
CDM (N = 54)		
Monotherapy	60%	72%
Oxaliplatin	64%	79%

3590 Poster Session (Board #83), Sun, 8:00 AM-11:30 AM

Clinico-pathological and molecular characterisation of *BRAF* mutant metastatic colorectal cancer (mCRC): Are all mutations created equal? *First Author: Marta Schirripa, Unit of Medical Oncology 1, Department of Clinical and Experimental Oncology, Veneto Institute of Oncology IOV – IRCCS, Padua, Italy*

Background: Functional studies on preclinical models (Yao, Nature 2017) identified 3 classes of *BRAF* mutations: activating *RAS*-independent *BRAF* mutations signaling as monomers (class 1-*BRAF* V600E) or as dimers (class 2-codons 601/597) and *RAS*-dependent *BRAF* mutations with impaired kinase activity (class 3-codons 594/596). While clinico-pathological and molecular features of class 1 mutation are well known, limited data are available with regard to class 2 and 3 mutations, due to their rarity in CRC. **Methods:** Clinico-pathological, molecular and outcome data from *BRAF* mutated mCRC patients were collected. A group of *BRAF* wild-type (wt) patients was included as control. IHC analyses were performed to determine the consensus molecular subtypes (CMS). Clinical features were compared by chi-square or fisher's exact test. PFS and OS were evaluated by Kaplan-Meier and log-rank test. **Results:** Class 1, 2 and 3 included 92, 12 and 13 patients respectively. *BRAF* wt patients were 540. No clinico-pathological differences were observed comparing class 1 to class 2 *BRAF* mutated. Conversely, *BRAF* class 3 mutated were more frequently left sided ($p = 0.0028$), well differentiated ($p = 0.0120$), pN0 ($p = 0.0159$), and with no peritoneal metastases ($p = 0.0176$) compared to class 1. With regard to CMS, class 2 and 3 tumors were all assigned to CMS2-3. Class 1 tumors were assigned to CMS1, 2 or 3 in 39%, 44% and 17% of cases. Outcome results are reported in the Table below. **Conclusions:** Our data confirm previous findings describing specific features associated with *BRAF* rare mutations. For the first time clinico-pathological characteristics and outcome data are reported according to the 3 classes categorization of *BRAF* mutations. In particular, class 1 and 2 share similar features and worse outcome compared to class 3 and wt patients.

	Overall Survival			Progression Free Survival		
	Median (months)	HR (95% CI)	p-value	Median (months)	HR (95% CI)	p-value
BRAF wild type (N = 540)	42.2	-	< 0.0001	10.1	-	< 0.0001
BRAF mutant class 1 (N = 92)	21.0	2.38 (1.61-3.54)		7.3	2.02 (1.39-2.94)	
BRAF mutant class 2 (N = 12)	23.4	1.90 (0.85-4.26)		7.0	2.49 (0.92-6.74)	
BRAF mutant class 3 (N = 13)	44.5	0.93 (0.51-1.69)		13.8	0.85 (0.47-1.54)	

3591 Poster Session (Board #84), Sun, 8:00 AM-11:30 AM

Somatic DNA mutations, tumor mutational burden (TMB), and MSI Status: Association with efficacy in patients (pts) with metastatic colorectal cancer (mCRC) of FIRE-3 (AIO KRK-0306). *First Author: Volker Heinemann, Department of Medicine III, University Hospital, LMU Munich, Munich, Germany*

Background: FIRE-3 compared 1st-line therapy with FOLFIRI plus either cetuximab or bevacizumab in 592 KRAS exon 2 wt mCRC patients (pts). **Methods:** Tumor DNA was profiled by next-generation sequencing to explore molecular markers of prognosis. The biomarker evaluable subpopulation (n = 373) was representative of the ITT population. Treatment efficacy was determined in the quadruple wild-type (wt) population (RAS, BRAF, AKT, PI3K = "MAPK/mTOR wt"). Kaplan-Meier estimation and log-rank tests were employed for overall survival (OS). Hazard ratios (HR) were estimated using the Cox proportional hazard method. P-values were not adjusted for multiple testing **Results:** Overall frequencies were (%,n): MSI-h 2.7% (10); BRAFmut 12.1% (45); RASmut 32.7% (122); quadruple wt: 47.7% (178); TMB > 8: 15% (56). RAS, BRAF, MSI-h and quadruple-wt status were prognostic. Pts with low-frequent RAS mutations (RASmut < 5%) had a significantly longer OS when compared to pts with higher RAS mutational frequency. **Conclusions:** NGS analysis revealed distinct subgroups of mCRCs with different prognosis. MSI status had prognostic impact, but TMB could not be validated as a prognostic or predictive marker.

Overall survival.

		N	Events N (%)	Median [95%CI]		N	Events N (%)	Median [95%CI]	HR [95%CI], p-value
MSI	MSI-H	10	10 (100)	18.8 [2.5, 24.5]	MSS	343	298 (87)	25.4 [23.1, 27.6]	1.92 [1.02, 3.62], 0.0432
TMB status 1	high	10	9 (90)	19.8 [2.5, 25.2]	intermediate	114	100 (88)	25.7 [21.5, 29.1]	1.28 [0.65, 2.54], 0.4725
	high	10	9 (90)	19.8 [2.5, 25.2]	low	236	206 (87)	23.8 [21.4, 26.7]	1.16 [0.60, 2.27], 0.6568
	intermediate	114	100 (88)	25.7 [21.5, 29.1]	low	236	206 (87)	23.8 [21.4, 26.7]	0.91 [0.71, 1.15], 0.4186
TMB status 2	< = 8	304	268 (88)	23.8 [21.8, 26.1]	> 8	56	47 (84)	27.5 [18.7, 31.1]	1.23 [0.90, 1.68], 0.1924
BRAF	wt	328	289 (88)	26.4 [23.9, 28.8]	Mut	45	39 (87)	15.9 [10.9, 19.1]	0.57 [0.41, 0.80], 0.0012
RAS	wt	251	212 (85)	27.9 [24.7, 31.9]	Mut	122	116 (95)	20.6 [17.4, 23.6]	0.62 [0.49, 0.78], 0.0000
MAPK	wt	178	151 (85)	30.8 [26.4, 35.2]	mut	195	177 (91)	20.8 [18.5 , 23.7]	0.64 [0.51, 0.79], 0.0001

3592 Poster Session (Board #85), Sun, 8:00 AM-11:30 AM

Distinct somatic alterations in right- versus left-sided colorectal cancers. *First Author: Robin Imperial, University of Missouri - Kansas City, Kansas City, MO*

Background: Right-sided (RCC) and left-sided colon cancers (LCC) have different clinical/biological characteristics. Comprehensive genomic analysis (Whole exome/genome, Copy number, RNA, MicroRNA) using The Cancer Genome Atlas (TCGA) was performed to identify underlying genomic differences between RCRC, LCRC and rectal cancers (RC). **Methods:** 443 microsatellite stable RCC, LCC and RC samples were analyzed. Transverse and rectosigmoid tumors were excluded. MutsigCV and ConsensusDriver were used for significantly mutated gene analysis, GISTIC for copy number alterations (CNA), deSeq2 for RNA and microRNA analysis. Supervised clustering was applied to somatic mutations using Fuzzy ARTMAP. **Results:** AMER1 (gene in Wnt pathway) was mutated in 24% of RCC, 3% of LCC and 3% of RC. Mutations in AMER1 and other key Wnt family members (CTNNB1, GSK3, AXIN1, AXIN2, LRP5, LRP6) were mutually exclusive of each other. A novel driver B Melanoma Antigen Family, Member 2 (BAGE2) not previously described in CRC was discovered in a subset of samples using Fuzzy ARTMAP. KRAS, PIK3CA, SOX9 (all $p < 0.05$) mutations were enriched in RCC. New driver mutations in BCOR, MUC4, RELN, ROBO2, RP1L1, and MGAM were also enriched in RCC (all $p < 0.05$). Hotspot mutation analysis revealed distinct oncogenic mutations in RCC, including in APC (R1450*, $p = 0.0246$). We identified unique amplifications and deletions in RCC (1 amplification/10 deletions) and LCC (13 amplifications/10 deletions). Somatic mutation, CNA and hotspot analysis revealed similar changes in LCC and RC. RNA analysis revealed 53 genes differentially expressed between RCC and LCC and 73 genes between RCC and RC. The top upregulated and downregulated genes were common between the two groups (n = 32). INSL5 and PRAC1 are among the most downregulated genes while SLC10A2, DRD5, and APOA4 are among the most upregulated genes. MicroRNA analysis showed 12 miRNA differentially expressed between RCC and LCC. **Conclusions:** RCC and LCC have distinct molecular profiles, whereas LCC and RC appear to be similar at the genomic level. Several specific/novel gene mutations are associated particularly with RCC (APC and AMER1 genes among others). A novel driver gene, BAGE2, was discovered in a subset of colorectal cancers.

3593 Poster Session (Board #86), Sun, 8:00 AM-11:30 AM

Differences in the characteristics of younger and older MSI-H colorectal cancer (CRC) as determined by universal reflex testing. *First Author: Aaron J Franke, University of Florida, Gainesville, FL*

Background: DNA mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) CRC is found in ~15% of early stage and ~5% of metastatic disease. Universal or reflex testing to identify dMMR/MSI-H has been proposed. The CRC incidence in young patients (pts) is also rising with unclear etiology. We present a large, single-institutional database of universal reflex dMMR/MSI-H testing in CRC comparing clinicopathologic and molecular profiles of younger (≤50) and older (> 50) pts. **Methods:** For all CRC pts diagnosed at University of Florida between 2009-2017, reflex somatic testing for dMMR by IHC (MLH1, PMS2, MSH2, MSH6), MSI by PCR (Promega MSI kit) and NGS was performed with appropriate positive and negative controls. IHC protein loss was confirmed by second GI pathologist. Equivocal IHC results triggered MSI testing. Review of associated clinical EMR data was retrospectively performed and analysis conducted with student's t-test. Study was IRB approved. **Results:** 375 pts were analyzed by ≤50yo (n = 80; median age 44, range 17-50) or > 50yo (n = 295; median age 66, range 51-98). There was 100% concordance of MMR and MSI of all patient samples. dMMR/MSI-H incidence was 14% (11/80) in pts ≤50, compared to 22% (64/295) in pts > 50 ($p < 0.001$). For stage IV CRC, dMMR/MSI-H incidence was 4% vs. 13% ($p = 0.003$) between the age groups. Younger pts presented with more advanced disease (36% Stage III, 36% Stage IV) compared to older pts (32% Stage III, 26% Stage IV). Associated BRAF mutations were more common in pts > 50 (20% vs. 67%; $p = 0.005$). **Conclusions:** In our dataset, younger CRC pts are diagnosed with more advanced disease but with dMMR/MSI-H cancers at the expected rate. However, we identified more (likely sporadic) dMMR/MSI-H stage IV cancers in pts > 50yo than expected. Further studies to identify risk factors for younger patients and the ultimate clinical impact of universal reflex MSI testing is warranted to maximize IO therapy offering and survival.

3594 Poster Session (Board #87), Sun, 8:00 AM-11:30 AM

International harmonization of diagnostic criteria for *HER2*-amplified metastatic colorectal cancer and application of targeted next-generation sequencing panel as a diagnostic method. *First Author: Satoshi Fujii, National Cancer Center, EPOC, Chiba, Japan*

Background: *HER2* amplification (*HER2*$^+$) in metastatic colorectal cancer (mCRC) is associated with resistance to anti-EGFR antibodies and response to HER2 targeted therapies. This study assessed the diagnostic criteria on *HER2*$^+$ mCRC among four groups (GI-SCREEN-Japan, SWOG-USA, HERACLES-Italy, and Korea) and harmonized the criteria for patient enrollment in clinical trials that target these patients (pts). **Methods:** Samples from 475 and 16 pts with mCRC were used in exploratory and validation cohorts, respectively. We assessed *HER2* status by immunohistochemistry (IHC) and *HER2/CEP17* ratio and gene copy number (GCN) by fluorescence in situ hybridization (FISH) and copy number variations (CNV) by targeted next-generation sequencing (NGS) panel. OCA by ThemoFisher and AMC v3 by illumina were used in exploratory and validation cohorts, respectively for the cross-validation of NGS panels. **Results:** The consensus diagnostic criteria for *HER2*$^+$ mCRC was reached; IHC 3+ or IHC 2+ and *HER2/CEP17* ratio by FISH $\geq$ 2.0, and tumor content $>$ 10% for surgically resected specimens (separate quantity criteria were established for biopsy specimens). The median GCN and CNV for pts who met consensus criteria for *HER2*$^+$ was 10.9 and 27.7 compared to 2.5 ($P<$ 0.0001) and 3.5 ($P<$ 0.0001), respectively in pts who were *HER2*$^-$. These findings were validated in validation cohort (GCN: 16.2 v 2.4, $P=$ 0.0002; CNV: 42.5 v 2.0, $P=$ 0.0003). GCN also showed strong correlation with CNV in both cohorts (r: exploratory: 0.90, validation: 0.97; $P<$ 0.0001). CNV in cross validation of OCA and AMC v3 also showed strong correlation (r: 0.97, $P<$ 0.0001). The CNV for pts fulfilling the consensus criteria was more than 4.0 in the two cohorts. The accuracy of the IHC/FISH criteria was validated for mCRC pts, providing cross-validation of NGS panels. **Conclusions:** We were able to verify the HER2 classification consistency between CNV by NGS and IHC/FISH by harmonizing diagnostic criteria for *HER2*$^+$. This strategy can help establish diagnostic criteria for *HER2*$^+$ cancer by allowing for different methodologies to be used for pts screening for trial eligibility.

3595 Poster Session (Board #88), Sun, 8:00 AM-11:30 AM

The characteristics of ARID1A mutations in colorectal cancer. *First Author: Amir Mehrvarz Sarshekeh, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: AT-rich interactive domain 1A (ARID1A) is a component of the SWI/SNF chromatin remodeling complex that regulates gene expression. Inactivating mutations of ARID1A have been reported in a variety of cancers but data on characteristics and associated clinicopathologic features in colorectal cancer (CRC) are limited. **Methods:** Data for patients (pts) with CRC whose tumors underwent comprehensive genomic profiling were reviewed using the Cancer Genome Atlas (TCGA), Nurses' Health Study and Health Professionals' Follow-up Study (NHS/HPFS), AACR Project GENIE and MD Anderson Cancer Center databases. **Results:** Among 3127 pts, 196 (6.2%) had a mutation in ARID1A. Across the datasets, 249 mutations in ARID1A were identified. Mutations were more likely to be frameshift or nonsense as compared with mutations in other genes (64.0% vs. 9.1%, OR = 7.0, 95% CI 5.6-8.7; $p<$ .001) and the majority were considered clonal by allele frequency (defined as $>$ 25%). The mutation locations were broadly distributed, although 10 recurrent (hot-spot) regions were identified. ARID1A mutations were associated with MSI-H status (OR = 8.1, 95% CI 4.4-14.8; $p<$ .001), with PIK3CA mutations (OR = 2.8, 95% CI 2.1-3.9; $p<$ .001), and BRAF mutations (OR = 3.1, 95% CI 2.2-4.4; $p<$ .001) but had inverse correlation with TP53 mutations (OR = 0.5, 95% CI 0.4-0.7; $p<$ .001). Of note, 18/23 (74%) of tumors with ARID1A mutations were classified as consensus molecular subtype-1 (CMS-1) with OR of 17 (95% CI 4.8-63.7; $p<$ .001). The mutations were associated with PPAR and HNF4 transcription factor activity. ARID1A mutations were more common in early stages (OR = 1.83, 95% CI 1.09-3.07; $p=$ 0.019) and right-sided tumors (OR = 1.66, 95% CI 1.01-2.71; $p=$ 0.034). There was no association between ARID1A mutation and race, gender, age at the time of diagnosis, grade, or presence of distant metastases. **Conclusions:** This is the largest study evaluating ARID1A mutations in CRC. The majority of mutations appear to be truncating and clonal, suggesting that they have functional significance. ARID1A-mutated tumors demonstrate enrichment of wild-type TP53 but they are more likely to have MSI-H, PIK3CA and BRAF mutations. The transcriptional signature may indicate future therapeutic strategies for this subgroup.

3596 Poster Session (Board #89), Sun, 8:00 AM-11:30 AM

A prospective cohort study in colorectal cancer assessing the relationship between post-surgery detection of methylated *BCAT1* or *IKZF1* ctDNA and risk for residual disease and survival. *First Author: David Murray, Clinical Genomics Technologies Pty Ltd., North Ryde, Australia*

Background: The methylated ctDNA biomarkers *BCAT1* and *IKZF1* are common events in colorectal cancer (CRC), play a role in its development and drugs targeting *BCAT1* are available. As these biomarkers disappear from blood after surgery in most patients, a prospective study was conducted to assess the relationship between their persistence post-surgery and presence of and risk for residual disease as well as survival. **Methods:** ctDNA status using these biomarkers was determined within 12 mo of initial surgical resection. Detection of either marker was related by logistic regression and survival analysis (Cox proportional hazards) to pathologically-determined presence or risk of residual disease ("RD", margins involved, metastases present or nature of node involvement) and to recurrence-free survival. **Results:** 172 CRC patients were tested for the biomarkers and then followed for a median 37.1mo (IQR 22.6-49.8) during which 23 experienced recurrence and 10 died from CRC. 28 (16%) were ctDNA positive post-surgery. Univariate analysis showed that a positive result was more likely if any of three markers of RD was present (OR 7.7, 95% CI: 2.3-25.0 p = 0.001); while increasing number of lymph nodes (OR 8.3, 95% CI: 1.8-37.7 p = 0.004) and involved peritoneum (OR 3.8, 95% CI: 1.6-9.2 p = 0.003) where also associated with a positive result. Multivariate modelling with adjustment for treatment status at time of venesection indicated that features of RD was an independent predictor of post-surgery ctDNA status: cases with 3 features (margins or apical node involved, distant metastases) were 5.3 times (95% CI: 1.5-18.4, p-value = 0.008) more likely to be positive. Modelling recurrence-free survival showed that post-surgery ctDNA positivity was associated with an increased risk of recurrence (HR 3.8, 1.5-9.5, p = 0.004). **Conclusions:** CRC cases positive for these ctDNA biomarkers within 12 months of surgery are at increased risk of residual disease and subsequently for recurrence. This has implications for adjuvant therapy and monitoring of cases; randomised studies are now indicated to determine if such can provide survival benefit. Clinical trial information: 12611000318987.

3597 Poster Session (Board #90), Sun, 8:00 AM-11:30 AM

Prognostic impact of BRAF V600E mutation in patients with non-metastatic colorectal cancer with microsatellite instability: A systematic review and meta-analysis. *First Author: Sashidhar Manthravadi, University of Kansas Medical Center, Kansas City, KS*

Background: Colorectal cancer (CRC) displaying high levels of microsatellite instability (MSI-H) has been associated with improved survival in colorectal cancer. MSI-H CRC is also known to be enriched in V600E mutations in the BRAF gene (BRAF-Mut). BRAF-Mut is a known adverse prognostic factor in patients with non-metastatic MSI-low CRC. However, the prognostic role of BRAF V600E mutations in non-metastatic MSI-H CRC remains unclear. **Methods:** Following PRISMA guidelines, a systematic review of PubMed and Embase was performed from inception through January 2018 to identify studies which described the impact of BRAF-Mut on outcomes in patients with non-metastatic MSI-H CRC. Summary hazard ratios (HR) with 95% confidence intervals (CI) for overall survival (OS) and recurrence-free survival (RFS) were estimated using a random effects model and heterogeneity was estimated using the inconsistency index (I^2). **Results:** After reviewing 988 reports, 8 studies which described the association between BRAF status and outcomes in non-metastatic MSI-H CRC were selected for inclusion. These were reported from Europe, North America and Asia. A total of 1164 patients with MSI-H CRC were included of whom 553 were found to carry BRAF V600E mutation. Data regarding RFS and OS for BRAF-Mut vs BRAF-Wild type was provided in 5 and 8 studies respectively. No association was found between BRAF-Mut and RFS in patients with non-metastatic MSI-H CRC (HR 1.13; 95% CI 0.77- 1.67, I^2= 0%). In contrast to these findings, BRAF-Mut had an adverse impact on OS in patients with non-metastatic MSI-H CRC (OS = HR 1.53; 95% CI 1.15- 2.03, I^2= 0%). **Conclusions:** BRAF V600E mutation appears to have no association with disease recurrence but does correlate with adverse overall survival in patients with non-metastatic colorectal cancer with high levels of microsatellite instability. Clinical trials planned in the future must therefore consider adding BRAF status as a stratification factor.

3598 Poster Session (Board #91), Sun, 8:00 AM-11:30 AM

$CD3^+$ and $CD8^+$ tumor-infiltrating lymphocyte (TIL) densities to prognostically stratify DNA mismatch repair-deficient (dMMR) colon cancer patients (pts): NCCTG N0147 (Alliance). *First Author: Harry H. Yoon, Mayo Clinic, Rochester, MN*

Background: Colorectal cancers (CRC) with dMMR typically have abundant TILs indicating an enhanced host immune response. However, the prognostic impact of TILs identified by $CD3^+$ and $CD8^+$ T cells has not been adequately studied in dMMR tumors. While dMMR is considered a predictive biomarker for anti-PD-1 therapy in advanced CRC, ~60% of dMMR pts do not respond, which may be relevant in dMMR stage III where adjuvant PD-L1 blockade is being studied. We report the first evaluation of $CD3^+$/$CD8^+$ TILs with prognosis in dMMR tumors from a clinical trial cohort. **Methods:** $CD3^+$ and $CD8^+$ TILs at the invasive margin (IM) and central tumor (CT) were analyzed in 561 stage III colon cancers (dMMR n = 278; randomly selected pMMR n = 283) from a phase 3 trial of FOLFOX-based adjuvant therapy (N = 3270 [dMMR 376, pMMR 2894]). Median follow up was 6.3 y. Immunostaining was quantified by image analysis (0-100 scale). Associations with overall survival (OS) were evaluated by multivariable Cox regression. **Results:** Densities of $CD3^+$ and $CD8^+$ TILs were higher in dMMR *vs* pMMR tumors ($P < .001$), and were heterogeneous between pts in each MMR group. $CD3^+$ IM was the strongest prognostic marker; the other markers ($CD3^+$ CT, $CD8^+$ IM, $CD8^+$ CT), alone or combined, did not add further value. Among dMMR tumors, using an optimized cutpoint, 58% had low $CD3^+$ IM, and these pts had significantly shorter OS *v* dMMR tumors with high $CD3^+$ IM, independent of covariates. See Table for full results. OS of dMMR tumors with low $CD3^+$ IM was comparable to the overall pMMR cohort (n = 2611; $P = .8$). Pts with high $CD3^+$ IM pMMR tumors had an OS similar to TIL-unselected dMMR tumors (n = 376; $P = .3$). **Conclusions:** $CD3^+$ IM TILs can prognostically stratify pts with dMMR stage III colon cancer for OS. These findings of heterogeneity within dMMR may have implications for immunotherapy responsiveness in dMMR tumors.

	$CD3^+$ IM (cutpoint)	n (%)	HR_{adj}	P_{adj}	5y OS rate
dMMR	Per 10-unit decrease		1.1	.015	
	High (≥ 49)	111 (42)	Ref	.026	84%
	Low (≤ 48)	167 (58)	2.1		70%
pMMR	Per 10-unit decrease		1.2	.009	
	High (≥ 21)	177 (63)	Ref	.073	83%
	Low (≤ 20)	106 (37)	1.7		73%

Adjustments included T, N, grade, *BRAF/KRAS*, tumor side, age, smoking

3599 Poster Session (Board #92), Sun, 8:00 AM-11:30 AM

Effect of age, gender, and performance status (PS) on the duration results of adjuvant chemotherapy for stage III colon cancer: The IDEA collaboration. *First Author: Anthony Frank Shields, Karmanos Cancer Institute, Wayne State University, Detroit, MI*

Background: The IDEA collaboration pooled data from nearly13,000 patients (pts), comparing 3 vs. 6 months (m) of adjuvant fluoropyrimidine plus oxaliplatin to test noninferiority for disease-free survival (DFS) in stage III colon cancer. We reported that duration of adjuvant therapy (Rx) should be individualized with consideration of recurrence risk, regimen, and toxicity. Here we consider the influence of age, gender, and PS. **Methods:** Using stratified Cox proportional hazard models we stratified the IDEA cohort by age (≤ 70 or > 70), gender, and PS (0 v 1/2), testing for interactions with subgroups and duration of Rx. **Results:** Overall, DFS results comparing 3 vs 6m of Rx did not significantly differ across age, gender or PS subgroups. However, significant (sig) interactions were detected within subgroups (Table). For pts ≤ 70 who received CAPOX, 3m Rx is as good as 6m (HR 0.9). 6m of Rx is required for pts ≤70 (HR 1.16) with FOLFOX and may be best for pts > 70 on either regimen (p = .068, 3 way interactions). It was found that gender influenced the impact of risk group on the duration comparison (p = .078, 3 way interaction); 3m Rx was as good as 6m for male low-risk pts (HR 0.94) but 6m is required for high risk male (HR 1.18). For females, risk group did not alter the relative merits of 3 v 6m of Rx. PS did not influence the impact of regimen/risk group on the duration comparison. **Conclusions:** Overall age, gender, or PS didn't modify the comparison of 3 v 6m Rx. The biologic and clinical rationales for the differences observed within certain subgroups need to be explored before they are used to make treatment choices. Clinical trial information: NCT01150045.

		Events/Total	HR(3 v 6m)	95% CI	Pi 2-way
Age < = 70	FOLFOX	1439/5845	1.16	1.05-1.29	< 0.01
	CAPOX	917/3759	0.9	0.79-1.03	
Age > 70	FOLFOX	505/1813	1.12	0.94-1.33	0.7
	CAPOX	380/1290	1.19	0.97- 1.46	
Male	T1-3N1	789/4220	0.94	0.82-1.08	0.01
	T4 or N2	1126/2964	1.18	1.05-1.33	
Female	T1-3N1	523/3247	1.09	0.91-1.29	0.7
	T4 or N2	809/2290	1.04	0.9 -1.20	

3600 Poster Session (Board #93), Sun, 8:00 AM-11:30 AM

Total neoadjuvant treatment versus chemoradiotherapy in locally advanced rectal cancer: A propensity score analysis from two prospective phase II clinical trials. *First Author: Jianwei Zhang, Sixth Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China*

Background: Fluorouracil-based neoadjuvant chemoradiotherapy (CRT) is still the standard of treatment for locally advanced rectal cancer, but it delays administration of systemic chemotherapy, leading to high incidence of distant metastases. To enhance systemic chemotherapy and improve the outcome of rectal cancer, totally neoadjuvant therapy (TNT) has been investigated recently. Here, we aimed to compare the efficacy of TNT with CRT in locally advanced rectal cancer. **Methods:** A total of 180 patients with clinical stage II or III locally advanced rectal cancer who received either total neoadjuvant treatment (n = 79) or CRT (n = 101) followed by total mesorectal excision (TME) were identified from two prospective clinical trials (NCT01211210 and NCT02217020) in our institutional database. Propensity score analysis was performed to mitigate selection biases. The patients in TNT group received 1 cycle of mFOLFOX6 as induction chemotherapy and radiotherapy would be delivered accompanied with 3 cycles of mFOLFOX6. Another 4 cycles would be added after radiotherapy and before TME. The CRT group received five 2-week cycles of infusional fluorouracil plus radiotherapy. **Results:** Of the 180 patients, the pathologic complete response (pCR) rate was 21.7%. Following propensity score matching, each group contained 79 patients. The baseline characteristics were well balanced. The pCR rate of TNT group and CRT group was 34.2% vs. 15.2%, respectively ($p < 0.005$). And the tumor downstaging rate was 60.8% vs. 35.4%, respectively (p = 0.001). Grade3/4 neutropenia was the more common in TNT group, which was 30.4% vs. 8.9% (P = 0.0007) in the TNT group and CRT group, respectively. Grade 3/4 Leukopenia (21.5% vs. 12.7%, p = 0.14) and thrombocytopenia (5.1% vs. 11.4%, p = 0.15) was similar between the two groups. **Conclusions:** TNT showed higher pCR rate and tumor downstaging rate than that of CRT, which was a promising strategy for improving outcome of rectal cancer, although the grade 3-4 adverse events were a little bit higher in TNT group. But this finding requires further analysis from long-term survival data. The phase III study comparing TNT with CRT is ongoing.

3601 Poster Session (Board #94), Sun, 8:00 AM-11:30 AM

Association of adverse events (AEs) with outcomes in early stage colon cancer (CC): An analysis of 10,695 CC patients from the ACCENT database. *First Author: Winson Y. Cheung, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: Initial dosing of adjuvant chemotherapy (ACT) is largely based on body surface area, but studies show that drug metabolism can vary significantly across patients. ACT-related toxicities may serve as proxies for these pharmacodynamics and pharmacokinetic variations. Thus, AEs may predict for treatment efficacy and survival. In some tumors, dose titration until toxicity has been proposed. We aimed to explore the relationship between AEs and outcomes in early stage CC. **Methods:** A retrospective analysis of individual CC patient data from 12 randomized trials of ACT was conducted. Severity of selected AEs was categorized as per NCI criteria. Using stratified Cox models with a landmark approach, we examined overall survival (OS), disease-free survival (DFS), time to recurrence (TTR), and time from recurrence to death (TRD) in relation to AEs, adjusting for treatment duration as well as clinical and pathological factors. Analyses were performed based on the type of ACT that patients received, including fluoropyrimidine (FP) alone, FP + irinotecan (Iri), or FP + oxaliplatin (Ox). Due to multiple comparisons, the significance level was set at 0.001. **Results:** We included 10,695 patients of whom 79.5%, 5.8%, and 14.7% received FP, FP + Iri, and FP + Ox, respectively. Women were more likely to experience worse toxicities than men, independent of ACT regimen (all $p < 0.001$). Diarrhea and neutropenia were the most common grade 3+ AEs across all ACT while neuropathy was a frequent grade 3+ AE in the FP + Ox group. Other AEs, such as grade 3+ thrombocytopenia and transaminitis, were rare. Grade 3+ transaminitis was associated with worse OS (3-year OS 68.9 vs. 87.3%; adjusted hazard ratio 2.46, 95% CI 1.49 – 4.06, $p < 0.001$), but not DFS, TTR and TRD, in patients who received FP + Ox. There were no consistent correlations between additional AEs and outcomes in all other ACT regimens. No differences were observed when the analyses were stratified by disease stage. **Conclusions:** In this large cohort of clinical trial patients, most clinically observable AEs do not appear to be reliable biological correlates of optimal dose intensity or survival outcomes.

3602 Poster Session (Board #95), Sun, 8:00 AM-11:30 AM

Patients' preferences for 3 months versus 6 months of adjuvant chemotherapy (ACT) for colon cancer in the SCOT trial: what survival benefits make longer chemotherapy worthwhile? *First Author: Prunella Louise Blinman, Concord Repatriation General Hospital, Concord, NSW, Australia*

Background: The optimal duration of ACT following surgery for colon cancer remains controversial. SCOT is an international, randomised trial that compared 3 months versus 6 months of ACT in this setting. We sought the survival benefits that patients participating in SCOT judged necessary to make extra 3 months of ACT worthwhile. **Methods:** SCOT participants from Australia & New Zealand completed a validated questionnaire 3 and 18 months after randomisation to elicit the minimum survival benefit each participant judged necessary to make it worthwhile having ACT for 6 months rather than 3 months. Standardised hypothetical scenarios used the following baseline survivals with 3 months of ACT: life expectancies (LE) of 5 years (5Y) and 15 years (15Y), and 5-year survival rates (5YS) of 65% and 85%. Comparisons were non-parametric, 2-sided, and considered statistically significant if $p < 0.05$. **Results:** Questionnaires were completed by 160 participants, 82 allocated 3 months ACT, and 78 allocated 6 months ACT. ACT was FOLFOX in 121 (75%), XELOX in 39 (25%), and the mean age was 64. Preferences varied substantially among participants, and did not differ according to the randomly allocated treatment group. The median survival benefits judged necessary to make the extra 3 months of ACT worthwhile were an extra: 3 years beyond a LE of 5Y; 3 years beyond a LE of 15Y; 15% beyond a 65% 5YS; and 5% beyond an 85% 5YS. Preferences were similar at 3 months and 18 months. Participants with symptomatic peripheral neuropathy (132, 82%) judged a median benefit of an extra 5% beyond a 65% 5YS necessary to warrant their symptoms. **Conclusions:** Participants' preferences varied substantially, and many judged much larger benefits needed to warrant having ACT for 6 months rather than 3 months than the estimates of the benefits based on the IDEA meta-analysis.

3603 Poster Session (Board #96), Sun, 8:00 AM-11:30 AM

Association of sex and adverse events (AEs) of adjuvant chemotherapy (ACT) in early stage colon cancer (CC): A pooled analysis of 28,636 patients (pts) in the ACCENT database. *First Author: Anna Dorothea Wagner, Department of Oncology, Lausanne University Hospital, Lausanne, Switzerland*

Background: Sex is one of several factors known to affect drug efficacy and toxicity. Preliminary data in different types of cancers suggest a higher toxicity of chemotherapy in women. Aim of this pooled analysis was to understand the clinical relevance of sex differences in toxicity of ACT in CC. **Methods:** The primary aim was to compare these major AEs: nausea, vomiting, stomatitis, diarrhea, leucopenia, neutropenia, anemia, thrombocytopenia, and neuropathy (pts receiving oxaliplatin) between men (M) and women (W) treated with ACT after curative resection. Severity of AEs was categorized as per NCI criteria. Comparisons were conducted by chi-squared test and logistic regression based on type of ACT, including fluoropyrimidine (5-FU) as single-agent, 5-FU + irinotecan (FOLFIRI), or 5-FU + oxaliplatin (FOLFOX). $P < 0.001$ was considered significant due to multiple comparisons. **Results:** AE data were available in 28,636 pts (54% M) from 26 studies. Overall, women were at greater risk for the majority of toxicities (see Table). **Conclusions:** Further investigations are needed to better understand the impact of sex on toxicity and efficacy of chemotherapy. Possible differences in perception do not explain the significant differences in neutropenia. These results suggest that sex-specific strategies for drug dosing and supportive care may need consideration.

	5-FU (n = 22,770)		FOLFOX (n = 3,655)		FOLFIRI(n = 2,211)	
*Grade I-IV (III/IV) AE in %	W	M	W	M	W	M
Nausea	**57 (6.8)**	**49 (3.5)**	33 **(9.6)**	29 **(4.7)**	**77** (10)	**66** (6.9)
Vomiting	**31 (5.1)**	**21 (2.6)**	**24 (9.0)**	**18 (4.7)**	**52** (9.3)	**40** (6.0)
Nausea/vomiting	**59 (8.1)**	**51 (4.3)**	36 **(13)**	32 **(6.8)**	**80** (13)	**70** (9.6)
Stomatitis	**30 (7.2)**	**24 (4.4)**	16 (3.1)	16 (1.8)	32 (1.8)	27 (.87)
Diarrhea	**62 (20)**	**58 (16)**	**37 (21)**	**31 (15)**	**74** (21)	**68** (16)
Leucopenia	**40 (5.6)**	**32 (3.1)**	3.2 (2.3)	2.4 (1.4)	**68** (11)	**59** (7.4)
Neutropenia	**36 (16)**	**33 (11)**	**$ (27)**	**$ (18)**	**78 (40)**	**69 (26)**
Thrombocytopenia	**5.6** (.25)	**9.7** (.26)	26 (1.7)	30 (1.5)	17 (1.4)	21 (1.7)
Anemia	**33** (.53)	**25** (.40)	37 (1.5)	41 (.47)		
Neuropathy			69 (18)	71 (15)		

*** AEs with p < 0.001 are denoted by bold font; $ data with grade I-II were missing**

3604 Poster Session (Board #97), Sun, 8:00 AM-11:30 AM

Impact of adjuvant chemotherapy in higher risk stage II colon cancer with a deficient mismatch repair (dMMR)/ microsatellite instability-high (MSI-H) profile. *First Author: AMR Mohamed, Karmanos Cancer Institute, Detroit, MI*

Background: Randomized phase III trials have shown that patients with dMMR/ MSI-H stage II colon cancer (CC) do not benefit from adjuvant chemotherapy. However, a subgroup of stage II patients have a higher risk for recurrence but it is unclear whether those patients who also have dMMR/MSI-high tumors will in fact benefit from adjuvant chemotherapy. **Methods:** In this retrospective analysis of National Cancer Database (NCDB) we studied the impact of adjuvant chemotherapy in high risk stage II with dMMR/MSI-high CC. Higher risk was defined by at least one of the following criteria: < 12 lymph nodes examined, lymphovascular invasion (LVI), positive surgical margin, T4 tumor, and poorly differentiated/undifferentiated histology. No data were available for obstruction or perforation at diagnosis. **Results:** Between 2010 and 2013, 3851 CC patients (56.1% females, median age 69, 49.5% clinicopathologically high risk) were determined to have dMMR/MSI-high status. 24.6% of dMMR/MSI-high patients received adjuvant chemotherapy, of whom 67.8% received multiagent therapy. On univariate analysis no adjuvant chemotherapy, pT4A/B tumor, pathologic stage IIB/C, < 12 lymph nodes, LVI positive, positive margin, and older age at diagnosis were associated with worse overall survival (OS). On multivariable analysis no adjuvant chemotherapy, male sex, stage IIC, positive surgical margin, older age at diagnosis were associated with worse OS. High risk dMMR/MSI-high patients had better OS when given adjuvant chemotherapy, HR 0.50 (0.34-0.74, p < 001). Single and multiagent adjuvant chemotherapy were associated with better OS, HR 0.38 (0.19-0.76, p = 0.006) and 0.58 (0.37-0.90, p = 0.02), respectively. **Conclusions:** Adjuvant chemotherapy was associated with better OS in stage II CC patients with high-risk features plus dMMR/MSI-high profile. Benefit was observed with both single and multiagent chemotherapy. In the absence of prospective studies, this study supports the consideration of adjuvant chemotherapy in the subgroup of stage II CC patients with dMMR/MSI-high status if they also have high recurrence clinico-pathological features risk.

3605 Poster Session (Board #98), Sun, 8:00 AM-11:30 AM

Fish oil supplementation and inflammatory response during neoadjuvant chemoradiation for rectal cancer: Results from a prospective, randomized, controlled trial. *First Author: Juliana De Aguiar Pastore Silva, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: It has been proposed that omega-3 fatty acids can modulate inflammatory response and contribute to improve anti-cancer therapies. **Methods:** Patients clinically staged as T3,4 and / or N + rectal carcinoma were randomized to receive oral ingestion of encapsulated fish oil during neoadjuvant conventional chemoradiation (intervention group – IG) or chemoradiation without supplement (control group – CG). All patients were operated about 8 weeks after chemoradiation. Glasgow Prognostic Score (GPS) was the primary endpoint. Other inflammatory and nutritional parameters and quality of life (QOL) measurements were also collected at 4 moments: M1: at diagnosis; M2: at the end of chemoradiation; M3: at 4 weeks after end of chemoradiation; and M4: preoperatively. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were quantified in blood samples by gas chromatography. **Results:** 179 patients were referred for neoadjuvant treatment between January, 2013 and July, 2017. 120 met eligibility criteria. 114 were randomized (IG: 55 and CG: 59). Mean age were 59.5 years, ranging from 30-86 years. There was no difference between groups in M1. In M2 and M3 there were differences between the supplemented group (IG) and the CG in systemic inflammatory response measured by Glasgow Prognostic Score (M2:P = 0.001; M3:P = 0.027), serum protein C reactive (PCR)(M2: P = 0.001; M3: P = 0.045) and ratio CRP / Albumin (M2:P = 0.00; M3: P = 0.005) - the lowest values in the IG. About QOL, CG presented more symptoms in M2 for dysuria (P = 0.031), M3 for pain (P = 0.023), buttock pain (P = 0.005) and dyspareunia (P = 0.041); IG presented less anxiety (P = 0.040). In M4 the differences between the groups were about recent lost weight (P = 0.025), with lowest values in IG, and CG present more symptoms for appetite loss (P = 0.016), buttock pain (P = 0.044) and bloating (P = 0.007). There were no differences in food intake, body composition, global subjective assessment and classification of nutritional status at any study moment. **Conclusions:** This dietary intervention was able to modulate inflammatory response, has impact on some nutritional markers and some components of quality of life. Clinical trial information: NCT02534389.

3606 Poster Session (Board #99), Sun, 8:00 AM-11:30 AM

Who should undergo lateral pelvic node dissection after neoadjuvant chemoradiation for rectal cancer? *First Author: Songphol Malakorn, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The optimal surgical strategy for rectal cancer patients with suspected lateral pelvic lymphadenopathy (LPN) in unknown. Despite the use of neoadjuvant chemoradiation (CRT), lateral compartment treatment failure has emerged as an important clinical problem. The purpose of this study was to evaluate association between preoperative LPN size on imaging and disease diagnosed at pathology in order to determine the indication for lateral pelvic lymph node dissection (LPND). **Methods:** Rectal cancer patients with lateral pelvic node metastasis who underwent TME with LPND between 2006 and 2017 were identified from the institutional database of a tertiary cancer center and their medical records were retrospectively reviewed for information regarding patient, tumor, and treatment. Indication for LPND was suspected LPN based on CT or MRI. Patients with locally recurrent cancers at presentation were excluded. Primary outcome was rate of pathologic LPN positivity. Associations between LPN size on post-neoadjuvant CRT imaging and pathologic lateral pelvic lymph node positivity were evaluated. **Results:** A total of 70 patients who underwent TME & LPND met criteria and were analyzed. The median number of LPN evaluated was 3 (IQR 1 – 5) per patient. The mean LPN size before and after CRT was 15.7 ± 12.7 mm and 11.0 ± 10.0 mm, respectively and the minimum size of positive LPN was 6 mm on post-treatment imaging. Overall, a total of 56 of 256 LPN were positive (22%). Twenty patients (28.6%) had only ≤ 5 mm LPN after CRT; none were positive at pathology. Among 50 (71.4%) patients who had > 5 mm LPN after CRT; 34 patients (68%) were positive at pathology. 3 year OS was higher among patients who had ≤ 5 mm LPN vs > 5 mm LPN after CRT (OS 90.9% vs 70.4%, P = 0.05) but the difference in DFS was not statistically significant (77.9% vs 56.7%, P = 0.12). After a median 43 months of follow-up, one patient developed local recurrence (≤ 5 mm group). **Conclusions:** Post-CRT LPN size > 5 mm was strongly associated with pathologically positive LPN but no patients with size ≤ 5 mm had positive LPN at pathology. Following LPND no patients with positive LPN developed local recurrence. Therefore, patients with LPN > 5 mm on post-CRT MRI should undergo TME with LPND.

3607 Poster Session (Board #100), Sun, 8:00 AM-11:30 AM

Mesorectal excision with or without lateral lymph node dissection for clinical stage II, III lower rectal cancer: Long-term follow-up data of Japan Clinical Oncology Group study JCOG0212. *First Author: Mitsuyoshi Ota, Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan*

Background: We conducted the non-inferiority study of mesorectal excision (ME) alone to ME with lateral lymph node dissection (LLND) for clinical stage II/III rectal cancer without lateral pelvic lymph node enlargement. Non-inferiority of ME to ME with LLND was not confirmed in terms of efficacy in the primary analysis. This is the long-term follow-up data of the study with a median follow- up of 84 months for all randomized patients. **Methods:** Eligibility criteria included clinical stage II/III; main lesion located in the rectum with the lower margin below the peritoneal reflection; no lateral pelvic lymph node swelling larger than 10 mm. After surgeons had confirmed R0 resection by the ME procedure, patients were randomized intraoperatively to ME alone or ME with LLND. The primary endpoint was relapse-free survival (RFS), with a non-inferiority margin for the hazard ratio (HR) of 1.34. The planned sample size was 700 with a power of 75% and a one-sided alpha of 5%. **Results:** A total 701 of patients enrolled from 33 institutions were randomized to ME+LLND (n = 351) or ME (n = 350) between June 2003 and August 2010. The 7-year RFS was 71.1% and 70.7% in the ME+ LLND group and the ME group, respectively. The HR was 1.09 [95% CI: 0.84-1.42] (non-inferiority P =0.064). In subgroup analysis shown in the table, RFS of clinical stage III patients in the ME+LLND group was significantly better than that of those in the ME group (HR: 1.49 [95% CI: 1.02-2.17]). **Conclusions:** Long-term follow-up data supported that the non-inferiority of ME to ME with LLND was not confirmed in terms of efficacy in the primary analysis. ME with LLND is recommended especially for clinical stage III patients who do not undergo preoperative chemoradiotherapy. Clinical trial information: NCT00190541.

Characteristics	HR	95% CI
Sex		
Male	0.95	0.69-1.29
Female	1.54	0.92-2.56
Clinical stage		
II	0.82	0.56-1.19
III	1.49	1.02-2.17
Distance from anal verge		
≤ 5 cm	1.11	0.78-1.56
> 5 cm	1.03	0.68-1.56
Tumor size		
≤ 5 cm	0.88	0.61-1.28
> 5 cm	1.30	0.88-1.91

Subgroup analysis of RFS

3608 Poster Session (Board #101), Sun, 8:00 AM-11:30 AM

Predicting treatment outcome of rectal cancer patients underwent neoadjuvant chemoradiotherapy by ctDNA: The potential use of ctDNA monitoring as organ-sparing approach. *First Author: Lifeng Yang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Neoadjuvant chemoradiotherapy (nCRT) is widely accepted for the treatment of locally advanced rectal cancer (LARC). Watch & wait (W&W) strategy can improve life quality, but needs strict patient selection. We investigated the ability of circulating tumor DNA (ctDNA) to predict treatment outcome and improve risk stratification. **Methods:** Between 2015 and 2016, we enrolled LARC (T3/T4 and/or N+) patients planned for nCRT. Plasma samples were collected pretreatment, in the middle of nCRT, post-nCRT, before surgery and one week after surgery. Somatic mutations in individual patient were identified via massively parallel sequencing of 455 genes. Responders (ypTRG 0–1) or non-responders (ypTRG 2–3) were recorded. Chi-square test was used to compared ctDNA levels to clinical, radiological and pathological response. **Results:** We analysed 440 serial plasma samples from 88 patients. Ten cases were pathological complete response (pCR). CtDNA was detectable in 65.9% (58/88), 14.7% (13/88) and 3.4% (3/88) of pretreatment, post-nCRT and post-surgery samples, with most frequent mutations as TP53, APC, KRAS. The rates of responders and non-responders are 24.1% (14/58) and 75.9% (44/58), but no difference was found in baseline ctDNA. 65.5% (38/58) of the patients' ctDNA level decreased *sharply* to zero before the end of nCRT, which was consistent to their radiological and pathological changes. CtDNA was detectable in 60% (6/10) pCR cases, most of their ctDNA vanishing at the middle of nCRT. 29.3% (17/58) of the patients' ctDNA status changed in irregular patterns. However, 5.2% (3/58) of the patients' ctDNA status goes up during nCRT, all of the three developed metastatic disease during the follow up period. Increased level of ctDNA post-nCRT indicated high rates of disease progression, which was not appropriate for W&W strategy. **Conclusions:** The baseline ctDNA were not helpful in distinguishing responders from non-responders. Post-nCRT analysis stratifies patients with LARC into subsets at high or low risk of progression. CtDNA analysis could potentially be used to guide patient selection for W&W strategy or adjuvant chemotherapy.

3609 Poster Session (Board #102), Sun, 8:00 AM-11:30 AM

Reasons for urban-rural differences in colon cancer outcomes: A population-based analysis. *First Author: Nicholas Adam Bosma, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: Previous studies showed that rural patients with colon cancer tend to have worse overall survival (OS). In the US, this disparity is due in part to poorer healthcare access or lack of insurance in rural populations. It is unclear what drives this disparity in single payer healthcare systems. **Methods:** Patients diagnosed with stage II and III colon cancer from 2004 to 2015 in a large Canadian province were identified. Demographics, disease, treatment, and outcome data were collected. Using residential postal codes, we classified patients as living in urban, regional, or rural areas. OS was measured from the time of diagnosis to death and analyzed using the Kaplan-Meier method. Multivariate Cox regression models were used to assess the impact of residence on outcomes, while adjusting for measured confounders. **Results:** We included 6,163 patients: 3,691 in urban, 693 in regional, and 1,779 in rural areas. Median age at diagnosis was 71 years, with 52% men, 51% stage II disease, 54% left-sided colon cancer, and 59% Charlson score 0. In comparison, there were more younger patients ($p = 0.033$) and more right-sided colon cancers ($p = 0.042$) in urban areas. In addition, urban patients experienced shorter times from diagnosis to surgery ($p < 0.001$), but longer delays from surgery to adjuvant chemotherapy ($p = 0.002$) (see Table). In survival analysis, median OS among urban, regional, and rural populations was 104, 83, and 94 months, respectively (log-rank $p < 0.001$). After adjusting for measured confounders and observed variations in baseline characteristics across patient populations, residence continued to predict for OS (HR 1.3, 95% CI 1.1-1.4, $p < 0.001$) for regional and HR 1.1, 95% CI 1.0-1.2, $p = 0.040$) for rural, when compared to urban. **Conclusions:** Urban-rural differences in colon cancer survival persist, even in settings with universal healthcare coverage. These findings may be partly driven by a younger population and more expedited surgical intervention in urban populations, but they do not fully explain the disparities.

Median time to surgery and adjuvant chemotherapy.

	Urban	Rural	Regional
Time to Surgery	12 days	16 days	15 days
Time to Adjuvant Chemotherapy	61 days	60 days	55 days

3610 Poster Session (Board #103), Sun, 8:00 AM-11:30 AM

Prognostic impact of CDX2 in stage II colon cancer: Results from two nationwide cohorts. *First Author: Torben Hansen, Danish Colorectal Cancer Center South, Vejle Hospital, Vejle, Denmark*

Background: The aim of the present study was to validate the prognostic impact of CDX2 in stage II colon cancer and confirm its clinical potential. **Methods:** Individual patient data and formalin fixed, paraffin embedded tumor tissue were collected from two unbiased, population-based cohorts representing all patients operated for stage II colon cancer in Denmark in 2002 and 2003. The CDX2 expression was evaluated by immunohistochemistry on whole tumor sections. Patients were classified into three groups, of CDX2 expression: *positive, intermediate, and negative,* for comparison with the clinical data. The endpoint was disease free survival (DFS). **Results:** A total of 1,157 patients was included. We found a significant relationship between loss of CDX2 expression and poor DFS in both cohorts, p = 0.0267 and p = 0.0118, respectively. Five-year DFS rates were 66%, 72%, and 74% in the test cohort and 62%, 65%, and 75% in the validation cohort for the negative, intermediate, and positive CDX2 expressing groups, respectively. Multiple Cox regression analysis performed on the combined cohorts confirmed an independent prognostic impact of CDX2 on DFS, hazard ratio 1.543 (95% confidence interval 1.129-2.108), p = 0.0065. CDX2 loss was also associated with an adverse prognosis in patients with tumors harboring microsatellite instability (MSI) (p = 0.0001). Tumors with focal loss of CDX2 expression in the budding cells constituted a specific group with a very poor prognosis, demonstrating a 5-year DFS of only 60%. **Conclusions:** The present study provides further strong evidence regarding prognostic impact of CDX2 in patients with stage II colon cancer. CDX2 expression should be considered when deciding on adjuvant chemotherapy, especially in the group of patients with MSI tumors.

3611 Poster Session (Board #104), Sun, 8:00 AM-11:30 AM

Molecular characterization of appendiceal cancer and comparison with right-sided (R-CRC) and left-sided colorectal cancer (L-CRC). *First Author: Ryuma Tokunaga, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: The natural history and prognosis of appendiceal adenocarcinomas (AA) differ from that of adenocarcinomas arising in other large bowel sites. Compared to CRC, AA has more peritoneal dissemination and worse outcome. **Methods:** A total of 184 samples from AA (42 pseudomyxoma peritonei (PMP), 70 mucinous (MU), 24 signet ring (SR) and 48 adenocarcinoma, NOS (NOS)), 1080 samples from L-CRC, and 994 from R-CRC were tested with Next-Generation Sequencing (NGS) on a 592-gene panel and immunohistochemistry (IHC). Microsatellite instability (MSI) and tumor mutational burden (TMB) were tested by NGS, and PD-L1 by IHC (SP142). Statistical comparisons of AA and L-and R-CRC were done by Chi-square test. **Results:** High mutation rates in AA were seen in *KRAS* (55%), *TP53* (40%), *GNAS* (31%), *SMAD4* (16%), *APC* (10%), *ARID1A* (8%), *RNF43* (7%), *PIK3CA* (6%) and *BRAF* (5%). MSI-high was seen in 2.2%, TML-high (> = 17mut/MB) in 2.2% and PD-L1 expression in 2.8%. Compared to both L- and R-CRC, AA showed significantly higher mutation rates of *GNAS, SMAD4* and lower *TP53*, *APC*, *PIK3CA* and *FBXW7*. Alterations associated with immune checkpoint inhibitor responses (MSI-high, TML-high, PD-L1) showed similar frequency in AA compared to L-CRC, but not R-CRC. Histopathological subtypes of AA showed different molecular patterns: PMP carried the highest *KRAS* (78%), *GNAS* (63%) and no *PIK3CA* or *BRAF* mutations. SR showed the lowest *KRAS* (17%) and *APC* (0%) mutation rates. MU was characterized by *GNAS* mutation rate of 36%. SR and PMP had no MSI-high or TML-high cases. **Conclusions:** Molecular characterization of AA revealed different characteristics compared with CRC; similarities were observed between AA and L-CRC despite anatomical distance, and molecular heterogeneity among histological subtypes were seen. These molecular differences may be critical to develop new treatments for appendiceal adenocarcinoma.

%

	AA, %	L-CRC, %	R-CRC, %	*p* values (AA vs. L)	*p* values (AA vs. R)
GNAS	31	1*	2*	< 0.01	< 0.01
SMAD4	16	10*	11*	0.02	0.04
TP53	40	75*	66*	< 0.01	< 0.01
APC	10	83*	70*	< 0.01	< 0.01
PIK3CA	6	17*	22*	< 0.01	< 0.01
FBXW7	3	9*	11*	0.04	0.01
MSI-high	2	3	15*		< 0.01
TML-high	3	5	15*		< 0.01
PD-L1	3	3	7*		0.048
BRAF	5	5	17*		< 0.01

* $p < 0.05$ compared to AA

3612 Poster Session (Board #105), Sun, 8:00 AM-11:30 AM

***HER2* positive rates are enriched amongst colorectal cancer brain metastases: A study amongst 1,920 consecutive patients.** *First Author: Ryan Tan, National Cancer Centre Singapore, Singapore, Singapore*

Background: Brain metastases (BM) from colorectal cancer (CRC) are a rare but increasing event as patients survive longer. While human epidermal growth factor receptor 2 (*HER2*) gene amplification in breast cancer is well described and known to increase risk of brain metastases, information in CRC patients with brain metastases is lacking. **Methods:** A retrospective review of all radiologic imaging amongst 1920 consecutive CRC patients seen at National Cancer Centre Singapore identified 40 patients with radiological evidence of brain metastases. We retrieved resected primary tumour specimens or biopsies of metastatic sites from these 40 patients for fluorescence in situ hybridization (FISH) testing for *HER2* gene amplification. *HER2* amplification was defined as *HER2/CEP17* ratio ≥2.0. Clinical characteristics were evaluated in relation to *HER2* status. **Results:** The incidence of clinically evidence brain metastases in this cohort of CRC patients was 2% (40 of 1920). *HER2* amplification was observed in 20% (8 of 40) of CRC patients who develop brain metastases. *HER2* amplification was observed across most CRC primary sites (4 rectum, 3 right colon and 1 left colon) and was also seen in *KRAS* mutant CRC (2 of 8 patients). Mean *HER2* copy number of *HER2* positive (*HER2+)* patients was 10.7 (range 5.7 – 17.5). Brain metastases was preceded by metastases in either the lung or liver in 95% of patients (38 or 40) including all of the *HER2+* patients. In 1 patient, *HER2+* brain metastases was observed after Trastuzumab/Lapatinib therapy. **Conclusions:** Brain metastases in CRC is rare. However, compared to a reported *HER2* positive rate of 5% amongst 912 KRAS wild-type metastatic CRC patients in the HERACLES study and 0% (0/44) amongst KRAS mutant patients reported in literature, *HER2* amplification was observed in 20% (8 of 40) of all CRC patients in our study who develop brain metastases. This is one of the first studies to point to *HER2+* disease being enriched amongst patients with brain metastases providing insight into a potential organotrophic site of metastases in *HER2+* positive CRC.

3613 Poster Session (Board #106), Sun, 8:00 AM-11:30 AM

Age-related real-world outcomes for patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Melissa Curtis, Flatiron Health, New York, NY*

Background: There are scant data regarding the diagnosis, treatment, and outcomes for mCRC pts diagnosed at a very young age (< 30 yrs). We therefore explored age-related pt and tumor characteristics, treatment patterns and OS among mCRC pts treated in routine clinical practice. **Methods:** We retrospectively analyzed a national sample of pts ≥18 yrs old with confirmed mCRC diagnosed on or after 01/1/2014 (N = 10,990) using the Flatiron Health database. Descriptive statistics summarized pt and tumor characteristics and treatment patterns. Overall survival (OS) was indexed to mCRC diagnosis date. OS curves were estimated with Kaplan-Meier method. P-values were calculated for trend across all age groups. **Results:** Pt characteristics, mutation testing and 1st-line (1L) therapy trends differed significantly across age groups (results for < 30 and > 70 yrs age groups in Table). Median OS significantly differed by age, with a peak for those 40-49 yrs at diagnosis: 21.8 mos (< 30 yrs), 21.0 mos (30-39 yrs), 27.5 mos (40-49 yrs), 26.5 mos (50-59 yrs), 22.3 mos (60-69 yrs), 15.8 mos (> 70 yrs), p-value < 0.0001. **Conclusions:** 1L treatment and OS for mCRC pts differed significantly by age at diagnosis in unadjusted analysis. Despite more often receiving 1L aggressive therapy (FOLFOX/FOLFIRI/FOLFOXIRI +/- ab), younger age groups had worse OS compared to all other age groups except > 70 yrs. Over-representation (compared to US 2010 census) of young African Americans supports earlier screening. Documentation of standard mutational testing significantly differed by age, and mutation positivity differed for BRAF. These findings suggest that a complex interplay between biologic, diagnostic and treatment factors may affect age- and race-based disparities in mCRC outcomes.

	Age group (yrs)		
	< 30 (%) N = 62	> 70 (%) N = 4339	*p*-value (across all age groups)
Stage 4 at diagnosis	77.4	50.8	< 0.001
African American	19.6	9	< 0.001
Mutation Tested			
BRAF	54.8	26.2	< 0.001
positive	11.8	16.5	< 0.001
KRAS	75.8	57.7	< 0.001
positive	40.4	40.5	0.3
NRAS	50.0	27.6	< 0.001
positive	0	4.6	0.5
1L regimen			
FOLFOX/FOLFIRI	14.5	12.8	< 0.001
FOLFOX/FOLFIRI + antibody (ab)	50	29.7	
FOLFOXIRI +/- ab	8.1	0.3	
Other	11.3	31.5	
None	16.1	25.7	

3614 Poster Session (Board #107), Sun, 8:00 AM-11:30 AM

Effects of proton pump inhibitors (PPIs) on FOLFOX and XELOX regimens in colorectal cancer (CRC). *First Author: Grace Wong, Cross Cancer Institute, Edmonton, AB, Canada*

Background: First-line adjuvant chemotherapy options for stage II-III CRC include XELOX (capecitabine (cape), oxaliplatin) and FOLFOX (oxaliplatin, leucovorin, 5FU). Cape is an oral 5FU prodrug, and recent studies suggested that PPIs may detrimentally affect cape efficacy. Conversely, some literature posits that PPIs may negatively impact CRC itself. Our primary objective was to compare 3-year recurrence-free survival (RFS) rates between XELOX-treated PPI-users and non-PPI users, and FOLFOX-treated PPI users and non-PPI users. Our main secondary objective was to compare overall survival (OS). **Methods:** We conducted a retrospective chart review of 389 stage II-III CRC patients (pts) who received adjuvant XELOX or FOLFOX from a tertiary cancer center in Alberta, Canada between 2004-2013. Information regarding PPI use, cancer treatment, and pt outcomes were gathered and analyzed from pharmacy databases. **Results:** 23.4% of XELOX-treated pts and 28.0% of FOLFOX -treated pts used PPIs concurrently with treatment. 3-year RFS was significantly lower in XELOX-treated PPI pts than non-PPI pts (69.5 vs. 82.6%, $P = 0.029$). Unadjusted analysis showed that XELOX-treated PPI pts were twice as likely to experience cancer recurrence or death as XELOX-treated non-PPI pts (HR 2.03, $P = 0.033$). FOLFOX-treated PPI pts had a non-significant increase in three-year RFS versus non-PPI pts (82.9 vs. 61.7%, $P = 0.066$), and no significant difference in recurrence or death (HR 0.51, $P = 0.071$). No significant differences were seen in OS. **Conclusions:** Our results suggest that PPIs negatively impacted RFS in early-stage XELOX-treated CRC pts, and yielded no significant effect amongst FOLFOX-treated patients. Further studies are required to corroborate our findings.

RFS in stage II-III CRC.

Chemotherapy	Overlapping PPI use	3-year RFS (%)	*P* value
FOLFOX	Yes (n = 49)	82.9	0.066
	No (n = 126)	61.7	
XELOX	Yes (n = 50)	69.5	0.029
	No (n = 164)	82.6	

Cox Proportional Hazards Model: RFS Analysis

Patients analyzed	HR	*P* value
XELOX PPI vs. no PPI	2.03	0.033
FOLFOX PPI vs. no PPI	0.51	0.071
PPI XELOX vs. FOLFOX	1.93	0.161
No PPI XELOX vs. FOLFOX	0.41	< 0.001

TPS3615 Poster Session (Board #108a), Sun, 8:00 AM-11:30 AM

Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) study (NRG- GI004/SWOG-S1610): A randomized phase III study of mFOLFOX6/ bevacizumab combination chemotherapy with or without atezolizumab or atezolizumab monotherapy in the first-line treatment of patients with deficient DNA mismatch repair (dMMR) metastatic colorectal cancer. *First Author: James J. Lee, NSABP Foundation, and The University of Pittsburgh, Pittsburgh, PA*

Background: DNA mismatch repair defect (dMMR) colorectal cancer (CRC) cells are highly immunogenic. Preclinical data showed that oxaliplatin-containing chemotherapy in combination with anti-VEGF enhances the antitumor activity of programmed cell death-1 (PD-1) pathway blockade in murine CRC models. Prior phase I study showed that mFOLFOX6/ bevacizumab (bev) plus atezolizumab was well tolerated and enhanced intratumoral infiltration of $CD8^+$ T cells. We hypothesize that the dMMR subset of CRC may be effectively targeted with the combination of PD-1 pathway blockade and mFOLFOX6/bev to promote tumor regression. **Methods:** This is a prospective randomized phase III open-label trial. Patients (pts) (N=347) with metastatic dMMR CRC will be randomized to 3 trial arms (1:1:1): mFOLFOX6/bev; atezolizumab monotherapy; or mFOLFOX6/ bev plus atezolizumab. Stratification factors include *BRAF* status, metastatic site, and prior adjuvant therapy for CRC. Primary objective is to evaluate the efficacy of mFOLFOX6/bev/atezolizumab and atezolizumab monotherapy as compared to mFOLFOX6/bev. Primary endpoint is progression-free survival (PFS) assessed by study investigator. Secondary endpoints include overall survival, objective response rate, safety profile, surgical conversion rate, disease control rate, duration of response, and PFS by retrospective central review. Exploratory objective includes health-related quality of life. Archived tumor tissue and blood samples will be collected for correlative studies. Key inclusion criteria are: Metastatic CRC without prior chemotherapy for metastatic disease; Tumor determined to be dMMR by local CLIA-certified IHC assay (MLH1/MSH2/MSH6/PMS2); Availability of archived tumor tissue for central confirmation of dMMR status; and measurable disease per RECIST. Activated as of Nov 7, 2017, the 1st of the planned 347 pts has been enrolled. **Clinical trial #:** NCT02997228. **SUPPORT:** U10CA180868, -180822, UGICA189867, U24CA196067 Clinical trial information: NCT02997228.

TPS3616 Poster Session (Board #108b), Sun, 8:00 AM-11:30 AM

Novel PET/CT imaging biomarkers of CB-839 in combination with panitumumab and irinotecan in patients with metastatic and refractory RAS wildtype (WT) colorectal cancer: A phase I/II study. *First Author: Satya Das, Vanderbilt University Medical Center, Nashville, TN*

Background: Irinotecan plus panitumumab is active in RAS WT metastatic CRC (mCRC) patients who progress on 5-FU based regimens. Inevitably, patients develop resistance to EGFR inhibition; one such pathway is mediated by the enzyme glutaminase, which converts glutamine to glutamate and is a downstream effector of the EGFR/RAS pathway. Inhibition of this pathway with the selective glutaminase inhibitor CB-839 has stopped growth of cetuximab-sensitive and -resistant HLA-7 CRC cell lines. Greater antitumor response with the doublet of cetuximab (or panitumumab) and CB-839 was seen in mouse xenografts of the human CRC line SW48 than with either agent alone. Given this data, we proposed the combination of CB-839 plus panitumumab in RAS WT mCRC patients; to demonstrate on target effect of the therapy, we are utilizing two PET tracers, one which recognizes glutamine and the other glutamate. In addition to safety and efficacy aims, another aim of our study is to correlate SUV changes in pre-treatment and post-cycle 1 carbon-11-labeled glutamine (11C-glutamine) and (4S)-4-(3-[18F]fluoropropyl)-L-glutamate (18F-FSPG) PET with clinical outcome and glutamate levels in plasma. **Methods:** NCT03263429 is a single arm phase I/II study exploring the combination of CB-839, panitumumab ± irinotecan in RAS WT mCRC patients with at least one prior line of chemotherapy exposure. Phase I has 2 dose levels of CB-839 BID (600 mg and 800 mg) administered with panitumumab 6 mg/kg and irinotecan 180 mg/m2 D1 and D15 each 28-day cycle. Dose escalation is being performed according to a Bayesian continual reassessment method. The Phase II study evaluates CB-839's ability to reverse panitumumab resistance in EGFR inhibitor refractory patients. Irinotecan is included in the phase I for future potential studies in panitumumab-naïve patients. The primary objectives of the phase I and II portions of the study are to demonstrate the maximum tolerated dose and overall response rate of the combination, respectively. A Simon two-stage design is being used in phase II; if ≥ 1 response is seen in the first 10 patients, accrual will continue until 29 patients are enrolled. Clinical trial information: NCT03263429.

TPS3617 Poster Session (Board #109a), Sun, 8:00 AM-11:30 AM

NuTide 302: A phase IB study to assess the safety, pharmacokinetics and clinical activity of NUC-3373 in combination with standard agents used in colorectal cancer treatment. *First Author: Sarah Patricia Blagden, University of Oxford, Oxford, United Kingdom*

Background: 5-FU and its other forms, floxuridine and capecitabine, exert their anti-cancer activity mainly due to the active metabolite, fluorodeoxyuridine-monophosphate (FUDR-MP), which inhibits the enzyme thymidylate synthase (TS). Although these agents remain the cornerstone of combination treatments for colorectal cancer (CRC), key cancer resistance mechanisms of breakdown, activation and transport limit their effectiveness. NUC-3373 is a phosphoramidate transformation of FUDR-MP designed to bypass the key resistance mechanisms associated with 5-FU. NuTide 301 is an ongoing first-in-human study of NUC-3373 in patients with advanced solid tumors. PK/PD data obtained to date demonstrate NUC-3373 has a long plasma $t_{1/2}$ (9.7 h v 8-14 mins for 5-FU) and generates high levels of the active intracellular anti-cancer metabolite, FUDR-MP (Ghazaly *et al* ESMO, 2017). TS is efficiently inhibited and sequestered into TS-ternary complexes (TS-T), depleting the pool of dTMP within 2-4 hours. **Methods:** NuTide:302 is a two-part, Phase Ib study in patients with CRC who have relapsed after ≥2 prior lines of therapy. The primary objective is to identify a recommended NUC-3373 dose when administered every 2 weeks in combination with standard agents used in CRC treatment. Secondary objectives included safety, PK/PD and anti-tumor activity. In Part 1, NUC-3373 is being administered with leucovorin (LV) to determine if the folate is beneficial in the formation of TS-T. Approximately 12 patients will be enrolled in Part 1 of the study. If LV augments TS-T formation, it will be administered in Part 2. In Part 2, the following combination agents will be administered with NUC-3373 (±LV): oxaliplatin; oxaliplatin + bevacizumab; oxaliplatin + panitumumab; irinotecan; and irinotecan + cetuximab. In Part 2, patients will be enrolled in cohorts of 3-6, in a modified 3+3 design. Up to 62 patients will be recruited, depending on cohort expansion. Clinical trial information: NCT03428958.

TPS3618 Poster Session (Board #109b), Sun, 8:00 AM-11:30 AM

First-line treatment with panitumumab plus FOLFIRI in elderly patients with *RAS/BRAF* wild-type unresectable metastatic colorectal cancer and good performance status: OPALO trial. *First Author: Jaime Feliu, Hospital Universitario La Paz, Madrid, Spain*

Background: Approximately 60% of colorectal cancer (CRC) patients are ≥ 70 years, of whom 50-60% already have metastasis at the time of diagnosis. Available data indicate that elderly patients with good performance status may, like younger patients, benefit from intensive treatment approaches. The objective of this trial is to assess the efficacy and safety of first-line therapy with panitumumab + FOLFIRI in elderly patients with *RAS/BRAF* wild-type unresectable metastatic colorectal cancer and good performance status. **Methods:** OPALO is a phase II, single-arm, multicentre clinical trial. Primary objective: progression-free survival (PFS) at one year. Main eligibility criteria: 1. Patients ≥70 years; 2. colorectal carcinoma with unresectable metastatic disease; 3. *RAS/BRAF* wild-type status; 4. Independence in activities of daily living (ADL) based on the Katz Index and in instrumental activities of daily living (IAL) based on the Lawton Index; 5. To have one or no comorbidity according to the Charlson Comorbidity Index; 6. Patients starting therapy with FOLFIRI + panitumumab with a treatment aim other than achieving potential resectability of the disease. Treatment: all patients are receiving panitumumab (6 mg/kg) plus FOLFIRI every two weeks. Tumour response is evaluated every 8 weeks till disease progression. A blood sample is taken at baseline and at the time of disease progression to determine the *RAS/BRAF* mutation status. Statistical design: a sample size of 80 patients is deemed appropriate (assuming a precision of 11.45%, a two-sided confidence interval of 95%, a proportion of interest of 60% and a loss to follow-up rate of 10%). The recruitment of patients has begun in October 2017.

TPS3619 Poster Session (Board #110a), Sun, 8:00 AM-11:30 AM

ABT-165 plus FOLFIRI vs bevacizumab (bev) plus FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine/oxaliplatin and bev. *First Author: Zev A. Wainberg, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: The dual variable domain immunoglobulin ABT-165 targets human vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4). Combined VEGF and DLL4 blockade increased inhibition of subcutaneous xenograft growth of human colon cancer-derived cell lines vs blockade of either axis alone. *In vivo*, ABT-165 plus chemotherapy (CT) induced tumor regression with improved efficacy, vs anti-VEGF monoclonal antibody plus CT. In a phase 1 study, a tolerable recommended phase 2 dose was identified for ABT-165 plus FOLFIRI and showed promising efficacy. This phase 2 trial in progress assesses the efficacy/safety of ABT-165 plus FOLFIRI vs bev plus FOLFIRI in pts with second-line mCRC. **Methods:** This is an open-label, multicenter, phase 2 randomized (1:1) trial (NCT03368859) in pts (≥18 years; Eastern Cooperative performance status: 0–1) with histologically/cytologically confirmed mCRC who progressed after fluoropyrimidine/oxaliplatin and bev. ABT-165 (2.5 mg/kg) plus FOLFIRI (irinotecan: 180 mg/m^2; leucovorin: 400 mg/m^2; fluorouracil bolus: 400 mg/m^2, infusion: 2400 mg/m^2) or bev (5 mg/kg) plus FOLFIRI are given intravenously on day 1 of each 14-day cycle, until disease progression/intolerable toxicity. The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response rate (ORR), and safety. Exploratory endpoints include biomarkers predictive for efficacy/safety, correlation of DLL4 levels with PFS, OS, and ORR, pharmacodynamic effects, and the efficacy/safety-exposure relationships in the ABT-165 arm. The hazard ratios of PFS and OS comparing the 2 groups are estimated using the Cox proportional hazard model. Kaplan-Meier methodology is used to estimate the PFS and OS curves, median PFS and OS, and their 90% confidence intervals. Safety is assessed by ABT-165 exposure, adverse events (AEs), serious AEs, all deaths, and changes in laboratory data and vital signs. Archival tissue is collected and evaluated for DLL4 expression and angiogenesis signature. Approximately 100 pts are planned to be enrolled, with recruitment initiated in January 2018. Clinical trial information: NCT03368859.

TPS3620 Poster Session (Board #110b), Sun, 8:00 AM-11:30 AM

A randomized phase II study of trastuzumab and pertuzumab (TP) compared to cetuximab and irinotecan (CETIRI) in advanced/metastatic colorectal cancer (mCRC) with HER2 amplification: S1613. *First Author: Kanwal Pratap Singh Raghav, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite advances in systemic therapy, few patients are cured, creating a large unmet need for strategies targeting novel signaling and resistance pathways. The HER2 pathway, which has been successfully targeted in breast and gastric cancer, is one such unique potential target in mCRC. HER2 amplifications (HER2amp) have been identified in a small but distinct subset (6-8%) of KRAS wild-type mCRC. HER2amp is associated with resistance to anti-EGFR therapy (cetuximab/panitumumab) and short progression-free survival (PFS) (< 3 mos.) (*Raghav ASCO 2016*). Preliminary clinical data (MyPathway Study) has shown promising activity of dual-anti-HER2 inhibition using TP in HER2amp and KRAS wild-type mCRC (Response rate 52%, 95% CI 31 - 72%; and median PFS 5.7 months, 95% CI 4 – 12 mos.) (*Hurwitz GIASCO 2017*). **Methods:** S1613 is a multicenter, randomized phase 2 study assessing efficacy of TP relative to CETIRI in HER2amp mCRC. This is a 2 step study. All anti-EGFR naïve mCRC patients (pts) without known activating mutations in KRAS/NRAS/BRAF will be screened in step 1 for HER2amp by a central lab using immunohistochemistry and dual-probe in-situ hybridization. Screening can be performed at any time, even during treatment on 1st/2nd line of therapy. If HER2amp positive, pts will be randomized in step 2 after progression on 1st/2nd lines of therapy to either TP [pertuzumab (840mg loading dose + 420mg every 3 weeks) and trastuzumab (8mg/kg loading dose + 6mg/kg every 3 weeks)] or CETIRI [irinotecan (180 mg/m2 IV every 14 days) and cetuximab (500 mg/m2 IV every 14 days)]. Prior irinotecan is allowed. Crossover to TP will be allowed after progression on CETIRI arm. A total of 122 eligible patients will provide 80% power to detect an increase in median PFS to 5.1 months from 3 months (HR 0.59) based on a two-sided type I error of 5%, 33 months of accrual and 7 months of follow-up. The primary endpoint of PFS will be analyzed in all eligible patients per intent-to-treat. Randomization will be stratified by prior use of irinotecan and HER2/CEP17 ratio. The study is now activated and open to enrollment to all NCI - NCTN institutions. Clinical trial information: NCT03365882.

TPS3621 Poster Session (Board #111a), Sun, 8:00 AM-11:30 AM

Physical activity program in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy: A randomized controlled phase III trial—(ACTIVE-2 SAKK 41/14). *First Author: Viviane Hess, University of Basel and University Hospital Basel, Medical Oncology, Basel, Switzerland*

Background: Exercise has become a main focus of basic and clinical research worldwide during the current pandemic of physical inactivity. A clear link between inactivity and cancer incidence/relapse has been established, particularly for colon cancer, the third most common cancer. However, whether exercise has an impact on disease course and survival in advanced disease is unknown. Exercise modifies key host factors that are determinants of chemotherapy efficacy such as metabolic and immunologic tumor microenvironment, drug tolerability and treatment adherence. Thus, we aim to assess whether a supervised exercise program concomitant to first-line palliative chemotherapy for patients with metastatic colorectal cancer (mCRC) enhances chemotherapy efficacy and, therefore, increases survival and decreases symptom burden as compared to patients treated with chemotherapy alone. **Methods:** Patients with newly diagnosed mCRC are stratified (pre-diagnosis physical fitness, RAS-mutational status, primary tumor location, alkaline phosphatase levels) and randomly assigned to undergo standard systemic treatment and care-as-usual or standard systemic treatment combined with a 12-week structured physical activity (PA) program with twice weekly supervised, heart-rate guided interval training on a bike ergometer. Both groups undergo regular imaging with CT/MRI in order to assess the 1°endpoint of progression-free survival (PFS), i.e. the time between diagnosis and disease progression or death. Radiologists who are blinded to the group assignment will review imaging. A total of 439 events occurring in 524 patients will be needed to show a clinically meaningful HR of 0.75 for PFS with 80% power and an α of 0.03. Co-primary endpoint is self-reported symptom burden as measured by the revised Edmonton Symptom Assessment Scale (rESAS). 50 patients from 17 Swiss and Austrian Centers have been randomized. A planned feasibility analysis of the first 40 patients is ongoing. Clinical trial information: NCT02597075.

TPS3622 Poster Session (Board #111b), Sun, 8:00 AM-11:30 AM

PRODIGE 52-UCGI 29-CCTG/CO.27 (IROCAS): A multicenter, international, randomized phase III trial comparing adjuvant modified (m)FOLFIRINOX to mFOLFOX6 in patients with high-risk stage III (pT4 and/or N2) colon cancer (a UNICANCER GI-PRODIGE trial). *First Author: Jaafar Bennouna, Centre Hospitalier Universitaire Nantes, Digestive Oncology, Nantes, France*

Background: According to the IDEA trial (Shi Q et al. ASCO 2017;LBA1), 6-month adjuvant chemotherapy should remain the standard in stage III T4 or N2 colon cancer. The relatively poor survival in this high-risk subgroup (3-year disease-free survival ([DFS] rate, 66%) and the potential synergistic efficacy of 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (demonstrated in stage IV colon and pancreatic cancers) suggest FOLFIRINOX as a regimen of particular interest in this setting. **Methods:** This multicenter, international, phase III trial (NCT02967289) conducted in 47 centers in France and Canada, plans to include 640 patients, aged 18 to 70 years, ECOG performance status $\leq$1, within 42 days (start treatment, within 56 days) after curative-intent R0 surgical resection of a pT4N1 or pT1-4N2 colon adenocarcinoma. Patients are randomized (1:1; minimization method) between adjuvant mFOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2, and 5-FU 2.4 g/m^{2}over 46 h) or mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-FU bolus 400 mg/m^2 then 2.4 g/m^{2}over 46 h), every two weeks for 24 weeks (12 cycles). Patients will be followed up for 5 years after the end of adjuvant chemotherapy. A gain of 9% in 3-yr DFS (primary endpoint) is expected (74% in the experimental arm vs. 65% in the control arm; α, 5% [two-sided log-rank test]; 1-b, 80%). Secondary endpoints include 2-yr DFS, overall survival, and toxicity. Since April 2017, 49 patients have been enrolled to date (accrual period, 4 years). Clinical trial information: NCT02967289.

TPS3623 Poster Session (Board #112a), Sun, 8:00 AM-11:30 AM

Phase I trial of TAS-102 and concurrent radiation therapy for patients with locally recurrent, unresectable or metastatic, rectal cancer. *First Author: Joleen Marie Hubbard, Mayo Clinic, Rochester, MN*

Background: After primary therapy for rectal cancer (chemotherapy, surgery, and/or radiotherapy), 7-10% of patients will develop locally recurrent disease. Re-irradiation +/- resection of recurrent rectal cancer is possible for select patients. Trifluridine/tipiracil (TAS-102) is a combination nucleoside analog and thymidine phosphorylase inhibitor (TPI) with activity in colorectal cancer refractory to fluoropyrimidines. Trifluridine has a similar mechanism of action as the fluoropyrimidines, which are known radiosensitizing agents, and pre-clinical data shows TPI can potentiate the effects of radiation on colon cancer cell lines. TAS-102 in combination with radiation therapy may have a synergistic effect treating recurrent rectal cancers in patients previously exposed to a fluoropyrimidine. The primary objective of this trial is to determine the maximum tolerated dose and dose-limiting toxicity of TAS-102 when administered in combination with concurrent radiation therapy in patients with locally recurrent rectal cancer. **Methods:** This is a phase I trial with a standard 3 + 3 dose escalation design (see table). All patients will receive TAS-102 administered PO twice daily on days 1-5 and days 8-12. All patients will also receive radiation therapy at a dose of 300 cGy/day, for a total dose of 3000 cGy in 10 fractions, Monday through Friday for days 1-5 and days 8-12. Patients $\geq$ 18 years with histological confirmation of locally recurrent rectal adenocarcinoma within the pelvis after primary therapy are eligible. Patients with pelvic disease that is resectable or unresectable and metastatic disease outside the pelvis are allowed. Patients with the first occurrence of rectal cancer amenable to treatment with trimodality therapy will be excluded. Prior treatment with TAS-102 and cancer treatment $\leq$ 28 days prior to registration is not allowed. Patients with prior pelvic radiation therapy $>$ 54 Gy are ineligible. This trial is currently accruing patients to the first cohort. Clinical trial information: NCT03297710.

Dose Level	Dose	**TAS-102 Dose (2X daily)
-1	-57%	15 mg/m^2
0*	-43%	20 mg/m^2
1	-29%	25 mg/m^2
2	-14.3%	30 mg/m^2
3	100%	35 mg/m^2

*Starting dose. **Round dose to the nearest 5 mg. Maximum dose 80 mg.

TPS3624 Poster Session (Board #112b), Sun, 8:00 AM-11:30 AM

NSABP FR-2: Phase II study of durvalumab following neoadjuvant chemotherapy (NAC) in stage II-IV rectal cancer. *First Author: Thomas J. George, NSABP Foundation and The University of Florida Health Cancer Center, Gainesville, FL*

Background: Locally-advanced rectal cancer (LARC) remains a clinical challenge with few improvements noted over the past few decades. Although immunotherapy has no current clinical role in microsatellite stable (MSS) colorectal cancer, preclinical models suggest that radiotherapy (RT) can induce neoantigen presentation, modulate the microenvironment, and improve the likelihood of immunogenic activation with checkpoint inhibitor use. This prospective phase II study will test that hypothesis in addition to confirming safety of this approach using a "window-of-opportunity" study design with the anti-PDL1 agent durvalumab (MEDI4736). **Methods:** This multi-center phase II trial is currently enrolling patients (pts) with rectal cancer who are undergoing standard NCCN guideline-compliant NAC and RT. Eligibility includes pts with MSS stage II-IV rectal cancer with adequate organ function and pre-treatment diagnostic tumor available for profiling who are undergoing NAC with intentions to proceed to surgical resection. Stage IV disease must be limited such that the primary pelvic tumor requires definitive management. Standard ineligibility criteria include active infections, systemic steroid use, or other conditions making immunotherapy use unsafe. Treatment includes durvalumab (750mg IV infusion once every 2 wks) for 4 total doses beginning within 3-7 days after NAC completion. Surgery must be within 8-12 wks of the final RT dose. Primary endpoint is a demonstrated improvement in Neoadjuvant Rectal Cancer (NAR) score compared to historical controls representing a 20% relative risk reduction in DFS HR and 3-4% absolute OS improvement. Secondary endpoints include comparisons of OS, DFS, toxicity, pCR, cCR, therapy completion, negative surgical margins, sphincter preservation, off-target "abscopal" effects for the subset of stage IV pts, and exploratory assessments of tumor infiltrating lymphocytes, circulating immunologic profiles, and molecular predictors of response. A safety run-in portion of the study will precede full enrollment. Enrollment continues to 47 total pts to achieve 41 surgically evaluable pts. Support: AstraZeneca-Medimmune, NSABP Foundation Clinical trial information: NCT03102047.

4000 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

FOLFIRINOX until progression, FOLFIRINOX with maintenance treatment, or sequential treatment with gemcitabine and FOLFIRI.3 for first-line treatment of metastatic pancreatic cancer: A randomized phase II trial (PRODIGE 35-PANOPTIMOX). *First Author: Laetitia Dahan, La Timone University Hospital, Marseille, France*

Background: Metastatic pancreatic cancer (mPC) still harbors a dismal prognosis (5-year overall survival [OS] <5%). Our previous trial (PRODIGE4-ACCORD11) has demonstrated the superiority of 6-month [m] chemotherapy with FOLFIRINOX over gemcitabine in terms of progression-free survival [PFS] (6.4 vs. 3.3 m; HR: 0.47; 95%CI: 0.37-0.59; p<0.001) and OS (11.1 vs. 6.8 m; HR: 0.57; 95%CI: 0.45-0.73; p<0.001), at the expense of higher toxicity, notably cumulative, often limiting, peripheral neuropathy with oxaliplatin. In this randomized Phase II trial, we aimed to assess an oxaliplatin 'stop-and-go' strategy and an alternative sequential strategy in mPC. **Methods:** Patients (pts) were randomized to receive either 6m FOLFIRINOX (arm A), 4m FOLFIRINOX followed by LV5FU2 maintenance treatment for controlled pts, and treatment reintroduction at disease progression (arm B), or a sequential treatment alternating gemcitabine and FOLFIRI.3 every 2m (arm C). The primary endpoint was to evaluate the 6m-PFS rate (H0: 30%, H1: 45%, Fleming design) in order to select the best therapeutic strategy for a future Phase III clinical trial. **Results:** Between Jan 2015 and Nov 2016, 273 pts (mean age: 63 years; range: 40-76) were enrolled (A: 91; B: 92; C: 90). The median durations of treatment were 5.1, 6.2, and 4.4 m in A, B, and C respectively. Grade 3/4 neurotoxicity occurred in 10% of pts in arm A and 19% of pts in arm B. Median ratio of oxaliplatin was 83% in A and 92% in B. 6m-PFS rates were 47% in A, 44% in B, and 34% in C. 4m objective response rates were 35% in A, 41% in B, and 17% in C. Median PFS was respectively 6.3, 5.7 and 4.5 m in A, B and C. Median OS was 10.1 in A, 11.2 in B and 7.3 m in C. The median duration of first maintenance therapy in B was 3.3 m (range: 0.03-22.6). **Conclusions:** Maintenance with LV5FU2 appears to be feasible and effective in patients with mPC controlled after 4m of induction chemotherapy with FOLFIRINOX. Severe neurotoxicity rate was higher in the maintenance therapy arm, likely because of higher cumulative oxaliplatin dose.[1]*Conroy NEJM 2011.* Clinical trial information: NCT02352337.

LBA4001 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Unicancer GI PRODIGE 24/CCTG PA.6 trial: A multicenter international randomized phase III trial of adjuvant mFOLFIRINOX versus gemcitabine (gem) in patients with resected pancreatic ductal adenocarcinomas. *First Author: Thierry Conroy, Institut de Cancérologie de Lorraine, Vandoeuvre-Les-Nancy, France*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Monday, June 4, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

LBA4002 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1) : A randomized, controlled, multicenter phase III trial. *First Author: Geertjan Van Tienhoven, Department of Radiation Oncology, Academic Medical Center, Amsterdam, Netherlands*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Monday, June 4, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

4003 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib. *First Author: Andrew X. Zhu, Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Patients (pts) with advanced HCC and elevated AFP have a poorer prognosis compared to the general HCC population, and need effective, well tolerated treatment options. Increased VEGF and VEGFR2 expression is associated with high AFP expression in HCC tumors. Ramucirumab (RAM), a human IgG1 mAb, inhibits activation of VEGFR2. REACH-2 was designed to confirm the benefit of RAM treatment observed in the REACH study in pts with baseline AFP ≥400 ng/mL. **Methods:** Eligible pts were ≥18 yrs, had HCC with BCLC stage C or B disease refractory or not amenable to locoregional therapy, baseline AFP ≥400 ng/mL, Child-Pugh A, ECOG PS 0 or 1, adequate hematologic and biochemical parameters, had progressed on or following, or were intolerant to sorafenib. Pts were randomized (2:1) to receive RAM 8 mg/kg iv or placebo (PL) Q2W plus best supportive care, until disease progression or unacceptable toxicity. Primary endpoint was overall survival (OS). Secondary objectives included progression-free survival (PFS), objective response rate (ORR) per RECIST v1.1 and safety. **Results:** 292 pts were randomized to RAM (197) or PL (95). Baseline characteristics were generally balanced between arms. RAM treatment significantly improved OS (median OS 8.5 mo vs 7.3 mo PL; HR 0.710; 95% CI 0.531, 0.949; p=.0199). RAM significantly improved PFS (median PFS 2.8 mo vs 1.6 mo PL; HR 0.452; 95% CI 0.339, 0.603; p<.0001). ORR was 4.6% RAM vs 1.1% PL (p=.1156) and disease control rate (ORR + stable disease) was 59.9% RAM vs 38.9% PL (p=.0006). Grade ≥ 3 adverse events occurring in ≥ 5% pts in the RAM arm were hypertension (12.2% RAM, 5.3% PL) and hyponatremia (5.6%, 0%). **Conclusions:** REACH-2 met its primary endpoint showing a significant survival benefit, with RAM treatment reducing the risk of death (29%) in pts with HCC and AFP ≥ 400 ng/mL who progressed on or were intolerant to sorafenib. Treatment was well tolerated, with a safety profile consistent with the established profile for single agent RAM. REACH-2 is the first positive phase 3 study conducted in a biomarker-selected pt population with HCC. Clinical trial information: NCT02435433.

4004 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *First Author: Pamela L. Kunz, Stanford University School of Medicine, Stanford, CA*

Background: Patients with advanced pancreatic neuroendocrine tumors (pNETs) have few treatment options that yield objective tumor regression. Somatostatin analogues, everolimus, and sunitinib yield prolonged progression-free survival (PFS) but low response rates (RRs). Retrospective and small, prospective studies suggest that temozolomide-based therapies may have activity and the combination of temozolomide and capecitabine (TC) is associated with high RRs and relative long PFS. However, there are no randomized, prospective studies of these agents and this trial was initiated to establish a role for the combination of TC. **Methods:** E2211 was a two-arm, randomized, phase II trial comparing T (200 mg/m2 PO QD days 1-5) vs. TC (T 200 mg/m2 PO QD days 10-14; C 750 mg/m2 PO BID days 1-14) in patients with advanced pNETs. Eligibility criteria included: metastatic or unresectable, low or intermediate grade pNETs, progression within preceding 12 months, and no prior T, C, DTIC, or 5-FU. The primary endpoint was PFS; secondary endpoints were Overall Survival (OS), RR, safety, and predictive value of MGMT as evaluated by immunohistochemistry and promoter methylation. This trial had at least 81% power to detect a difference in median PFS of 9 vs. 14 months (hazard ratio of 0.64) using a two-sided log-rank test at the 0.20 significance level. **Results:** 144 patients were enrolled at 66 US sites between 8/2013 to 3/2016 to T (n = 72) or TC (n = 72) (intention to treat population). Median age, 62 years; women, 44%. Median PFS was 22.7 months for TC vs. 14.4 months for T (HR = 0.58, p = 0.023) and crossed the pre-specified protocol efficacy boundary. Median OS was 38.0 months for T and has not been reached for TC (HR = 0.41, p = 0.012). Median follow-up was 29 months. RR data will be presented at the meeting. The treatment was well-tolerated with expected AEs and higher rates in the combination arm. **Conclusions:** In E2211, TC was associated with improved PFS and OS compared to T alone in advanced low or intermediate grade pNETs. This is the first prospective randomized trial of these agents and shows the longest PFS reported for pNET-directed therapy. Clinical trial information: NCT01824875.

4005 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Azedra (iobenguane I 131) in patients with malignant, recurrent and/or unresectable pheochromocytoma or paraganglioma (PPGL): Updated efficacy and safety results from a multi-center, open-label, pivotal phase 2 study. *First Author: Daniel Pryma, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: AZEDRA, a high-specific-activity iodine-131 meta-iodobenzylguanidine (HSA I-131 MIBG), has been developed for the treatment of iobenguane-avid malignant (metastatic) or recurrent or unresectable pheochromocytoma or paraganglioma (PPGL). **Methods:** MIBG-avid PPGL patients (pts) ineligible for curative surgery or chemotherapy, and on a stable antihypertensive regimen for tumor-related hypertension were enrolled. Pts received a dosimetric dose (111-222 MBq) followed by up to 2 therapeutic doses (each at 296 MBq/kg to a maximum of 18.5 GBq) approximately 3 months (mths) apart. Pts were followed for 12-mths (efficacy period) and an additional 4 years for long-term follow-up. The primary endpoint was defined as proportion of pts with at least 50% reduction, including discontinuation, of all antihypertensive medications lasting ≥6 mths beginning during the efficacy period. Secondary endpoints included objective tumor response (OTR) by RECIST and overall survival (OS). **Results:** Of 81 pts enrolled, 74 pts received a dosimetric dose of AZEDRA. 68 pts received 1 therapeutic dose (full analysis; FA) and 50 received two (per protocol; PP). At study entry, 52% (35/68) had prior surgery and systemic therapy (I-131 MIBG and/or chemotherapy) for PPGL. 50% (32/64) of evaluable pts had lung and/or liver metastases at baseline. The primary endpoint was met by 25% (95% CI 16%-37%) of FA and 32% (95% CI 21%-46%) of PP pts, achieving pre-specified success criteria. For OTR, 23% and 30% of FA and PP populations achieved partial response (PR). The 12-month OS was 91% in FA pts. Median OS was 36.7 mths (95% CI 29.9, 49.1), and median survival appeared similar in pts with and without lung/liver metastasis at baseline (42.6 and 41.1 mths, respectively). The most common (≥50%) treatment-emergent adverse events were myelosuppression, nausea, and fatigue. No acute drug-related hypertensive events were observed. **Conclusions:** Updated results from this pivotal phase 2 study suggest that AZEDRA is an efficacious and safe treatment for an ultra-orphan disease with no approved therapies in the United States. Clinical trial information: NCT00874614.

4007 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized phase III study comparing S-1 plus docetaxel with S-1 alone as a postoperative adjuvant chemotherapy for curatively resected stage III gastric cancer (JACCRO GC-07 trial). *First Author: Yasuhiro Kodera, Nagoya University, Nagoya, Japan*

Background: Although postoperative adjuvant chemotherapy with S-1 is among the standard treatments for curatively resected pStage II/III gastric cancer (GC) in Asia, the outcome of pStage III GC remains unsatisfactory. Postoperative S-1/docetaxel had been among candidates for the new standard treatment. **Methods:** JACCRO GC-7, a randomized controlled trial to explore postoperative S-1/docetaxel, was participated by 138 Japanese institutions. After R0 resection by D2 gastrectomy, patients with pStage III GC were randomly assigned to either the S-1/docetaxel group (oral S-1 at 80-120mg/body on days 1-14 with 7 days of rest was followed by 6 cycles of S-1 at the same dosage and schedule combined with docetaxel 40mg/m^2 on day 1 of each cycle, and then 4 further cycles of S-1 at 80-120mg/body on days 1-28 every 42 days) or the control group (8 cycles of S-1 at 80-120mg/body on days 1-28 every 42 days). Block randomization was performed by a central interactive computerized system stratified by the institution, stage (IIIA, IIIB, or IIIC) and histological type (differentiated or undifferentiated). The sample size of 1,100 was necessary to detect a 7% increase in the 3-year RFS, the primary endpoint, in the S-1/docetaxel group (HR 0.78, 2-sided alpha = 0.05, beta = 0.2). The secondary endpoints were OS, TTF and safety. **Results:** At the planned second interim analysis, the 3y RFS of the S-1/docetaxel arm (65.9%) was significantly superior to that of the S-1 arm at 49,6% (HR 0.632, 99% CI: 0.400~0.998, p = 0.0007), and the independent data and safety monitoring committee recommended termination of the trial. S-1/docetaxel suppressed all types of recurrences including hematogenous, lymphatic and peritoneal. Although ≥grade 3 adverse events including leucopenia, anorexia, stomatitis and anemia were more frequent, postoperative S-1/docetaxel was safe and manageable. **Conclusions:** Postoperative adjuvant S-1/docetaxel after D2 gastrectomy is recommended as the new standard of care for patients with pStage III GC. Clinical trial information: UMIN 000010337.

LBA4008 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Chemoprevention of esophageal cancer with esomeprazole and aspirin therapy: Efficacy and safety in the phase III randomized factorial ASPECT trial. *First Author: Janusz Jankowski, University of Central Lancashire, Preston, United Kingdom*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Monday, June 4, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

4009 Poster Discussion Session; Displayed in Poster Session (Board #198), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Phase III study comparing triplet chemotherapy with S-1 and cisplatin plus docetaxel versus doublet chemotherapy with S-1 and cisplatin for advanced gastric cancer (JCOG1013). *First Author: Yasuhide Yamada, National Cancer Center Hospital, Tokyo, Japan*

Background: Doublet chemotherapy with S-1 and cisplatin (CS) is one of the standard first-line chemotherapy for advanced gastric cancer in Japan. Triplet chemotherapy with docetaxel added to CS (DCS) showed a promising activity associated with feasible toxicities in a phase II study. We conducted a phase III study, JCOG1013, to investigate whether DCS improved overall survival (OS) compared with CS. **Methods:** Patients with previously untreated, human epidermal growth factor receptor 2 negative or unknown, unresectable or recurrent gastric adenocarcinoma, performance status 0 to 1, and adequate organ function were eligible. They were randomly 1:1 assigned to receive CS (S-1 40-60 mg orally twice a day for 3 weeks, cisplatin 60 mg/m^2 on day 8, repeated every 5 weeks), or DCS (docetaxel 40 mg/m^2, cisplatin 60 mg/m^2 on day 1, S-1 40-60 mg orally twice a day for 2 weeks, repeated every 4 weeks). The primary endpoint was OS. A total of 740 patients were required to detect an increase in median OS from 13.5 months in the CS arm to 16.5 months in the DCS arm, corresponding to a hazard ratio (HR) of 0.8435, with a one-sided alpha of 5% and power of 80%. **Results:** From Apr 2012 to Mar 2016, 741 patients were enrolled in total (CS 371, DCS 370). Median OS was 14.2 and 15.3 months for DCS and CS, respectively (HR 0.99; 95% confidence interval [CI] 0.85-1.16; one-sided stratified log-rank p = 0.47). By histological subtypes, median OS was 13.3 months for DCS and 14.2 months for CS (p = 0.83) in the diffuse type (n = 482), and 17.5 months for both DCS and CS (p = 0.65) in the intestinal type (n = 259). Median progression-free survival was 7.4 months for DCS and 6.5 months for CS (HR 0.99; 95% CI, 0.86-1.15; p = 0.92). The overall response rate was 59.3% for DCS and 56.0% for CS (p = 0.50). The most common adverse events of grade 3 or 4 were neutropenia (DCS 58.5%, CS 32.1%), febrile neutropenia (DCS 7.6%, CS 5.7%), and diarrhea (DCS 7.0%, CS 7.4%). **Conclusions:** Addition of docetaxel to CS failed to improve OS of patients with untreated advanced gastric cancer. Therefore, CS remains the standard treatment for first-line chemotherapy for advanced gastric cancer. Clinical trial information: UMIN000007652.

4010 Poster Discussion Session; Displayed in Poster Session (Board #199), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

The BRIGHTER trial: A phase 3 randomized double-blind study of napabucasin (NAPA) plus paclitaxel (PTX) versus placebo (PBO) plus PTX in patients (pts) with pretreated advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Manish A. Shah, Weill Cornell Medicine/ New York Presbyterian Hospital, New York, NY*

Background: NAPA is an oral investigational agent, hypothesized to inhibit cancer stemness pathways, including STAT3 pathway implicated in cancer stem-cell viability. Synergistic antitumor activity of NAPA + PTX was observed in preclinical and early clinical testing. **Methods:** BRIGHTER is a randomized, double-blind, placebo-controlled phase 3 trial (NCT02178956), assessing efficacy and safety of NAPA + PTX versus PBO + PTX in pts with pretreated, advanced gastric and GEJ adenocarcinoma. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response (ORR) and disease control (DCR) rates, and safety. Pts were randomized 1:1 to NAPA (960 mg total daily dose) + weekly PTX (80 mg/m^2) or PBO + weekly PTX (80 mg/m^2). **Results:** 714 pts were randomized from October 2, 2014, to December 12, 2016. At interim analysis of 380 events, the data safety monitoring board recommended trial unblinding when meeting the primary endpoint at final analyses appeared unlikely, though no safety concerns of clinical significance were identified. OS follow-up continued with median follow-up of 6.8 m (0.10-32.4) with final analysis performed at 565 events: 36.7%/63.2% (ECOG 0/1), 72.1%/27.9% (M/F), 74.6%/25.4% (gastric/GEJ). The mOS was 6.93 m vs 7.36 m in NAPA and PBO arms (HR 1.01 [95% CI, 0.86-1.20] p=0.8596), respectively. The mPFS was 3.55 m vs 3.65 m in NAPA and PBO arms (HR 1.00 [95% CI, 0.84-1.17] p= 0.9679), respectively. Among evaluable pts, DCR was 55 % vs 58% in NAPA and PBO arms Diff -3% (95% CI, -11%-5%, p= 0.6555), respectively, with an ORR of 16% vs 18% in NAPA and PBO arms Diff -2% (95% CI, -8%-4%, p=0.7358), respectively. The overall incidence of adverse events (AEs) was 98.6% vs 96.6% in NAPA and PBO arms without any additive toxicity. AEs $\geq$ Grade 3 occurred in 69.2% vs 59.7% in NAPA and PBO arms, with $\geq$Grade 3 diarrhea in 16.0% vs 1.4%, respectively. **Conclusions:** An international, placebo controlled phase 3 2nd line study of NAPA + PTX did not improve OS or PFS in pts with gastric and GEJ adenocarcinoma. Addition of NAPA to PTX was tolerable. Clinical trial information: NCT02178956.

4011 Poster Discussion Session; Displayed in Poster Session (Board #200), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). *First Author: Akitaka Makiyama, Department of Hematology/Oncology, Japan Community Health Care Organization Kyushu Hospital, Kitakyushu, Japan*

Background: Trastuzumab (Tmab) is a key drug for HER2-positive breast and gastric or gastro-esophageal junction (G/GEJ) cancer. While continuous use of Tmab beyond progression (TBP) showed a benefit in HER2-positive metastatic breast cancer, it has not been studied in HER2-positive G/GEJ cancer. We compared weekly paclitaxel alone (P) with weekly paclitaxel plus Tmab (PT) in patients (pts) with HER2-positive advanced G/GEJ cancer progressing during Tmab-containing therapy. **Methods:** Pts with HER2-positive advanced G/GEJ cancer progressing during first-line chemotherapy with Tmab + fluoropyrimidine + platinum were enrolled, and randomized to receive either P (80mg/m2, day1, 8, 15, q4w) or PT (P + initial Tmab 8mg/kg followed by 6mg/kg, q3w). The primary endpoint was progression-free survival (PFS). Major secondary endpoints included overall survival (OS), response rate, safety, and translational biomarker research. A total of 69 events was required to achieve 80% power for one-sided log rank test with 10% significance level, expecting median PFS of P and PT arms was 3 and 5 months, respectively. **Results:** From December 2012 to October 2016, 91 pts were randomized to P (n = 45) or PT (n = 44) arms. Median PFS was 3.19 (95% CI 2.86-3.48) and 3.68 (95% CI 2.76 to 4.53) months in the P and PT arms, respectively (HR = 0.91, 95% CI 0.67-1.22, p = 0.33). Median OS was 9.95 months in the P arm and 10.2 months in the PT arm (HR = 1.23, 95% CI 0.75-1.99, p = 0.20). In the P and PT arms, the overall response rates were 31.6 and 33.3% (p = 1.00), and the disease control rates were 71.1 and 61.5% (p = 0.47), respectively. PT treatment was associated with longer PFS in pts whose interval between the last Tmab administration and the randomization $\geq$30 days (HR = 0.45, 95% CI 0.21-0.96), but not in pts $<$ 30 days (HR = 1.40, 95%CI 0.82-2.37). Safety was comparable between the arms. HER2-positivity of tumor tissues obtained from 16 pts before the study entry was lost in 69%. **Conclusions:** TBP strategy failed to improve PFS in pts with HER2-positive advanced G/GEJ cancer. Clinical trial information: UMIN000009297.

4012 Poster Discussion Session; Displayed in Poster Session (Board #201), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Survival outcomes from CALGB 80803 (Alliance): A randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer. *First Author: Karyn A. Goodman, University of Colorado, Denver, CO*

Background: We evaluated use of early PET response after induction chemotherapy (CT) to direct changing to alternative CT during preoperative chemoradiation (CRT) among patients (pts) with resectable esophageal and gastroesophageal junction (GEJ) adenocarcinomas who are PET nonresponders. We previously reported the primary endpoint of improving pathologic complete response (pCR) in PET nonresponders; pre-specified efficacy criteria were met for improvement in pCR rates with changing CT during CRT. We now report survival outcomes by PET response status. **Methods:** 257 pts enrolled, underwent baseline PET and were randomized to 1 of 2 induction CT arms: modified FOLFOX-6 (oxaliplatin, leucovorin, 5-FU) days 1, 15, 29 or carboplatin/paclitaxel (CP) days 1, 8, 22, 29. Repeat PET was performed days 36-42; change in maximum standardized uptake value (SUV) from baseline was assessed. PET nonresponders ($<$ 35% decrease in SUV: PET-NR) crossed over to alternative CT regimen during CRT (50.4 Gy/28 fractions). PET responders ($\geq$35% decrease in SUV: PET-R) continued on same CT during CRT. Pts underwent surgery at 6 weeks post-CRT. Overall survival (OS) was measured from randomization to death from any cause; 2-year (yr) OS rates were estimated using the Kaplan-Meier method. **Results:** 240 eligible pts received protocol treatment and 222 had an evaluable repeat PET. With median follow-up of 35.9 months (mo) (95% CI: 33.1-41.2), median OS was 34.4 mo (95%CI: 28.4-49.7) and 2-yr OS was 61.8% (95%CI: 55.7-68.5%). Median OS for PET-R was 40.2 mo (95% CI: 31.0, not estimable [NE]) and for PET-NR was 27.4 mo (95% CI: 20.3, NE). Median and 2-yr OS by induction CT and PET response appear below. Clinical trial information: NCT01333033. **Conclusions:** PET response after induction CT is prognostic for outcome in pts with esophageal and GEJ adenocarcinomas. Outcomes for PET-R pts receiving induction and concurrent FOLFOX are encouraging. Support: U10CA180821, U10CA180882

Response Group	Events/N	Median OS (mo)	95% CI (mo)	2-yr OS (%)	95% CI (%)
CP N = 111					
PET-R	31/63	31.0	(20.4, NE)	57.4	(46.2, 71.3)
PET-NR	28/48	26.4	(16.0, NE)	52.4	(39.8, 69.0)
FOLFOX N = 111					
PET-R	29/72	48.7	(33.1, NE)	73.3	(63.4, 84.7)
PET-NR	20/39	30.9	(25.4, NE)	64.0	(50.0. 82.0)

4013 Poster Discussion Session; Displayed in Poster Session (Board #202), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

A multi-center, randomized, prospective study evaluating the optimal radiation dose of definitive concurrent chemoradiation for inoperable esophageal squamous cell carcinoma. *First Author: Yanjun Xu, Zhejiang Cancer Hospital, Hangzhou, China*

Background: To determine the optimal radiation dose for definitive concurrent chemoradiation in esophageal squamous cell carcinoma (ESCC) using modern radiation technology. **Methods:** Pathologically confirmed ESCC patients with stage IIA-IVA were randomized into high-dose (60Gy) and low-dose group (50Gy). The total radiation doses were delivered 2 Gy per fraction, 5 fractions per week, by intensity-modulated radiation therapy (IMRT). Concurrent weekly docetaxel (25 mg/m^2) followed by cisplatin (25 mg/m^2) and 2 cycles consolidation chemotherapy with docetaxel 70mg/m^2 plus cisplatin 25mg/m^2 day1-3 were administrated. The primary endpoint was local/regional progression-free survival (LRPFS). **Results:** From April 2013 to May 2017, 305 patients were randomized into the high-dose (n = 152) and low-dose group (n = 153). There were no significant differences in gender, age, KPS, clinical stage, location, the length of tumor between the two groups. The radiotherapy completion rate was 87.5% (133/152) and 95.4% (146/153) in the high and low dose groups respectively (*P*= 0.002) . The concurrent weekly chemotherapy completion of receiving 5, 4, ≤3 weeks drugs were 61.2% (93/152) 、66.7% (102/153) ; 21.1% (32/152) 、20.9% (32/153) ; 17.8% (27/152) 、12.4% (19/153) (*P*=0.406) . There was no significantly difference in the completion of consolidation chemotherapy (*P*= 0.207). At a median follow-up of 14.4 months (1.3-51.4 months) , The disease progression rate was 15.8% (24/152) 、15.7% (24/153) in the high-dose and low-dose group, respectively. The 1, 2-year LRPFS rate was 85.8%、74.4% and 85.1%、78.4% (*P*= 0.676) . The 1, 2-year PFS and OS rate was 78.6%、67.6%, 76.9%、67.7% (*P*= 0.859) ; 84.6%、67.3%, 86.4%、72.2% (*P*= 0.981) . The treatment toxicity equal to or greater than grade 3 included leukopenia; radiation esophagitis and pneumonitis. There were no significant differences between the two groups. **Conclusions:** There was no difference towards LRPFS, PFS, OS and toxicity between high-dose (60Gy) and low-dose (50Gy) group. A total radiation dose of 50Gy was recommended for definitive concurrent chemoradiation in ESCC. Clinical trial information: NCT01937208.

4014 Poster Discussion Session; Displayed in Poster Session (Board #203), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Randomized phase III study of gemcitabine plus S-1 combination therapy versus gemcitabine plus cisplatin combination therapy in advanced biliary tract cancer: A Japan Clinical Oncology Group study (JCOG1113, FUGA-BT). *First Author: Makoto Ueno, Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan*

Background: Gemcitabine (GEM) plus cisplatin (GC) is the standard of care for advanced biliary tract cancer (BTC). However, GC is considered to be toxic because of nausea, vomiting, and appetite loss, and inconvenient due to requiring hydration before and after administration. GEM plus S-1 (GS) was reported to be promising with preferable efficacy and acceptable toxicity profile. This phase III study aimed to confirm the non-inferiority of GS to GC in terms of overall survival (OS). **Methods:** Eligibility criteria included chemotherapy-naïve patients with recurrent or unresectable biliary tract adenocarcinoma (gallbladder, intrahepatic biliary tract, extrahepatic biliary tract, or ampulla of Vater), an ECOG-PS of 0–1, and adequate organ function. In the GC arm, 1 g/m^2 of GEM and 25 mg/m^2 of cisplatin was infused on days 1 and 8 of a 21-day cycle. In the GS arm, 1 g/m^2 of GEM was infused on days 1 and 8, and S-1 60, 80, or 100 mg/day according to body-surface area was administered from days 1 to 14 of a 21-day cycle. The primary endpoint was OS and the secondary endpoints included progression-free survival (PFS), response rate (RR), adverse events (AEs), clinically relevant AEs predefined as any of grade 2 or more fatigue, appetite loss, nausea, vomiting, oral mucositis, and diarrhea. The sample size was calculated to be 350 with a one-sided alpha of 5%, a power of 80%, non-inferiority margin of 1.155 in terms of hazard ratio (HR). **Results:** From May 2013 to March 2016, 354 patients were enrolled. The non-inferiority of GS to GC was demonstrated (median OS: 13.4 months (m) in GC and 15.1 m in GS, HR 0.95; 90% confidence interval (CI), 0.78 to 1.15; P = 0.046 for non-inferiority). Median PFS was 5.8 m in GC and 6.8 m in GS (HR 0.86, 95% CI, 0.70-1.07). RR was 32.4% in GC and 29.8% in GS. Both treatments were generally well tolerated. Clinically relevant AEs were observed 35.1% in GC and 29.9 % in GS. **Conclusions:** GS demonstrated non-inferiority to GC in OS with good tolerability and was considered as new convenient option of standard of care without hydration for advanced BTC. Clinical trial information: UMIN000010667.

4015 Poster Discussion Session; Displayed in Poster Session (Board #204), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Phase 2 trial of the IDO pathway inhibitor indoximod plus gemcitabine / nab-paclitaxel for the treatment of patients with metastatic pancreas cancer. *First Author: Nathan Bahary, University of Pittsburgh Medical Center Cancer Center Pavilion, Pittsburgh, PA*

Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism that is exploited by tumors to prevent and evade anti-tumor immunity. Inhibitors of the IDO pathway, such as indoximod, are an increasingly validated class of potential cancer therapeutics. The combination of gemcitabine (G) and nab-paclitaxel (N) is a current SOC for metastatic pancreas cancer (MPC). Pre-clinical models have demonstrated synergy between indoximod and chemotherapy. **Methods:** Single arm study with indoximod (1200mg BID continuous) plus G / N (1000mg/m^2 / 125mg/m^2 q week x3 per 4-week cycle). Patients had treatment naïve MPC or 1st line therapy after previous resection and adjuvant therapy. Treatment continued until disease progression or toxicity. Primary endpoint was an improvement in median overall survival (mOS) from a historical 8.5 months for G / N to 12.1 months (hazard ratio (HR) of 0.70). Secondary endpoints included overall response rate (ORR) by site review RECIST 1.1. An expansion cohort enrolled patients undergoing pre and on-treatment (end Cycle 2) tumor biopsies. **Results:** A total of 135 patients initiated treatment in Phase 2 including 36 in the biopsy group. 104 were efficacy evaluable (EE) per the pre-specified definition of completing one cycle of therapy with one on-treatment imaging study. The ORR in the EE was 46.2% (48/104) with 1% CR (1/104) and 45.2% PR (47/104). The mOS in the EE was 10.9 months. Combination was generally well tolerated with fatigue, nausea, and anemia being the most commonly observed adverse events. Immunologic data by immunohistochemistry from biopsy samples (n = 11) indicate responders have increased intra-tumoral CD8 density after 2 cycles of therapy compared to non-responders (p = 0.030). **Conclusions:** EE patients had a mOS of 10.9 months and ORR of 46.2%; responding patients had an increased intra-tumoral CD8 density. The study did not meet the pre-specified primary goal of a 30% reduction in HR. However, the combination demonstrated activity with a promising ORR and immunologic correlation with response. These data support the continued development of combination indoximod immunochemotherapy for MPC. Clinical trial information: NCT02077881.

4016 Poster Discussion Session; Displayed in Poster Session (Board #205), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Effect of anti-CTGF human recombinant monoclonal antibody pamrevlumab on resectability and resection rate when combined with gemcitabine/nab-paclitaxel in phase 1/2 clinical study for the treatment of locally advanced pancreatic cancer patients. *First Author: Vincent J. Picozzi, Virginia Mason Hospital and Medical Center, Seattle, WA*

Background: Pancreatic ductal adenocarcinomas exhibit high degree of desmoplasia with extensive connective tissue growth factor (CTGF) expression and extracellular matrix production. CTGF overexpression is associated with aberrant fibrous tissue in mouse model, in which progression of tissue adhesion was inhibited by pamrevlumab. We hypothesize that pamrevlumab, an anti-CTGF antibody, may influence resectability of locally advanced pancreatic cancer (LAPC) by inhibiting effects of CTGF. **Methods:** Pamrevlumab + gemcitabine/Nab-paclitaxel (G/N) (Arm A) vs G/N (Arm B) was given to treatment-naïve LAPC patients to improve resection rate and overall survival (OS). Patients (N = 37) were randomized 2:1 in Arm A vs Arm B. Patients who completed 6 cycles of treatment underwent resectability assessment per protocol criteria (NCCN, CA 19-9, PET, RECIST) and, if found eligible, underwent resection. No adjuvant therapy was given; second line therapy was administered per investigator discretion. **Results:** In the ITT population, a higher percentage of patients discontinued treatment in Arm B (46.2%) vs Arm A (25%), mainly due to disease progression or adverse events. More patients normalized PET in Arm A (35%) vs Arm B (23%). Thirty percent of patients overall had best objective RECIST response (CR + PR). More patients were eligible for surgery and were resected in Arm A vs Arm B; 70.8% vs 15.4% and 33.3% vs 7.7%, respectively. Improvement in OS was noted in patients eligible for surgery vs not (27.73 vs 18.40 months, p-value = 0.0766) and in patients resected vs not (NE vs 18.56 months, p-value = 0.0141). Progression-free survival showed similar trend (16.39 vs 10.09 months, p-value = 0.1049) and (16.39 vs 10.38 months, p-value = 0.3778), respectively. No increase in serious adverse events or delay in wound healing post-surgery was observed in Arm A vs. Arm B. **Conclusions:** These findings indicate that pamrevlumab may be a valuable addition to neoadjuvant therapy in LAPC without added toxicity. These results warrant a follow-on study in a larger patient population. Clinical trial information: NCT02210559.

4017 Poster Discussion Session; Displayed in Poster Session (Board #206), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Randomized, open label, multicenter, phase II trial of transcatheter arterial chemoembolization (TACE) therapy in combination with sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *First Author: Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kindai University School of Medicine, Osaka, Japan*

Background: There is no proven evidence that combination therapy of TACE with sorafenib (TS group) prolong progression-free survival (PFS) and/or overall survival (OS) compared to TACE alone (T group) in patients with unresectable HCC. **Methods:** In this randomized, open label, multicenter, comparative trial (NCT01217034), patients with unresectable HCC, Child-Pugh score ≤7, ECOG performance status 0-1, no vascular invasion (VI), no extrahepatic spread (EHS), size≤10 cm and number≤10 and adequate organ function were randomized 1:1 (stratification by institution, Milan criteria in or out, and number of previous TACE 0 or 1-2) to T or TS. In TS group, sorafenib 400 mg once daily was pretreated for 2-3 weeks prior to TACE followed by 800mg once daily during on-demand conventional TACE sessions until the time to unTACEable progression (TTUP), which was defined as the time to the date of a state when TACE continuation is not possible due to untreatable tumor progression, deterioration to Child-Pugh C or appearance of VI/EHS. Co-primary endpoints are PFS and OS. Multiplicity is adjusted using a gatekeeping hierarchical testing. PFS event in this trial was defined as death or time to TTUP. Key secondary endpoints were time to progression and safety. PFS is expected to 40% extension from 18 months (control arm) to 25 months, target HR was 0.71, with a power of 0.80. **Results:** The trial was conducted in 33 institutions and a total of 156 patients were randomized to T (n = 76) or TS (n = 80). Median PFS in the T group and TS group was 13.5 and 25.2 months (HR = 0.59, 95%CI 0.41-0.87; p = 0.006), respectively. The number of OS events has not reached. Median TTP was 13.5 and 24.1 months in the T and TS groups (HR = 0.56, 95%CI 0.38-0.83; p = 0.004). Median TTUP was 20.6 and 26.7 months in the T and TS groups (HR = 0.57, 95%CI 0.35-0.92; p = 0.02), respectively. There was no unexpected toxicity. **Conclusions:** Sorafenib in combination with TACE significantly improved PFS over TACE alone in patients with unresectable HCC. Adverse events were consistent with the known safety profile with previous TACE combination trials. Clinical trial information: NCT01217034.

4018 Poster Discussion Session; Displayed in Poster Session (Board #207), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): Global OPTIMIS final analysis. *First Author: Markus Peck-Radosavljevic, Medical University of Vienna/ Klinikum Klagenfurt am Wörthersee, Vienna/Klagenfurt, Austria*

Background: TACE is often used to treat unresectable HCC (uHCC). However, there is no globally accepted consensus on the indication and definition of TACE failure. It is critical to reassess the risk/benefit of continuing TACE after failure as it may delay or prevent pts from receiving subsequent treatments. **Methods:** OPTIMIS, an international, prospective, observational study, enrolled pts with uHCC for whom a decision to treat with TACE was made at study entry. Practice patterns, safety, subsequent treatments, and outcomes data were collected. TACE ineligibility was defined and consistent with international and regional guidelines. Data were analyzed using descriptive statistical methods. **Results:** Overall, 1650 pts received TACE; 529 pts (32%) were BCLC stage C, 118 (7%) had extrahepatic spread, and 123 (7%) had portal vein thrombosis. At inclusion visit, 636 pts (39%) received TACE despite being TACE ineligible according to protocol-specified criteria. After first TACE, the proportion of pts with chronic liver function deterioration (worsening in CTCAE grade 30–90 days post TACE) ranged from 11% to 29% across assessed liver parameters. Complete and partial response rates to first TACE (N=1650) were 14% and 26%, respectively, which decreased by second (10% and 16%; n=1002), third (10% and 15%; n=580), and fourth (8% and 17%; n=338) TACE. Progressive disease rate increased by number of TACE procedures: 18%, 21%, 25%, and 27% for first, second, third, and fourth TACE, respectively. In total, only 507 pts (31%) became TACE ineligible during the study. Of those 507 pts, 47 (9%) received sorafenib at the time of TACE ineligibility and 460 (91%) received sorafenib later or not at all. Considerable imbalances between the 2 cohorts were observed; a propensity score analysis is planned to analyze overall survival from TACE ineligibility. **Conclusions:** These results indicate that real-world TACE use appears to deviate from treatment guidelines. This heterogeneity highlights the need for a globally accepted consensus on the indication and definition of TACE failure. These observations also indicate the importance of monitoring liver function in pts receiving TACE. Clinical trial information: NCT01933945.

4019 Poster Discussion Session; Displayed in Poster Session (Board #208), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase 3 CELESTIAL trial. *First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: C, an inhibitor of MET, VEGFR, and AXL, has previously shown clinical activity in pts with advanced HCC. This phase 3 trial (NCT01908426) evaluated C vs P in previously treated pts with advanced HCC. **Methods:** In this double-blind, global, phase 3 trial, pts were randomized 2:1 to C (60 mg qd) or matched P stratified by etiology, geographic region, and presence of extrahepatic spread and/or macrovascular invasion (EHS/MVI). Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, and ECOG PS ≤1. Pts must have received prior sorafenib, were allowed to receive up to 2 lines of prior systemic therapy for HCC, and must have progressed following at least one. The primary endpoint was overall survival (OS). Secondary endpoints were investigator-assessed progression-free survival (PFS) and objective response rate (ORR) per RECIST 1.1. The study was designed to detect a hazard ratio (HR) for OS of 0.76 (90% power, 2-sided $\alpha = 0.05$) at the final analysis with 2 prespecified interim analyses at 50% and 75% of the planned 621 events. **Results:** As of 1 Jun 2017, 707 pts were randomized, and 484 deaths had occurred (317 out of 470 for C; 167 out of 237 for P). Baseline characteristics were balanced between the arms: median age was 64 years, 82% were male, 38% had HBV, 24% had HCV, 25% enrolled in Asia, 85% had EHS/MVI, and 27% had received 2 prior systemic regimens for advanced HCC. The study met the primary endpoint at the second planned interim analysis with median OS 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049). Median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; $p < 0.0001$), and ORR was 4% vs 0.4% (p = 0.0086). The most common grade 3/4 adverse events (predominantly grade 3) with higher incidence in the C vs P arm included hand-foot skin reaction (17% vs 0%), hypertension (16% vs 2%), increased aspartate aminotransferase (12% vs 7%), fatigue (10% vs 4%), and diarrhea (10% vs 2%). Subgroup analyses of OS and PFS by baseline characteristics will also be presented. **Conclusions:** C significantly improved OS and PFS vs P in previously treated pts with advanced HCC. Adverse events were consistent with the known safety profile of C. Clinical trial information: NCT01908426.

4020 Poster Discussion Session; Displayed in Poster Session (Board #209), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Pembrolizumab (pembro) in patients with advanced hepatocellular carcinoma (HCC): KEYNOTE-224 update. *First Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Initial results from KEYNOTE-224 (NCT02702414), an open label, phase 2 trial showed that pembro, an anti-PD-1 antibody, was active and safe in pts with advanced HCC previously treated with sorafenib. Here we report updated clinical results and biomarker studies. **Methods:** Eligible pts were age ≥18 y with histologically confirmed HCC, radiographic progression on/intolerance to sorafenib and disease not amenable to curative treatment, Child Pugh A, ECOG PS 0-1 and BCLC stage C or B. Pts received pembro 200 mg IV Q3W for 2 y or until disease progression, unacceptable toxicity, withdrawal of consent or investigator decision. Response was assessed every 9 wk. Primary endpoint was ORR (RECIST v1.1, central review). Secondary endpoints were DOR, DCR, PFS, OS and safety. Exploratory endpoint was relationship of PD-L1 IHC combined positive and tumor proportion scores (CPS and TPS; n = 52), and T cell inflamed gene expression profile (GEP; n = 42) with response. Data cutoff date was Nov 24, 2017. **Results:** Of 104 treated pts, 18 remained on therapy. Median age was 68 y (range 43-87), 21.2% were HBV^+, 26% were HCV^+, 94.2% were Child Pugh A, 79.8% had PD on sorafenib and 64.4% had extrahepatic disease. ORR was 16.3% (95% CI, 9.8 to 24.9, n = 17) and similar across differing etiologies; 66% of responders had duration ≥12 mo (Kaplan Meier) and median response duration was not reached (3.1 - 12.5+ mo). Best response was CR in 1 pt (1.0%), PR in 16 (15.4%), SD in 47 (45.2%) and PD in 34 (32.7%); DCR was 61.5%. Median PFS (95% CI) was 4.9 mo (3.4 to 7.0) and OS was 12.9 mo (9.7 to NA). PFS and OS 12 mo rates were 25.4% and 53.6%, respectively. Safety was similar to that observed for pembrolizumab in other indications. Immune-mediated hepatitis occurred in 3 (2.9%) pts; no cases of HBV/HCV flare were seen. Higher PD-L1 CPS in tumor and immune cells was associated with higher ORR and longer PFS, while PD-L1 TPS in tumor cells alone and GEP showed less robust associations with outcomes. **Conclusions:** These results confirm that pembro may be a promising treatment option for pts with advanced HCC. PD-L1 CPS was associated with clinical response to pembro while results for PD-L1 TPS and GEP were less robust; further study is needed to better define these relationships. Clinical trial information: NCT02702414.

4021 Poster Session (Board #210), Sun, 8:00 AM-11:30 AM

Two novel registry-based prediction models for overall survival in patients with metastatic esophageal or gastric cancer. *First Author: Héctor van den Boorn, Academic Medical Center, Amsterdam, Netherlands*

Background: Prediction models for decision-making in oncology are increasingly being used, but few are available for esophagogastric cancer, particularly in the metastatic setting. The aim of this study is to construct prediction models for overall survival in patients with metastatic esophageal or gastric cancer. **Methods:** Data from patients with metastatic esophageal (N = 8670) and gastric (N = 4804) cancer diagnosed in the period 2005-2015 were retrieved from the nationwide Dutch cancer registry. Multivariate Cox regression models, extended with treatment interactions, were created to predict overall survival. Multiple imputations were used to handle missing data. Predictor selection was performed via the Akaike Information Criterion (AIC) and was extended by a Delphi consensus among experts in the field of palliative esophagogastric cancer. Validation was performed with an 11-fold temporal validation. Both the concordance-index (c-index) and calibration were used to assess model quality. **Results:** The Delphi consensus yielded seven important predictors of survival and are shown with the AIC-selected predictors in Table 1. The c-indices show consistent discriminative ability during validation, i.e. 0.71 and 0.68 for respectively the esophageal and gastric cancer models. There is close agreement between predicted and observed survival, with an error of 1.7% and 2.2% for respectively the esophageal and gastric cancer models. **Conclusions:** The models yield fair discrimination and high calibration levels, and provide a good foundation for further investigation in clinical practice to determine their added value in decision-making.

Overview of selected predictors in the esophageal and gastric cancer models (#: selected during Delphi consensus).

Predictor	Esophageal cancer model	Gastric cancer model
Gender	X	X
Age#	X	X
cT-stage	X	X
cN-stage	X	X
Primary tumor location#	X	X
Tumor morphology#	X	X
Number of distant metastatic sites#	X	X
First line treatment type#	X	X
Metastasis only in distant lymph nodes	X	X
Liver metastasis#	X	
Peritoneal metastasis#	X	
Age * First line treatment	X	X
Liver metastasis * first line treatment	X	
Number of distant metastatic sites * First line treatment		X

4022 Poster Session (Board #211), Sun, 8:00 AM-11:30 AM

Oxaliplatin plus capecitabine (XELOX) in the perioperative treatment of locally advanced gastric adenocarcinoma in combination with D2 gastrectomy (NEO-CLASSIC). *First Author: Tianshu Liu, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: This multicenter, open-label study (NEO-CLASSIC) evaluated the efficacy and safety of oxaliplatin and capecitabine (XELOX), plus gastrectomy, in localized resectable gastric cancer. **Methods:** Patients aged 18–75 years with histologically confirmed gastric adenocarcinoma (stage T2–3/N+M0, or T4aN+M0) were given eight cycles of XELOX (four preoperatively, four postoperatively). Each 3-week cycle comprised capecitabine 1000 mg/m^2 twice daily on days 1–14, and oxaliplatin 130 mg/m^2 as an intravenous infusion over 2 hours on day 1. Curative D2 gastrectomy was scheduled 2–4 weeks after the last preoperative cycle. **Results:** Fifty-five patients were enrolled, and one was excluded because of screening failure. R0 resections were achieved in 45 of 54 intent-to-treat patients (83.3%), and four patients received R1 resections. There were no complete responses, 27 (50.0%) partial responses, 24 cases (44.4%) of stable disease, and 3 (5.6%) of progressive disease. The objective response rate was 50.0%. Median follow-up was 31.9 (range 17.4–48.1) months: 29 patients (54.7%) had disease progression, and median progression-free survival was 18.13 (95% confidence interval: 4.70, 31.56) months; median overall survival was not reached. Fifty-four patients completed 209 cycles of preoperative chemotherapy; 42 patients received 133 cycles of postoperative chemotherapy. The rate of grade 3–4 adverse events was 8.5% (29/342 cycles): the most frequent events were neutropenia (9/342 cycles) and leukopenia (4/342 cycles). **Conclusions:** These findings suggest that combination therapy with capecitabine and oxaliplatin as neoadjuvant chemotherapy, followed by D2 gastrectomy, is effective in late-stage, locally advanced gastric cancer. Clinical trial information: NCT01880632.

Clinical response in the intent-to-treat population (n = 54).

Response evaluation[a]	Number of patients	% patients
Objective response rate	27	50.0
Disease control rate	49	90.7
Complete response	0	0.0
Partial response	27	50.0
Stable disease	24	44.4
Progressive disease	3	5.6

[a]Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

4023 Poster Session (Board #212), Sun, 8:00 AM-11:30 AM

Final analysis of single-arm confirmatory study of diagnostic endoscopic resection(ER) plus selective chemoradiotherapy (CRT) for stage I esophageal squamous cell carcinoma (ESCC): JCOG0508. *First Author: Keiko Minashi, Clinical Trial Promotion Department, Chiba Cancer Center, Chiba, Japan*

Background: For clinical stage I submucosal (cT1b-SM) ESCC, surgery is the standard treatment and CRT is optional. We conducted a single-arm confirmatory study of diagnostic ER plus selective CRT for cT1bN0M0 ESCC and reported the 3-year survival at 2016 ASCO Annual Meeting. We will report the final data of survival analysis after 5-year follow-up with a cutoff date of Aug 2017. **Methods:** Clinical stage I ESCC (cSM1-2, N0M0), tumor size ≤ 5 cm and circumference ≤ 3/4 was eligible. After ER, additional treatment was selected based on the histological evaluation: Group A, pT1a with negative resection margin and no lymphovascular invasion (LVI) -no additional treatment; Group B, pT1b with negative resection margin and pT1a with LVI -prophylactic CRT; Group C, pT1b with positive resection margin -definitive CRT. CRT consisted of concurrent 2 courses of chemotherapy (5-fluorouracil and cisplatin with 4-week interval, and radiotherapy of 41.4 Gy/23 fr (Group B) or 50.4Gy/28 fr (Group C). Primary endpoint was 3-year overall survival (OS) of Group B. The sample size was 82 for primary analysis, with one-sided alpha of 0.05 and power of 90%, based on the expected and threshold 3-year OS as 90% and 80%. Final analysis was planned after 5-year follow-up for all pts. **Results:** Between Dec 2006 and July 2012, 177 pts were enrolled from 23 institutions in Japan. 176 pts underwent ER and Group A/B/C were 74/87/15, respectively. The 3- and 5-year OS of Group B was 90.8% (90% CI; 84.1- 94.8) and 89.7% (95% CI; 81.1-94.5). The 3- and 5-year OS of all pts was 92.6% (90% CI; 88.6-95.3) and 90.9% (95% CI; 85.6-94.3). Twenty pts relapsed (Group A; 1 primary, 1 distant LN, Group B; 4 primaries , 8 regional LNs, 2 distant, Group C; 2 regional LNs, 2 distant), 7 pts underwent salvage esophagectomy. Univariable analysis in 83 pts of Group B showed that vascular invasion , one course of chemotherapy, SM2 with LVI had lower progression-free survival. **Conclusions:** Five-year survival data was comparable to that of surgery or CRT for c stage I ESCC. Vascular invasion, one course of chemotherapy, SM2 with LVI may be a risk factor of recurrence for prophylactic CRT after ER. Clinical trial information: UMIN000000553.

4024 Poster Session (Board #213), Sun, 8:00 AM-11:30 AM

Updated report of a randomized phase III trial comparing 4 and 8 courses of S-1 adjuvant chemotherapy for p-stage II gastric cancer: JCOG1104 (OPAS-1). *First Author: Masanori Terashima, Shizuoka Cancer Center, Nagaizumi, Japan*

Background: Postoperative S-1 for 1 year (corresponding to 8 courses) is one of standard adjuvant chemotherapies for p-stage II gastric cancer. We reported 4-courses of S-1 was inferior to 8-courses of S-1 in terms of relapse-free survival (RFS) for p-stage II gastric cancer at the first planned interim analysis (ESMO2017). Here, we report the updated results of this trial. **Methods:** Patients with p-stage II except T1Nany and T3N0 (7th edition of TNM), performance status 0-1, R0 resection were randomized either 8-courses or 4-courses. Primary endpoint was RFS. The total sample size was determined to be 1,000 with a non-inferiority margin of hazard ratio (HR) of 1.37, with one-sided alpha of 5% and power of 80%. **Results:** Between Feb 2012 and Mar 2017, 590 (295 in each arm) patients were enrolled and analyzed. Proportion of patients in treatment of S-1 at 6 months was 76.9% for the 8-courses and was 80.1% for the 4-courses, and that at 12 months was 59.3% in 8-courses. The RFS at 3 years was 89.8% for 4-courses and 93.1% for 8-courses (HR 1.84, 95% CI 0.93-3.63). The overall survival at 3 years was 92.6% for 4-courses and 96.1% for the 8-courses (HR 3.34, 95% CI 1.22-9.12). The cumulative incidence of recurrence at 3 years was 7.7% for the 8-coursesand 5.5% for the 4-courses (HR 1.59, 95% CI 0.75-3.39). For safety analysis, 8 patients who did not receive the protocol treatment were excluded. Adverse events were mild in both arms, but slightly less frequent in the 4-courses arm than in the 8-courses arm. **Conclusions:** The updated primary results confirmed that non-inferiority of 4-courses S-1 were not demonstrated in RFS. S-1 adjuvant chemotherapy for p-stage II gastric cancer should be continued for one year considering the efficacy, acceptable toxicities, and high compliance. Clinical trial information: UMIN000007306.

4025 Poster Session (Board #214), Sun, 8:00 AM-11:30 AM

PD-L1 and IDO1 expression and clinical outcome in 305 patients with surgically resected esophageal cancer. *First Author: Yoshifumi Baba, Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan*

Background: Immunotherapy with the PD-1/PD-L1 inhibitors has produced potent long-lasting antitumor activity in patients with esophageal cancer. However, as responses are observed in only a fraction of patients and treatment responses are sometimes transient, additional strategies to reverse elements of immune suppression imposed by cancer are needed. IDO1 is the primary enzyme that generates immunosuppressive metabolite, and IDO1 inhibitors are being intensively developed and tested in clinical trials for various human cancers. Nonetheless, prognostic and immunological features of PD-L1 and IDO1 expressions remain still unknown in esophageal cancer. **Methods:** Using a non-biased database of 305 curatively resected esophageal cancers, PD-L1 expression, IDO1 expression, CD8 expression, and FOXP3 (a maker of Treg) were evaluated by immunostaining. The term "prognostic marker" is used throughout this article according to the REMARK Guidelines. **Results:** Compared with PD-L1 negative cases (n = 252), PD-L1 positive cases (n = 53) showed significantly worse overall survival [log-rank P = 0.016; hazard ratio (HR): 1.71; 95% confidence interval (CI): 1.08–2.61; P = 0.024; multivariate HR: 1.69; 95% CI: 1.05–2.67; P = 0.033]. The effect of PD-L1 was not significantly modified by any clinical factors ($P > 0.05$ for all interactions). Second, IDO1 expression was significantly correlated with poor overall survival (log-rank P = 0.0041), low CD8 expression (P = 0.044) and high counts of FOXP3 positive cells (P = 0.02). Importantly, a stratification based on PD-L1 expression and IDO1 expression was also significantly associated with overall survival (log rank P = 0.0013); both positive cases experienced unfavorable clinical outcome compared with other cases. **Conclusions:** PD-L1 and IDO1 expressions were associated with clinical outcome in esophageal cancer patients. In addition, the subgroups defined on the basis of PD-L1 and IDO1 status possessed diverse prognostic features. PD-L1 and IDO1 expressions in esophageal cancer may serve as a predictive tissue biomarker and may be used for patient selection in clinical trials of drugs targeting the PD-L1 pathway and IDO1.

4026 Poster Session (Board #215), Sun, 8:00 AM-11:30 AM

Survival outcomes in gastric and gastroesophageal junction adenocarcinoma treated with peri-operative chemotherapy with or without pre-operative radiotherapy. *First Author: Sibo Tian, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Peri-operative chemotherapy (POC) is one approach in treating resectable cancers of the stomach and gastroesophageal junction (GEJ). Pre-operative chemoradiotherapy plus adjuvant chemotherapy (PCRT) is a strategy under investigation with unclear outcomes. We aimed to compare survival between PCRT and POC using a large database. **Methods:** The National Cancer Data Base was queried for patients diagnosed between 2004 -2013 with clinical stage Ib-IIIC (excluding T2N0) adenocarcinoma of the stomach or GEJ. Patients treated with definitive surgery, POC with or without pre-operative radiotherapy of 41-54 Gy were included. Overall survival (OS) was defined from date of definitive surgery to death or last follow-up and estimated using Kaplan-Meier methods; distributions were compared using log-rank tests. 14 patient and treatment variables were used for propensity score matching (PSM). **Results:** 1,048 patients were analyzed: 53.2% received POC and 46.8% PCRT. The primary site was GEJ for 69.1% of cases, and stomach for 30.9% of cases. Median age at diagnosis was 60 years. The number of lymph nodes (LN) sampled were 1-14 for 35.8%, 15-29 LNs for 45.2%, and ≥30 LNs for 16% of patients. 90-day mortality was 1% in both POC and PCRT (p = 0.93). The use of PCRT was associated with a greater pathologic complete response (pCR) rate of 12.9% vs 8.1% (p = 0.01). In the univariate setting POC was associated with superior OS with hazard ratio (HR) 0.83 (POC vs PCRT, p = 0.043). OS was greater in patients who achieved pCR (HR 0.58, p = 0.002), and for gastric primaries (HR 0.76, $p < 0.01$). Treatment group was not significant for OS in the multivariable model (HR 0.83, p = 0.106). Using PSM cohorts, POC was associated with superior OS (HR 0.70, p = 0.015). Median OS was 45.1 vs 31.4 months, 1-year OS was 90.8 vs 84.6%, and 5-year OS 40.7% vs 33.1% (POC vs PCRT). Survival favored POC in both gastric (HR 0.41, p = 0.07) and GEJ subgroups (HR 0.77, p = 0.08). **Conclusions:** The addition of pre-operative radiotherapy to POC does not appear to benefit resectable gastric and GEJ cancers. Until results from the randomized setting on PCRT are known, POC should remain a standard of care.

4027 Poster Session (Board #216), Sun, 8:00 AM-11:30 AM

Racial disparities in surgical management and survival in hispanic patients with potentially resectable esophageal cancer. *First Author: Dave Gupta, Emory University, Atlanta, GA*

Background: Practice patterns for potentially resectable disease are highly variable due to limited objective data to guide optimal management. Expanding on the well-known disparity in mortality among Black and White patients with esophageal cancer, we explored differences in epidemiology, tumor characteristics, surgical resection, and mortality for Hispanic and White patients with locoregional disease. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) registry, we identified 6,250 cases of locoregional esophageal cancer (Stage I-III) occurring in Hispanic (n = 575) or White patients (n = 5675) between ages 18 and 65 (2003-2014). Cases were categorized by age, gender, education, tumor grade, histology, primary tumor site, and surgical status. Postdiagnosis survival was examined over time and compared by race and stratified by surgical status. **Results:** Hispanic patients with locoregional esophageal cancer are significantly less likely to receive surgery than White patients (46% vs 60%; $p < 0.001$), despite having comparable demographics (age, gender, income) and tumor characteristics (grade, histology, and primary site). There was a statistically significant difference in survival, with median OS of 22 months vs 29 months and long-term survival at 8 years of 24% vs 29% (p = 0.01) for Hispanics and Whites respectively. Patients who did not receive surgery had universally poor outcomes, with median OS of 15 vs 12 months and 8-year-survival of 15% vs 13% ($p > 0.10$). Patients treated with surgery had better overall survival with median OS of 40 vs 55 months and 8-year-survival of 35% vs 40% (p = 0.11), despite similar 1-year-survival of 83% vs 85%. **Conclusions:** Hispanic esophageal cancer patients experience higher mortality and use lower rates of potentially curative surgical management compared to White patients. These data support the need to better address patient barriers to surgical treatment and systemic biases present in medical care.

4028 Poster Session (Board #217), Sun, 8:00 AM-11:30 AM

Single-arm confirmatory trial of laparoscopy assisted total or proximal gastrectomy with nodal dissection for clinical stage I gastric cancer: Japan Clinical Oncology Group study JCOG1401. *First Author: Hitoshi Katai, National Cancer Center Hospital, Tokyo, Japan*

Background: Laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer is safe and feasible. Several phase III studies try to confirm non-inferiority of LADG to open surgery for early disease. No prospective study evaluating laparoscopy-assisted total gastrectomy (LATG) and laparoscopy-assisted proximal gastrectomy (LAPG) has been completed yet in terms of both safety and long-term survival. Considering that results of phase III trial to evaluate the long-term outcome of LADG (JCOG0912) would guarantee that of LATG/LAPG, we conducted a single-arm confirmatory trial to evaluate the safety of LATG/LAPG for clinical stage I (T1N0/T1N1/T2N0) proximal gastric cancer. **Methods:** Laparoscopic operators were limited to credentialed surgeons. The extent of nodal dissection was selected based on the Gastric Cancer Treatment Guidelines in Japan. The mini-laparotomy incision was required to be shorter than 6 cm. The primary endpoint was the proportion of a grade 2 (CTCAE ver. 4.0) or greater esophageal anastomotic leak. Sample size was determined to be 245 considering threshold of 8% and expected value of 3% with one-sided alpha error of 2.5% and statistical power of 90%. **Results:** Between April 2015 and February 2017, 245 eligible patients were enrolled. LATG/LAPG was performed in 195/50. Among them, only 6 patients (2.4%) converted to open surgery. Clinical T1N0/T1N1/T2N0 was 213/9/24. Extent of dissection was D1 in 0, D1+ in 230, and D2 in 15. Median operation time was 309 minutes (IQR: 265-350). Median blood loss was 30 ml (IQR: 10-85). Grade 2 or greater esophageal anastomotic leak was 2.4% (6/245; 95% CI, 0.9–5.3; one-sided p = 0.0002). The overall proportion of in-hospital grade 3 or 4 adverse events was 29% (71/245). The proportion of intra-abdominal abscess, anastomotic stricture, and pancreatic fistula was 3.7%, 3.3%, and 2.0%, respectively. There were no treatment-related deaths. **Conclusions:** This trial confirmed the safety of LATG/LAPG. When non-inferiority of LADG is confirmed in our phase III trial, LATG or LAPG will be established as one of the standard treatments for clinical stage I gastric cancer. Clinical trial information: UMIN000017155.

4029 Poster Session (Board #218), Sun, 8:00 AM-11:30 AM

Biomarker study for trastuzumab continuation beyond progression in a randomized phase II trial of weekly paclitaxel±trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum (WJOG7112G). *First Author: Yasutaka Sukawa, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan*

Background: WJOG7112G study, comparing paclitaxel plus trastuzumab (PT; n = 44) with paclitaxel alone (P; n = 45), did not demonstrate survival benefit of trastuzumab continuation beyond progression (TBP) in HER2-positive gastric or gastro-esophageal junction cancer. As a collaborative study, we analyzed biomarkers possibly associating with TBP efficacy. **Methods:** We prospectively collected tumor tissues and serum samples after progression of prior chemotherapy from patients enrolled into the WJOG7112G trial. HER2 status in tumor tissues was examined by immunohistochemitory (IHC) and fluorescent in situ hybridization (FISH). HER2 amplification in serum cell-free DNA (cfHER2amp) was assessed by droplet PCR. Serum level of neuregulin-1 (NRG1), a ligand of HER3 and an activator of HER2 heterodimerization, was measured by ELISA. **Results:** Tumor tissues and serum samples were collected from 18 (P; n = 10, PT; n = 8) and 68 (P; n = 33, PT; n = 35) patients, respectively. IHC 3+, 2+, and FISH positive tumors were 3 (17%), 3 (17%), and 8 (44%), respectively. All IHC 3+ and 2+ tumors were FISH positive except 1 unevaluable tumor. cfHER2amp was positive in 41 (60%) patients (P; n = 21, PT; n = 20). There was no benefit of TBP in progression free survival (PFS) regardless of cfHER2amp (+) and (-) [hazard ratio (HR) 0.93, 95% CI 0.49 - 1.76, and HR 0.81, 95% CI 0.36 - 1.85, respectively]. Serum NRG1 was detectable in 16 (24%) patients, and significantly associated with shorter survival in patients treated with PT (median PFS; 2.6 and 3.8 months, log-rank test p = 0.045, median OS; 7.4 and 10.9 months, p = 0.013). **Conclusions:** Two third of patients lost tumor HER2-positivity after the progression of prior trastuzumab-containing chemotherapy. Serum cfHER2amp was not associated with the efficacy of TBP. NRG1 might be a resistant marker to TBP in HER2 positive gastric or gastro-esophageal cancer. Clinical trial information: UMIN000009297.

4030 Poster Session (Board #219), Sun, 8:00 AM-11:30 AM

Margetuximab (M) plus pembrolizumab (P) in ERBB2-amplified PD-L1+ gastroesophageal adenocarcinoma (GEA) post trastuzumab (T). *First Author: Daniel V.T. Catenacci, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: T + chemo is standard 1st line therapy (tx) for HER2+ GEA patients (pts). However, pts typically progress within 6-8 months, with up to 30% demonstrating loss of HER2 positivity. No HER2 targeted agents have been shown effective in the post-T setting. We report the results of M, a novel anti-HER2 monoclonal antibody + P (anti-PD-1) in HER2+ GEA pts in 2nd line post T progression and describe a biomarker enrichment strategy that compensates for tumor heterogeneity. **Methods:** HER2+ (pre-T testing) PD-L1-unselected GEA pts were enrolled. Endpoints include safety, objective response rate (ORR) by RECIST, and progression free survival (PFS). Exploratory endpoints include *ERBB2* amplification (amp) status pre-M+P tx circulating-tumor DNA (ctDNA) by NGS (Guardant360) and PD-L1 on archival tissue by IHC (22C3 pharmDx). **Results:** As of 1/10/18, 60 pts were dosed in cohort expansion; 30 in North America (NA), 30 in Asia (A). Tx was well tolerated, with 13% of pts having TRAE ≥ grade 3, 3 drug-related SAEs, and 2 cases of autoimmune hepatitis and 1 pneumonitis. *ERBB2* amp was detected by ctDNA in 61% of pts tested, mainly distal gastric cancer (GC) over proximal GEJ pts, and was inversely correlated with acquired driver mutations. PD-L1 was positive in 34% of pts tested, and was independent of clinical metrics but was enriched in ctDNA *ERRB2*+ pts (41% vs. 33%). Of 57 evaluable pts to date in expansion (30 NA and 27 A), best ORR was 16% and disease control rate (DCR) was 54%. Both ctDNA *ERBB2* amp and PD-L1 positivity predicted response (24% vs. 0% [p = .0655] and 36% vs. 5% [p = .0367], respectively). In ctDNA *ERBB2*+/PD-L1+ pts, which were all GC, the ORR was 57% and DCR 86%. **Conclusions:** M+P is a well-tolerated regimen with antitumor activity in 2nd line HER2+ GEA. Consistent with prior tissue-based reports, many GEA pts progressing on T have lost *ERBB2*amp. *ERBB2* status by ctDNA NGS post-T could predict response to M+P, particularly in PD-L1+ pts. Our results suggest that M+P has encouraging preliminary activity in patients with advanced GC, and that biomarker selection based on ctDNA *ERBB2* and PD-L1 could enrich for the responding population. Clinical trial information: NCT02689284.

4031 Poster Session (Board #220), Sun, 8:00 AM-11:30 AM

Safety and efficacy of durvalumab in combination with tremelimumab, durvalumab monotherapy, and tremelimumab monotherapy in patients with advanced gastric cancer. *First Author: Ronan Joseph Kelly, Johns Hopkins Medicine, Baltimore, MD*

Background: The combination of durvalumab (D; anti–PD-L1) and tremelimumab (T; anti–CTLA-4) has the potential to amplify T-cell responses against tumors through immune checkpoint blockade, resulting in antitumor activity. **Methods:** This is an ongoing Phase Ib/II study in patients (pts) with metastatic or recurrent gastric or gastroesophageal junction carcinoma. An initial safety run-in was conducted in 6 pts who received D 20 mg/kg and T 1 mg/kg IV Q4W for 4 cycles followed by D 10 mg/kg Q2W for ≤12 mo. For Phase II expansion, all pts were immunotherapy naive and had progressed after systemic platinum- or fluoropyrimidine-based chemotherapy. Second-line (2L) pts were randomized 2:2:1 to D+T, D 10 mg/kg Q2W up to 12 mo, or T 10 mg/kg Q4W for 7 doses then Q12W for 2 doses. Third-line (3L) pts received D+T. Tumor cell PD-L1 expression was assessed by IHC (Ventana SP263). **Results:** As of Sept 13, 2017, 58 pts received D+T (35% PD-L1 > 1%), 24 pts received D (38% PD-L1 > 1%), and 12 pts received T (50% PD-L1 > 1%); median duration of follow-up was 9.2, 3.5, and 9.2 mo, respectively. Drug-related grade 3/4 adverse events (AEs) occurred in 17 pts (29%) who received D+T; most frequent was colitis (5%). Six (50%) and 4 (17%) pts had grade 3/4 AEs related to T or D alone, respectively. Ten pts (17%) who received D+T discontinued due to drug-related AEs; most frequent was colitis (5%). One pt (4%) with D and 4 pts (33%) with T discontinued due to drug-related AEs. There were no drug-related deaths. In the T cohort, 1 pt (8%) had a confirmed PR; progression-free survival (PFS) and overall survival (OS) rates are not presented due to small sample size. Clinical activity in the other cohorts is shown below. **Conclusions:** D+T has a manageable safety profile in 2L and 3L advanced gastric cancer, with encouraging OS versus D monotherapy. Clinical trial information: NCT02340975.

	2L D+T n = 27	3L D+T n = 25	2L D n = 24
Confirmed + unconfirmed ORR, n (%)	3 (11.1)	3 (12.0)	2 (8.3)
95% CI	2.4–30.2	3.0–36.3	1.5–36.4
DCR—8 wk, n (%)	12 (44.4)	11 (44.0)	3 (12.5)
95% CI	25.5–64.7	24.4–65.1	2.7–32.4
Median PFS (95% CI), mo	1.8 (1.6–3.3)	1.8 (1.6–3.5)	1.6 (1.0–1.8)
Median OS (95% CI), mo	9.2 (4.2–12.8)	10.6 (4.8–17.0)	3.2 (1.7–4.4)

4032 Poster Session (Board #221), Sun, 8:00 AM-11:30 AM

Safety and clinical activity of durvalumab monotherapy in patients with gastroesophageal cancers. *First Author: Antoine Hollebecque, Gustave Roussy Cancer Campus, Villejuif Cedex, France*

Background: PD-(L)1 checkpoint blockade has shown clinical benefits in gastroesophageal (GE) cancers. Durvalumab, a selective, high-affinity, engineered human immunoglobulin G1 anti-PD-(L)1 monoclonal antibody, has demonstrated durable clinical activity and a manageable safety profile in multiple tumor types. Here we present the first report of safety and activity in the GE cohort of the dose-expansion portion of an ongoing Phase I/II, multicenter, open-label study. **Methods:** Patients with histologically or cytologically confirmed GE cancers received durvalumab 10 mg/kg IV Q2W for 12 months or until unacceptable toxicity or disease progression. The primary objective was safety. A secondary objective was antitumor activity (investigator-assessed by RECIST v1.1). **Results:** As of Oct 16, 2017, 51 patients received durvalumab with median follow-up of 41.3 months (range, 1.3–49.2). 98% had received prior treatment, including 69% with ≥2 prior therapies (39% with ≥3 prior therapies). 7.8% completed the 12-month treatment period. Treatment-related adverse events (TRAEs) occurred in 56.9% of patients, most commonly fatigue (35.3%), nausea (13.7%), and diarrhea (13.7%). Grade 3–4 TRAEs were reported in 15.7% of patients (none immune-related), most commonly fatigue (11.8%) and vomiting (3.9%). TRAEs led to dose delays or interruptions in 7.8% of patients. There were no serious TRAEs or TRAEs leading to discontinuation or death. Confirmed overall response rate was 3.9% (2 patients; 1 complete response [CR] and 1 partial response [PR], both of which were ongoing at data cutoff; duration of response 9.7+ to 27.0+ months). Disease control rate 24 (CR + PR + stable disease ≥24 weeks) was 11.8% (95% CI, 4.4–23.9) and median time to response was 3.27 months (95% CI, 2.9–3.6). Median PFS was 1.4 months (95% CI, 1.2–2.4) and the 6-month rate was 9.5%; median overall survival was 4.9 months (95% CI, 2.6–9.1) and the 12-month rate was 31.9%. **Conclusions:** Findings are consistent with earlier reports from this and other studies; durvalumab showed a tolerable safety profile and evidence of antitumor activity in this mostly second line+ cohort of GE cancer patients. Clinical trial information: NCT01693562.

4033 Poster Session (Board #222), Sun, 8:00 AM-11:30 AM

A phase II study of perioperative intraperitoneal paclitaxel plus S-1/paclitaxel for curatively resectable gastric cancer with serosal invasion: The GAPS study. *First Author: Seiji Ito, Aichi Cancer Center Hospital, Aichi, Japan*

Background: The prognosis of gastric cancer with serosal invasion is extremely poor. Despite various perioperative adjuvant therapies, peritoneal recurrence is still difficult to control. Since the clinical efficacy of intraperitoneal (IP) paclitaxel (PTX) was suggested for the treatment of gastric cancer with peritoneal metastasis and positive cytology, IP PTX is a promising strategy for curatively resectable gastric cancer with serosal invasion. This multicenter, phase II study evaluated the efficacy and safety of IP PTX plus S-1/PTX for this target. **Methods:** Eligibility criteria included pathologically confirmed gastric adenocarcinoma with serosal invasion, but no peritoneal or distant metastases. Patients received three courses of preoperative IP PTX plus S-1/PTX (IP PTX 20 mg/m^2, intravenous PTX 50 mg/m^2 on days 1 and 8, and S-1 80 mg/m^2/day on days 1-14, q3 weeks) followed by D2 gastrectomy, and they then received three courses of IP PTX plus intravenous PTX postoperatively. The primary endpoint was the proportion of the completion of protocol treatment (% protocol completion). Secondary endpoints were safety, overall survival, and the response rate (RR). The sample size was calculated to be 50 cases, under the hypothesis of expected % protocol completion of 80% and threshold % protocol completion of 60% with one-sided testing at the 2.5% significance level and power of 80%. **Results:** Between May 2014 and August 2016, 51 patients were enrolled. Among the 51 eligible patients with a median age of 66 years, 41 completed the protocol treatment (80.4% completion; 95% confidence interval 66.9–90.2%, p = 0.0016). During perioperative chemotherapy, grade 3/4 neutropenia occurred in 31.4%, and grade 3/4 non-hematological adverse events occurred in 19.6%. The incidence of adverse events related to surgery was 19.1%. There were no treatment-related deaths. Follow-up for long-term survival is continuing. The clinical RR of preoperative chemotherapy was 71.4% (5/7). The pathological RR (residual tumor $<$ 2/3) was 68.1% (32/47). **Conclusions:** Perioperative IP PTX plus S-1/PTX is a safe and promising treatment for gastric cancer with serosal invasion. Clinical trial information: UMIN000013109.

4034 Poster Session (Board #223), Sun, 8:00 AM-11:30 AM

Lymph node ratio as a clinical determinant for selecting adjuvant chemotherapy regimen in curative D2 resected gastric cancer. *First Author: Jun-Eul Hwang, Department of Hemato-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of (South), Korea*

Background: Adjuvant chemotherapy in gastric cancer improves survival outcomes after curative D2 gastrectomy, especially in stage III. We investigated the clinical prognostic significance and usefulness of lymph node ratio (LNR: ratio between metastatic lymph nodes and examined lymph nodes) for selecting adjuvant chemotherapy regimen in D2 resected stage II/III gastric cancer. **Methods:** We reviewed the data of 741 patients who underwent curative D2 gastrectomy and received adjuvant chemotherapy. 275 patients received platinum-based chemotherapy, and 466 received TS-1 including oral 5-fluorouracil. The disease-free survival (DFS) was evaluated for the influence of LNR on the clinical outcomes, and the patients were categorized initially into 4 groups, according to LNR (0, $>$ 0-0.1, $>$ 0.1-025, $>$ 0.25), then group 0 and $>$ 0-0.1 were merged because of similar DFS of two groups (0-0.1, $>$ 0.1-0.25, $>$ 0.25). **Results:** The patients were well discriminated according to LNR irrespective of the adjuvant chemotherapy regimen and stage. On multivariate analysis, LNR was most potent independent prognostic factor for DFS (hazard ratio 2.589, 95% confidence interval 1.874-3.576, P $<$ 0.001). Platinum-based chemotherapy improved 3-year DFS compared with oral regimen (TS-1+oral 5-fluorouracil) in stage III and LNR $>$ 0.25 (P = 0.026). LNR $>$ 0.1 is the discriminant factor that favor platinum-base adjuvant chemotherapy in patients with combined stage III and lymphovascular invasion positivity (P = 0.037, platinum vs. oral regimen, median DFS: 46.867 vs. 21.767 months). **Conclusions:** The LNR has an important clinical prognostic significance, and the easily identifiable clinical determinant for selecting adjuvant chemotherapy regimen in gastric cancer patients underwent curative D2 resection, especially in stage III gastric cancer.

4035 Poster Session (Board #224), Sun, 8:00 AM-11:30 AM

Oxaliplatin, 5FU and nab-paclitaxel as neoadjuvant regimen in patients with resectable oesogastric adenocarcinoma: A GERCOR phase 2 study (FOXAGAST). *First Author: Sarah Sophie Watson, Institut Mutualiste Montsouris, Paris, France*

Background: Peri-operative chemotherapy is the standard of care in Resectable OesoGastric Adenocarcinoma (ROGA), with several validated regimens such as Cisplatin-5FU, FOLFOX, ECF/X, or FLOT. Nanoparticle-bound (Nab) paclitaxel is active in OGA. Tumor regression grade (TRG) is an objective parameter for assessing efficacy of neoadjuvant chemotherapy (NACT). The study objective was to evaluate TRG with Nab-paclitaxel combined with FOLFOX in ROGA patients (pts). **Methods:** HER2-negative ROGA pts over 18 yrs received Nab-paclitaxel (150mg/m2) and FOLFOX (oxaliplatin 85 mg/m2; 5FU 2400mg/m2 over 48h, and leucovorin 400mg/m2) on D1 q2w for 6 cycles in preoperative setting. 6 postoperative cycles were kept at investigator's discretion. Primary endpoint was pathological complete response rate (TRG1) after NACT. According to Fleming design 49 pts had to be included to test H0 (10% TRG1) and H1 (25% TRG1) with unilateral α of 5% and ß of 10%. To reject H_0, TRG1 had to be achieved in at least 8 pts. **Results:** 49 pts (36 male, median age 63.7 yrs, 53% N+) were included between 6/2015 and 3/2017. Median number of NACT cycles was 6 (range 3-6). Median dose-intensity was 96% (38-103), 97% (47-103) and 99% (50-112) for Nab-paclitaxel, oxaliplatin, and 5FU, respectively. Surgery could not be performed in 5 (10.2%) pts due to tumor progression or poor performance status. Tumor resection was R0 for 42/44 (95.5%) pts. Centrally blinded review classified tumors as TRG1 to TRG5 for 8 (16.3%), 11 (22.5%), 4 (8.2%), 18 (36.7%) and 3 (6.1%) pts, respectively. With a median follow-up of 14.2 m, 12 m-PFS was 88.4 % (95% CI: 74.2-95.0). Grade 3 or worse toxicities in NACT phase were non febrile neutropenia in 10 pts (20.4%), nausea in 4 (8.2%), diarrhea in 4 (8.2%) and neuropathy in 3 (6.1%). 14/44 (31.8%) pts experienced per or post-operative complications, including fistulas (5 pts), ischemic complications (4), infections (3), and anesthesia-related complications (2). 3/44 (6.8%) pts died from surgical complications. **Conclusions:** This regimen shows promising activity in ROGA with a high rate of TRG1/TRG2 responses. Toxicity is manageable but a high rate of surgical complications was observed. Clinical trial information: NCT02486601.

4036 Poster Session (Board #225), Sun, 8:00 AM-11:30 AM

Randomized, double-blind, phase 2 study of S-1 plus oxaliplatin (SOX) with or without ramucirumab (RAM) as first-line therapy followed by paclitaxel plus RAM as second-line therapy in patients with advanced gastric or gastroesophageal junction adenocarcinoma (AGC). *First Author: Kei Muro, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: RAM (a human IgG1 antibody against vascular endothelial growth factor receptor-2) plus paclitaxel has been found to improve overall survival compared with paclitaxel alone as second-line therapy in patients with AGC. This Asian phase 2 study (RAINSTORM) assessed whether adding RAM to SOX as first-line therapy could improve progression-free survival (PFS). **Methods:** Chemotherapy-naive patients with AGC were randomized to receive SOX (S-1: 80-120 mg/day, twice daily, Days 1-14; oxaliplatin: 100 mg/m^2, Day 1) with RAM (8 mg/kg, Days 1, 8) or placebo (PBO; Days 1, 8) in Part A (21-day cycle); patients received paclitaxel (80 mg/m^2, Days 1, 8, 15) and RAM (8 mg/kg, Days 1, 15) in Part B (28-day cycle). PFS (primary endpoint), objective response rate (ORR), disease control rate (DCR), and safety for Part A are reported. The PFS hazard ratio (HR) was estimated using a stratified Cox regression model, with a stratified log-rank test *P*-value of $<$ 0.2 interpreted as RAM+SOX being a useful regimen for first-line therapy in patients with AGC. **Results:** RAM+SOX (n = 96) did not show an improvement in PFS compared with PBO+SOX (n = 93) (median PFS: RAM+SOX, 6.34 months; PBO+SOX, 6.74 months; HR [80% CI]: 1.07 [0.86, 1.33]; *P* = 0.698). Among patients with measurable disease, the ORR was 58.2% and 50.0% (odds ratio [80% CI]: 1.37 [0.84, 2.24]; *P* = 0.402), and the DCR was 90.9% and 87.0% (odds ratio [80% CI]: 1.53 [0.68, 3.43]; *P* = 0.501), in the RAM+SOX (n = 55) and PBO+SOX (n = 54) arms, respectively. The most common treatment-emergent adverse events in both arms were peripheral sensory neuropathy (RAM+SOX: 58.3%; PBO+SOX: 75.3%), decreased appetite (56.3%; 62.4%), and nausea (56.3%; 39.8%). The most common adverse events of special interest in the RAM+SOX arm (vs PBO+SOX arm) were bleeding/hemorrhage events (37.5% vs 23.7%), hypertension (29.2% vs 12.9%), and proteinuria (25.0% vs 15.1%). **Conclusions:** Addition of RAM using a new scheduling regimen (8 mg/kg, Days 1 and 8 every 21 days) to a standard SOX regimen did not improve PFS in patients with AGC. Clinical trial information: NCT02539225.

4037 Poster Session (Board #226), Sun, 8:00 AM-11:30 AM

Psychiatric comorbidities among esophageal cancer survivors in South Korea: A nationwide population-based, longitudinal study. *First Author: Jaesung Heo, Department of Radiation Oncology, Ajou University School of Medicine, Suwon, Korea, Republic of (South)*

Background: Esophageal cancer has a relatively poor prognosis (< 15% overall 5-year survival), owing to a lack of initial symptoms and delayed diagnosis. Also, patients with this fatal cancer tend to have a high rate of mental disorders. The psychological problems can affect treatment compliance and could increase mortality in cancer survivors. **Methods:** The aim of this longitudinal study was to analyze the prevalence of mental disorders in esophageal cancer survivors using claims data in South Korea. We confirmed mental disorders in a nationwide cohort of 8,879 patients who were diagnosed with esophageal cancer between January 1, 2010 and December 31, 2014. We categorized the prevalence of mental disorders based on the age and the time of diagnosis. **Results:** In esophageal cancer, a total of 738 patients were diagnosed with a mental disorder, 1 year prior to the cancer treatment. Of those patients, 231 were diagnosed with depression (31.3%) and 245 with anxiety (33.2%) during their first visit. The overall frequency of mental disorders peaked within 2 months after the cancer treatment. The highest rate of increase after treatment was confirmed in stress reaction/adjustment disorders. Age and sex was a significant predictive factor for mental disorders ($p < 0.05$). Female patients were at a higher risk for mental disorders (hazard ratio: 1.30, $p = 0.002$), whereas patients with initial treatment as surgery were more likely to have mental disorders compared with radiotherapy (hazard ratio: 1.33, $p < 0.001$). **Conclusions:** Mental disorders in esophageal cancer survivors showed different patterns of prevalence depending on the nature of disease. Timely diagnosis and intervention for psychological distress could increase the quality of life for esophageal cancer survivors.

The frequency of mental disorders in esophageal cancer survivors (N = 8,879).

Age	Total number of esophageal cancer	Mental disorder	Substance abuse	Depressive disorder	Anxiety disorder	Stress/ adjustment disorder	Somatoform/ conversion disorder
10-39	25	2	1	1	0	0	0
40-49	367	34	14	7	8	3	2
50-59	2,072	174	51	53	41	9	20
60-69	3,212	285	50	83	91	29	32
70-99	3,203	243	13	87	92	22	29
Total	8,879	738	129	231	232	63	83

4038 Poster Session (Board #227), Sun, 8:00 AM-11:30 AM

Multicenter observational study on re-evaluation of HER2 status in patients with HER2-positive advanced or recurrent gastric cancer refractory to trastuzumab. *First Author: Tomomi Kashiwada, Division of Hematology, Respiratory Medicine and Oncology, Department of Internal Medicine, Faculty of Medicine, Saga University, Saga, Japan*

Background: Addition of trastuzumab to cisplatin and fluoropyrimidine-based doublet chemotherapy is the standard first-line treatment for patients with human epidermal growth factor receptor 2 (HER2)-positive advanced or recurrent gastric cancer. However, second-line anti-HER2 therapy did not demonstrate a survival advantage. We assessed the change in HER2 status in cases of HER2-positive gastric cancer refractory to trastuzumab, and analyzed potential biomarkers associated with resistance to trastuzumab. **Methods:** Key inclusion criteria were as follows; advanced or recurrent gastric adenocarcinoma with HER2-positive status (IHC3+ or IHC2+ with FISH amplification) before trastuzumab treatment; radiologically or clinically diagnosed with progressive disease following trastuzumab treatment; pathologically confirmed adenocarcinoma within 3 months following completion of trastuzumab treatment without receipt of any other anti-tumor agents. We collected biopsy samples from patients who had developed resistance to trastuzumab and evaluated HER2 status before and after. Amplification of EGFR and c-met, as well as PIK3CA mutation were also comparatively analyzed if samples were available. **Results:** Biopsy samples and clinical data were collected from 33 eligible patients as the full analysis set. HER2 loss was identified in 20 patients (60.6%) with refractory disease. IHC showed that HER2 overexpression was remarkably decreased after treatment (pre-HER2 IHC 3+: 24 [72.7%]; 2+: 9 [27.3%] vs. post-HER2 3+: 13 [39.4%]; 2+: 1 [3.0%]; 1+: 18 [54.5%]; 0: 1 [3.0%]). EGFR amplification, c-met amplification, and PIK3CA gene mutation before and after trastuzumab treatment was observed in 7.7% and 4.2%, 15.8% and 6.7%, and 6.3% and 7.1% of cases, respectively. **Conclusions:** HER2 loss occurred in a considerable number of patients who were initially diagnosed with HER2-positive gastric cancer, resulting in resistance to trastuzumab. EGFR, c-met and PIK3CA were rarely associated with acquired resistance. Re-evaluation of HER2 status might provide valuable clues with regard to anti-HER2 targeted therapy beyond disease progression.

4039 Poster Session (Board #228), Sun, 8:00 AM-11:30 AM

Development of non-hematological adverse events in apatinib-treated gastric cancer and their association with clinical outcome: Results from a phase IV study. *First Author: Yi Ba, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: Ahead-G201, a multicenter Phase IV study, is conducting to evaluate apatinib as third-line or beyond therapy in a routine practice setting of gastric cancer patients (pts). **Methods:** This analysis was undertaken to evaluate the non-hematological adverse events (AEs), and to explore their potential associations with survival. **Results:** This analysis was based on 1468 pts as of 12/21/2017. The most common non-hematological AEs were hypertension (HTN; 22.8%), proteinuria (PTN; 18.1%), fatigue (16.7%), diarrhea (11.9%) and hand-foot-skin reaction (HFSR; 9.7%), irrespective of the relationship with medication. They were not correlated with progression free survival (PFS); however, pts with diarrhea or HFSR had a statistically longer overall survival (OS) (8.41 *vs.* 6.14 mos, $p = 0.0048$; 8.31 *vs.* 5.98 mos, $p < 0.0001$) (Table). After adjusting for baseline characteristics and treatment dose, presence of HFSR was an independent predictor for prolonged OS (HR: 0.62 [95%CI, 0.44–0.88]). Besides, we assessed hepatotoxicity and cardiotoxicity in pts. 269 (18.3%) pts who developed hepatotoxicity had a statistically longer PFS (4.70 *vs.* 3.38 mos; $p = 0.0458$). A low incidence of cardiotoxicity (2.1%) was detected, and it was not related to survival. **Conclusions:** Occurrence of HFSR could be an effective prognostic factor for OS in apatinib-treated gastric cancer pts, whereas hepatotoxicity might predict PFS. Clinical trial information: NCT02426034.

Relationship between non-hematological AEs and survival.

		PFS, 95%CI (mos)	OS, 95%CI (mos)
HTN	+	3.25, 2.89–4.63	6.57, 5.49–7.59
	-	4.40, 3.32–4.70	6.51, 5.72–7.29
	p	0.1797	0.7761
PTN	+	4.27, 3.02–4.73	7.23, 6.21–7.85
	-	3.91, 3.09–4.63	6.05, 5.29–6.93
	p	0.9407	0.0849
Fatigue	+	4.07, 3.06–4.73	5.78, 4.93–7.23
	-	4.21, 3.09–4.67	6.67, 5.98–7.69
	p	0.8237	0.1813
Diarrhea	+	4.70, 3.55–5.29	8.41, 7.03–9.36
	-	3.71, 2.99–4.60	6.14, 5.49–6.67
	p	0.0713	0.0048
HFSR	+	4.70, 4.27–5.52	8.31, 6.93–12.75
	-	3.55, 2.99–4.60	5.98, 5.45–6.80
	p	0.1264	< 0.0001
Hepatotoxicity	+	4.70, 4.21–5.78	7.23, 5.78–8.67
	-	3.38, 2.96–4.47	6.08, 5.59–6.83
	p	0.0458	0.1860
Cardiotoxicity	+	5.52, 2.27–9.20	6.57, 4.70–9.20
	-	4.01, 3.15–4.63	6.51, 5.78–7.23
	p	0.3623	0.8523

4040 Poster Session (Board #229), Sun, 8:00 AM-11:30 AM

Role of neoadjuvant chemotherapy or chemoradiotherapy in oesophageal carcinoma. *First Author: Herui Yao, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*

Background: The role of neoadjuvant chemotherapy (NAC) or chemoradiotherapy (NACR) in patients with oesophageal carcinoma continues to be debated. This study aimed to assess the comparative efficacy and safety of NAC or NACR for oesophageal carcinoma. **Methods:** Randomized clinical trials reporting on NAC or NACR with local operable oesophageal carcinoma were identified. The primary endpoint was overall survival (OS). All trial results were combined and analysised using a fixed or random-effects meta-analysis. Quality of evidence was appraised with GRADE criteria. The PROSPERO registry number is CRD42017072242. **Results:** 40 trials with 8,393 patients were included. High-quality evidence indicated that NAC was associated with a significant benefit on OS (hazard ratio [HR] 0.86, 95% CI 0.80 to 0.92; $P = 0.000$) and relapse-free survival (RFS) (HR 0.78, 95% CI 0.72 to 0.84; $P = 0.000$) versus surgery alone, with an absolute difference at 5 years of 10% (6 to 13), and the treatment effect on survival was especially in favor of adenocarcinoma (HR 0.81, 0.72 to 0.91), but no significant difference in squamous-cell carcinoma (SCC) (HR 0.93, 0.81 to 1.08). High-quality evidence revealed that treatment with NACR, as compared with surgery alone, prolonged OS (HR 0.74, 95% CI 0.67 to 0.81; $P = 0.000$) and RFS (HR 0.74, 95% CI 0.65 to 0.84; $P = 0.000$), corresponding to an absolute difference at 5 years of 14% (9 to 20), with similar survival for different histological types of tumor: 0.73 (0.65 to 0.83) for SCC and 0.73 (0.62 to 0.93) for adenocarcinoma. There was moderate-quality evidence that the overall direct and indirect comparison of NACR with NAC showed a survival advantage (HR 0.83, 95% CI 0.73 to 0.94; P = 0.004), with results for SCC (HR 0.74, 0.63 to 0.89) and for adenocarcinoma (HR 0.89, 0.74 to 1.10). **Conclusions:** This study confirmed that a significant clinical benefit is evident for NACR in both adenocarcinomas and SCC of the esophagus, and NAC in patients with adenocarcinoma of the oesophagus. To our knowledge, this is the first evidence-based finding which provided advantage of NACR over NAC in patients with oesophageal carcinoma.

4041 Poster Session (Board #230), Sun, 8:00 AM-11:30 AM

Laparoscopy-assisted versus open D2 distal gastrectomy for advanced gastric cancer: Five year overall survival and morbidity results from a randomized phase II multicenter clinical trial (COACT 1001). *First Author: Young Woo Kim, National Cancer Center, Goyang, Korea, Republic of (South)*

Background: For advanced gastric cancer (AGC), D2 gastrectomy is the standard treatment. However, a laparoscopic D2 gastrectomy(LG) is technically challenging surgery. Our previous report of COACT 1001 study, which is randomized phase II study to evaluate the feasibility of LG compared with open surgery(OG) for AGC, showing primary endpoint of non-compliance of lymph node dissection and three-year disease-free survival supported role of LG for AGC. Herein we report five-year overall and disease-free survival outcome of the study. **Methods:** Patients with cT2-T4a and cN0-2 (AJCC 7th staging system) distal gastric cancer were randomly but not blindingly assigned to LG or OG groups. Patients were followed up for recurrence and survival for 5 years. **Results:** Between Jun 2010 and Oct 2011, 204 patients were enrolled and underwent either LADG (n = 105) or ODG (n = 99). Of those, 196 patients (100 in LADG and 96 in ODG) were included in the intention-to-treat analysis. There were no significant differences in the five-year overall survival between LG and OG groups (85.1% vs 84.1%, respectively; p = 0.749). In the subgroup analysis, five-year overall survival was not different in between the groups according to the clinical stage (stage I: 95.7 % vs 95.5 %; p = 0.988, stage II: 96.1 % vs 84.6 %; p = 0.057, stage III: 48.3 % vs 74.1 %; p = 0.156) and pathological stage (stage I: 97.5 % vs 94.4 %; p = 0.512, stage II: 100 % vs 90.8 %; p = 0.099, stage III: 48.7 % vs 72.7 %; p = 0.151, stage IV: 100 % vs 0 %; p = 0.18). Five-year disease-free survival also was not significantly different between two groups (74.5 % vs 78.7 %, respectively; p = 0.604). The trend of overall and disease-free survival was favorable for LG in stage II but OG in stage III. **Conclusions:** LG was feasible for AGC based on the five-year overall and disease-free survival rate. Further research should be done in large scale for stage III gastric cancer. Clinical trial information: NCT01088204.

4042 Poster Session (Board #231), Sun, 8:00 AM-11:30 AM

International retrospective cohort study of conversion therapy for stage IV gastric cancer 1 (CONVO-GC-1). *First Author: Masanori Terashima, Shizuoka Cancer Center, Nagaizumi, Japan*

Background: In spite of the recent advancement of palliative chemotherapy for stage IV gastric cancer (GC), its median survival time (MST) still remains around 13 to 16 months. Much attention has been paid to conversion therapy, however, its definition, operative indication nor survival benefit has not been demonstrated so far. CONVO-GC-1, a retrospective international cohort study, was designed to investigate the role of conversion surgery in Japan, Korea and China. **Methods:** Conversion therapy of GC was defined as a surgical treatment aiming at an R0 resection after chemotherapy, for tumors that were originally technically and/or oncologically unresectable or marginally resectable. Primary endpoint was the rate of operative complications (Clavien Dindo Grading) and the secondary endpoint was overall survival (OS) according to the 4 category criteria which we have previously published (Gastric Cancer:19; 2016.) (Category 1: resectable metastasis. Category 2: marginally resectable metastasis. Category 3: Macroscopically peritoneal dissemination. Category 4: non-curable metastasis with peritoneal and other organ metastasis.) **Results:** 1902 patients from 55 institutions were enrolled and 1206 patients (category 1: 206, category 2: 583, category 3:300, category 4: 117) were performed surgery after chemotherapy with curative intent. Operative complications were observed in 290 (24.0%) in all grade including pancreatic fistula and SSI etc, which were consistent with other studies (category 1: 19.9%, category 2:29.0%, category 3:18.3%, category 4: 21.4%). The MST of all resected patients were 36.7M (category 1: 42.4 M, category 2: 38.7 M, category 3: 33.4 M, category 4: 34.1 M). The MST of R0 resected patients was 56.6 M (category 1: 49.1 M, category 2: 82.2 M, category 3: 44.9 M, category 4: not reached) and R1 was 25.8 M (category 1: 26.8 M, category 2: 20.3 M, category 3: 30.4 M, category 4: 23.4 M) and R2 was 21.7 M (category 1: 25.0 M, category 2: 22.1 M, category 3: 18.5 M, category 4: 23.5 M), respectively. **Conclusions:** Conversion therapy for stage IV GC is a safe and might be a new therapeutic strategy to improve the survival of the patients, especially with R0 resection. Clinical trial information: UMIN000022321.

4043 Poster Session (Board #232), Sun, 8:00 AM-11:30 AM

Association between *Helicobacter pylori* infection and outcome in advanced gastric cancer patients treated with S-1 adjuvant chemotherapy. *First Author: Satoshi Nishizuka, Iwate Medical University School of Medicine, Morioka, Japan*

Background: The beneficial and deleterious effects of *Helicobacter pylori* (*H. pylori*) infection remain to be fully elucidated. A clear understanding of the infectious mechanism is crucial since the potential effect may result in a survival benefit for life-threatening diseases. To understand the potential beneficial effect in advanced gastric cancer, we analyzed survival for patients treated with surgery-only or adjuvant chemotherapy on the basis of *H. pylori* infection status. **Methods:** A cohort of 491 patients who underwent R0 resection for locally-advanced gastric cancer between 2000 and 2009 at 12 institutions in northern Japan from the Northern Japan Gastric Cancer Consortium was included. *H. pylori* infection status was assessed from paraffin-embedded formalin-fixed samples. Overall survival (OS) and disease-free survival (DFS) in surgery-only (Surgery) and adjuvant chemotherapy (S-1) groups were analyzed. A propensity score matching was employed to correct for confounding factors by indication. To evaluate the local immune response from the immune-evasion status of the tumor, immunostaining of Programmed Death-Ligand 1 (PD-L1) protein was performed with PharmDx antibody clone 22C3. **Results:** *H. pylori* infection was positive in 175 patients and negative in 316 patients. *H. pylori*-positive patients showed significantly better survival than *H. pylori*-negative patients in both OS [hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.42-0.84; $p = 0.003$)] and DFS (HR 0.68, 95% CI 0.49-0.94; $p = 0.018$). There were no significant interactions between *H. pylori* infection status and the clinicopathological background except for S-1 doses in DFS ($p = 0.0482$). Propensity score matching further confirmed that S-1 was virtually only effective when tumors were *H. pylori*-positive. The PD-L1 protein expression pattern suggests that *H. pylori*-positive status confers an advantage that might suppress immune-evasion of tumor cells. **Conclusions:** The favorable outcome of *H. pylori*-positive patients suggests that the host immune system is modulated by *H. pylori* enhancing postoperative chemotherapeutic efficacy (NCT01905969).

4044 Poster Session (Board #233), Sun, 8:00 AM-11:30 AM

Effect of post-discontinuation therapy (PDT) on survival in metastatic gastric-gastroesophageal junction (G-GEJ) adenocarcinoma patients from the RAINFALL trial: An exploratory analysis. *First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The global, randomized, placebo (PL)-controlled phase 3 RAINFALL trial evaluated if addition of ramucirumab (RAM) to first-line (1L) cisplatin plus fluoropyrimidine (chemo) improved survival. Imbalances in PDT (including cross over) could confound OS analysis comparison of 1L therapies. We report the PFS & OS, as previously disclosed at ASCO-GI 2018, and investigated the impact of PDT on survival in a post-hoc analysis. **Methods:** Study blinding was continued until final OS data-lock. Investigators could choose any treatment for PDT. To compare OS from randomization as well as from the start of second-line (2L) treatment (Landmark OS), PDT were categorized into RAM or Non-RAM containing, RAM+paclitaxel(PTX), or All Others. Analyses were stratified by ECOG PS, primary tumor location, disease measurability & geographic region. **Results:** 326 pts were randomized to chemo+RAM (8 mg/kg iv D1, D8, every 21d) & 319 pts to chemo+PL (ITT, *N*= 645). The primary endpoint of investigator-assessed PFS was met (HR, 0.75; 95% CI 0.61–0.94; p = 0.011; median, 5.7 vs 5.4 mo) while no OS benefit was observed (HR, 0.96; 95% CI 0.80–1.16; p = 0.68; median, 11.2 vs 10.7 mo). 150 pts (46%) in the RAM arm received PDT compared to 164 (51%) in the PL arm. Subgroup results are summarized in Table. **Conclusions:** PDT use was balanced in both arms. OS from Randomization and Landmark OS is numerically higher in patients who received RAM containing PDT compared to Non-RAM PDT. Despite the small sample size, the results are consistent with previously demonstrated OS benefit with RAM+PTX as 2L therapy. Clinical trial information: NCT02314117.

Summary of PDT* Results (any subsequent line).

	Median months, (95% CI)	(*n*)	Median months, (95% CI)	(*n*)
	All PDT pts		**All Non-PDT pts**	
OS from Randomization	13.4 (12.8, 15.2)	*314*	7.1 (6.5, 7.8)	*331*
OS from Randomization	**RAM Containing**		**Non-RAM Containing**	
1L RAM	16.2 (11.7, 19.4)	*40*	13.2 (11.9, 16.3)	*110*
1L PL	14.9 (12.6, 18.9)	*53*	13.0 (11.4, 15.0)	*111*
Landmark OS	**RAM + Paclitaxel**		**All Others**	
1L RAM	9.6 (6.0, 14.6)	*37*	6.5 (5.7, 7.9)	*113*
1L PL	8.6 (5.2, 10.9)	*46*	6.8 (5.5, 7.8)	*117*

* = overall, the most frequent PDTs included: PTX, RAM, & irinotecan in both arms

4045 Poster Session (Board #234), Sun, 8:00 AM-11:30 AM

Trastuzumab plus docetaxel and capecitabine for first-line treatment of Her2-positive advanced gastric cancer: A phase II, multi-center, open-label, single-arm study. *First Author: Feng Wang, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Gastric cancer (GC) is one of the most common tumors in China. The ToGA study has shown trastuzumab in combination with fluoropyrimidine plus cisplatin prolonged overall survival (OS) in patients with HER2-positive advanced GC (AGC). Although docetaxel plus capecitabine (DX) is a standard regimen for AGC, combination of trastuzumab plus DX has not been studied. In this study, the efficacy and safety of trastuzumab in combination with DX was evaluated in Chinese patients with HER2-positive advanced GC. **Methods:** This phase II, multi-center, open label, single arm study enrolled patients with HER2-positive metastatic gastric or gastro-esophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. Patients were treated with trastuzumab (8 mg/kg loading dose followed by 6 mg/kg on day 1), capecitabine (1000mg/m^2 twice daily, d1-14) and docetaxel (60mg/m^2 on day1 for 6 cycles), every 3 weeks. Primary endpoint is progression-free survival (PFS) and secondary endpoints are objective response rate (ORR), OS and toxicity profiles. **Results:** 67 patients with AGC were enrolled from 14 centers and 64 patients were in Full Analysis Set (median age 58, 73.4% male, 78.1% ECOG PS 1, 79.7% HER2 IHC 3+, 17.2% GE junction). Until November 2017, among 64 patients, the median PFS was 8.1 months (95 % CI: 5.6-12.8) and the median OS was 20.9 months (95 % CI: 15.1-33). Response was evaluated in 59 patients (5 missing in FAS), five patients achieved CR and thirty-five patients achieved PR, the ORR was 67.8%. In 67 patients who received at least one cycle of treatment, the most common adverse events of grade 3 or above were neutropenia (17.9%), leucopenia (19.4%), hand-foot syndrome (9%), febrile neutropenia (4.5%) and anemia (3%). **Conclusions:** Combination of trastuzumab and docetaxel/capecitabine is a well-tolerated and highly effective regimen in patients with HER2-positive advanced gastric cancer. Clinical trial information: NCT02004769.

4046 Poster Session (Board #235), Sun, 8:00 AM-11:30 AM

Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer: Japan Clinical Oncology Group study (JCOG0501). *First Author: Yoshiaki Iwasaki, Department of Surgery, IMS Tokyo-Katsushika General Hospital, Tokyo, Japan*

Background: Schirous type cancer, such as linitis plastica (type 4) or large (> = 8 cm) ulcero-invasive-type (type 3) gastric cancer (GC) is characterized by poorly differentiated adenocarcinoma including signet-ring cell histologically and by frequent peritoneal dissemination clinically. Based on the promising results in our previous phase II study (JCOG0210) evaluating neoadjuvant chemotherapy (NAC) with S-1 plus cisplatin (CDDP), we proceeded to phase III study to confirm the efficacy of NAC in these subtypes of GC. **Methods:** Eligibility criteria included histologically proven adenocarcinoma of the stomach; clinically resectable gastric cancer of type 4 or large type 3. Patients were randomized to surgery followed by adjuvant chemotherapy (S-1, days 1–28, q42 days for 1 year) (Arm A) or NAC (S-1, 80–120 mg/body, days 1–21 and cisplatin, 60 mg/m2, day 8, q28, 2 courses) followed by gastrectomy plus same adjuvant chemotherapy (Arm B). Primary endpoint was overall survival (OS). A total of 300 eligible patients were required to detect 10% difference in 3-year OS (hazard ratio = 0.74) with a one-sided 5% significance level and power of 80%. OS for the two treatments arms will be compared using a stratified log-rank test. Results: Between February 2007 and July 2013, 300 patients (149 in Arm A, 151 in Arm B) were enrolled. 98 (65.7%) and 112 (74.2%) patients underwent R0 resection in Arms A and B, respectively. Surgery-related death occurred in two in Arm A and one in Arm B. In the Arm B, NAC was completed in 131 patients (86.8%) and Grade 3/4 non-hematological toxicities were seen in 36 patients (22.4%). Pathological response induced by NAC, defined as disappearance of the primary tumor more than one third, was observed in 51.0% (95% CI, 42.7 to 59.2). At the median follow-up of 4.5 years for the 300 patients, the 3-year OS was 62.4% (95% CI, 54.1 to 69.6) in Arm A and 60.9% (52.7 to 68.2) in Arm B. The hazard ratio of Arm B against Arm A was 0.916 (0.679 to 1.236; p = 0.284). OS of both groups were by far better than those reported in the past. The 3-year progression-free survival was 47.7% (95% CI, 39.4 to 55.4) in Arm A and 47.7% (39.5 to 55.4) in Arm B (hazard ratio 0.976, 95% CI 0.738 to 1.292). Conclusions: S-1 adjuvant chemotherapy for 1-year showed remarkable survival results for type 4 or large type 3 gastric cancer and additional NAC with S-1 plus CDDP is not recommended. Clinical trial information: C000000279.

4047 Poster Session (Board #236), Sun, 8:00 AM-11:30 AM

Preliminary result of phase 1/2 study of ramucirumab plus nivolumab in patients with previously treated advanced gastric adenocarcinoma (NivoRam study). *First Author: Daisuke Takahari, Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Nivolumab (Nivo) has a significant survival benefit in salvage line of advanced gastric cancer (AGC) patients (pts) in ATTRACTION-2 trial. Based on synergistic anti-tumor effect induced by simultaneous blockade of PD-1 and VEGFR-2 in preclinical data, phase I/II study was conducted to investigate the safety and efficacy of Nivo plus ramucirumab (Ram) in the 2nd line chemotherapy for AGC. **Methods:** AGC pts with measurable lesions, ECOG PS 0-1, disease progression on 1st line chemotherapy containing platinum were eligible. Pts received Nivo (3mg/kg, Q2W) in combination with Ram (8mg/kg, Q2W) until unacceptable toxicity or disease progression. After feasibility was evaluated in six patients (phase I part), additional 40 patients were enrolled in a phase II part with the primary endpoint of a 6-months progression-free survival rate. Secondary endpoints included overall response rate, disease control rate, overall survival, and safety. PD-L1 tumor expression was assessed by immunohistochemistry (28-8 pharmDx assay) with a cut-off value for PD-L1 positivity set at 1% in tumor cells. **Results:** From 17-Jan-2017 to 31-Dec-2017, 46 AGC pts were enrolled. Patient characteristics were: median age 66 years, male 64%, ECOG PS1 40%, prior gastrectomy 35%, PD-L1 positive rate 44%. There were no dose limiting toxicities observed in phase I part. With median protocol treatment duration of 2.1 months, 40(87%) pts experienced any treatment-related AE (TRAE). Six (13%) pts had grade 3-4 TRAEs: hypertension (4%), hemorrhage (2%), colitis (2%), autoimmune pancreatitis (2%), liver dysfunction (2%), cholangitis (2%), hematoma (2%), and proteinuria (2%). There were no treatment-related deaths. Partial response was obtained in 10 (22%) pts with disease control rate (DCR) of 59%. With median follow-up time of 8.2 months, 20(44%) pts remain on treatment. **Conclusions:** Combination of Nivo and Ram showed no new safety signals and demonstrated promising antitumor activity in previously treated AGC. Clinical trial information: NCT02999295.

4048 Poster Session (Board #237), Sun, 8:00 AM-11:30 AM

Differential response to adjuvant chemotherapy based on Lauren subtype affects clinical outcome of gastric cancer: A cohort study and meta-analysis. *First Author: Kunning WANG, The First Hospital Affiliated to college of Medicine, Xi'an Jiaotong University, Xi'an, China*

Background: There remains significant questions on the efficacy of adjuvant chemotherapy for Lauren subtype of gastric cancer (GC). We aimed to clarify whether intestinal gastric cancer (IGC) patients have improved response to current chemotherapy regimens resulting in better survival when compared to diffuse gastric cancer (DGC) patients after adjuvant chemotherapy. **Methods:** A dataset comprising 8599 GC patients from 23 publications, combined with our cohort, was included in the meta-analysis. **Results:** In our cohort, the overall survival of IGC receiving adjuvant chemotherapy (chemoIGC) (median OS 5·01 years, IQR 2·63-6·71) was significantly higher than that of DGC receiving adjuvant chemotherapy (chemoDGC) (median OS 1·33 years, IQR 0·78-3·33, P = 0·0001). The HR for OS of the chemoIGC compared to chemoDGC was 0·27 (95% CI 0·13-0·52). There was a significant difference of OS between chemoIGC and IGC (HR 0·32, 95% CI 0·16-0·64, P = 0·001) whereas no difference between chemoDGC and DGC (HR 1·26, 95% CI 0·69-2·29, P = 0·46), indicating that IGC patients benefit more from adjuvant chemotherapy than DGC patients. After adjusting for age, gender and stage, adjuvant chemotherapy was an independent risk factor for survival in Lauren subtype of GC (HR for OS of the chemoIGC / chemoDGC 0·33, 95%CI 0·17-0·65, P < 0·001). Importantly, the meta-analysis results of 24 studies consisting of 4050 chemoIGC and 4549 chemoDGC patients indicated that chemoIGC showed significantly improved OS (HR 0·78; 95% CI, 0·72-0·84; P < 0·0001) and PFS (HR 0·80; 95% CI, 0·64-0·99; P = 0·04) comparing to similarly treated patients of chemoDGC. **Conclusions:** Our results support consideration of a change of clinical practice in the decisions related to administration of adjuvant chemotherapy for DGC patients. We found, DGC patients may not attain the same survival or efficacy as IGC from adjuvant chemotherapy. The Lauren subtype may be useful in treatment decisions in GC patients. We contend that Lauren classification and molecular subgroup should be used to stratify treatment regimens to GC patients, with particular relevance to diffuse subtype which is more difficult to treat with current regimens.

4049 Poster Session (Board #238), Sun, 8:00 AM-11:30 AM

Pembrolizumab for patients with previously treated metastatic adenocarcinoma or squamous cell carcinoma of the esophagus: Phase 2 KEYNOTE-180 study. *First Author: Manish A. Shah, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY*

Background: Effective therapy for patients (pts) with metastatic esophageal cancer progressing after at least 2 lines of prior therapy is an unmet need. The phase 2, open-label, KEYNOTE-180 (NCT02559687) study evaluated the activity of pembrolizumab (pembro) in pts with previously treated, advanced/metastatic adenocarcinoma (EAC) or squamous cell carcinoma (ESCC) of the esophagus or Siewert type 1 adenocarcinoma of the gastro-esophageal junction. **Methods:** Eligible pts with metastatic esophageal cancer, ≥2 prior lines of therapy, and tumor samples evaluable for biomarker expression, received pembro 200 mg Q3W for up to 2 years, or until disease progression, unacceptable toxicity, or withdrawal. Tumor response was assessed Q9W (RECISTv1.1, central review). PD-L1+ pts had combined positive score ≥10 using IHC (22C3 antibody). Primary endpoint was objective response rate (ORR). Secondary endpoints included safety, DOR, PFS, and OS. **Results:** Of 121 pts enrolled (Jan 12, 2016 to March 21, 2017), 100 (83%) were male, median age was 65 years (range 33-87), 63 (52%) had ESCC, and 58 (48%) had PD-L1+ tumors. As of September 18, 2017, median duration of follow-up was 5.8 mo (range, 0.2-18.3). ORR (CR+PR) was 10% (95% CI, 5%-17%); 12 (10%) pts had PR, 25 (21%) SD). Median DOR was not reached ([NR] range, 1.9+ mo to 14.4+ mo), and median PFS was 2 mo (95% CI, 1.9-2.1) with 6-mo PFS rate of 16% (95% CI, 10-23). Median OS was 5.8 mo (95% CI, 4.5-7.2) with 12-mo OS rate of 28% (95% CI, 20-37). In ESCC, ORR was 14% (95% CI, 7-25), and in EAC ORR was 5% (95% CI, 1-14). In PD-L1+ pts, ORR was 14% (95% CI, 6-25) and in PD-L1- pts ORR was 6% (95% CI, 2-16). Overall, 15 (12%) pts had treatment-related grade 3-5 AEs. Five (4%) pts discontinued due to a treatment-related AE. There was one treatment-related death from pneumonitis. **Conclusions:** Pembro provided durable clinical benefit with manageable safety for pts with heavily pretreated esophageal cancer. A phase 3 study, KEYNOTE-181 (NCT02564263), to evaluate the activity of pembro versus standard therapy in pts with metastatic esophageal carcinoma progressing after first-line therapy is ongoing. Clinical trial information: NCT02559687.

4050 Poster Session (Board #239), Sun, 8:00 AM-11:30 AM

The nationwide cancer genome screening project in Japan SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced gastric cancer (GC). *First Author: Satoshi Yuki, Department of Gastroenterology and Hepatology, Hokkaido University Hospital, Sapporo, Japan*

Background: We have conducted the Nationwide Cancer Genome Screening Project in Japan since April 2015 using Next Generation Sequencing in advanced non-colorectal gastrointestinal (GI) cancer (aNon-CRC), called as the SCRUM-Japan GI-SCREEN. **Methods:** Patients with aNon-CRC, who plan to or receive chemotherapy were eligible. DNA and RNA were extracted from FFPE tumor samples and were analyzed by the Oncomine Cancer Research Panel (OCP) which allows to detect gene mutation, copy number variant (CNV) and fusions across 143 genes in a CLIA certified CAP accredited laboratory. The detected genomic variant data were classified according to whether genetic drivers of cancer including gain- and loss-of-function or single nucleotide variant based on the Oncomine Knowledgebase. In this presentation, we show the results of advanced gastric cancer (aGC) cohort. **Results:** From April 2015 to March 2017, a total of 696 aGC samples from 20 cancer centers were analyzed. The sequence with the OCP was successfully performed in 513 (73.7%). The frequently detected mutations were *TP53* (47.8%), *PIK3CA* (9.2%), *KRAS* (6.0%), *SMAD4* (5.1%), *APC* (4.1%), *TET2* (3.9%), *ERBB2* (3.3%) and CNVs were *ERBB2* (11.3%), *CCNE1* (11.1%), *KRAS* (3.7%), *FGFR2* (3.3%), *ZNF217* (3.3%), MYC (2.7%), *CCND1* (2.3%) and *CDK6* (2.1%). *FGFR3-TACC3* fusion, *EGFR* vIII, *WIPF2-ERBB2* fusion, and *GOPC-ROS1* fusion were detected in 2, 2, 1, and 1 cases, respectively. Seven patients with druggable genomic alterations were enrolled for clinical trials of targeting therapies. We will show the clinical outcome based on certain key cancer genome alterations. **Conclusions:** This nationwide screening system is efficient to detect rare gene alterations in aGC. This novel knowledge provides an intriguing background to investigate new target approaches and represents a progress toward more precision medicine. This study is still ongoing with newer panel as Oncomine Comprehensive Assay version 3. Clinical trial information: UMIN000016344.

4051 Poster Session (Board #240), Sun, 8:00 AM-11:30 AM

A single-arm confirmatory study of definitive chemoradiotherapy (dCRT) including salvage treatment in patients (pts) with clinical (c) stage II/III esophageal carcinoma (EC) (JCOG0909). *First Author: Yoshinori Ito, Department of Radiation Oncology, Showa University School of Medicine, Tokyo, Japan*

Background: dCRT consisting of 5-fluorouracil (5-FU) and cisplatin (CDDP) with 60 Gy radiotherapy (RT) for cStage II/III EC is a standard treatment for pts refusing surgery (S) in Japan based on the previous trial (JCOG9906). However, poor survival, high incidence of late toxicities, and severe complications of salvage S are problems. We conducted this trial of CRT modifications including salvage treatment to reduce CRT toxicities and facilitate salvage treatment to improve survival. **Methods:** EC pts hoping esophagus preservation as initial treatment, with cStage II/III (UICC 6th, non-T4), PS 0-1, and age 20-75 years were eligible. Chemotherapy (CT) was CDDP (75 mg/m^2 on days 1, 29) and 5-FU (1000 mg/m^2/d on days 1-4, 29-32). RT was administered to a total dose of 50.4 Gy with elective nodal irradiation of 41.4 Gy. Good responders after dCRT received additional 1-2 cycles of CT. For residual or recurrent disease, salvage endoscopic resection (ER) or S was performed based on the prespecified criteria. The primary endpoint was 3-year OS. Key secondary endpoint was salvage treatment related toxicity. The sample size was 95, with one-sided alpha of 5% and power of 80%, expected and threshold 3-year OS as 55% and 42%. **Results:** From 4/2010 to 8/2014, 96 pts were enrolled, two were ineligible and 94 were included in efficacy analysis [M/F, 84/10; Age, median 63 (range 48-75); cStage IIA/IIB/III, 22/38/34]. Two cycles of CT and RT were completed in 93 pts (99%). Complete response was achieved in 55 pts (59%). Salvage ER and S were performed in 5 (5%) and 25 pts (27%). R0 resection of salvage S was achieved in 19 (76%). 3-year OS was 74.2% (90% CI 65.9-80.8%). 3-year progression-free survival and esophagectomy-free survival were 57.0% (95% CI 46.3-66.3%) and 63.6% (95% CI 52.9-72.4%). No complications occurred after salvage ER. Five pts (20%) showed ≥ grade 3 operative morbidities and 1 treatment related death due to bronchus-pulmonary artery fistula occurred after salvage S. Only 9 pts (9.6%) showed grade 3 late toxicities. **Conclusions:** This combined modality treatment of dCRT with salvage treatment could be a new standard treatment for cStage II/III EC. Clinical trial information: UMIN000003534.

4052 Poster Session (Board #241), Sun, 8:00 AM-11:30 AM

Comparison of clinical outcome and safety after minimally invasive esophagectomy: Ivor Lewis versus McKeown—A real-world multicenter observational study from China. *First Author: Yang Liu, Department of Thoracic Surgery,Chinese PLA General Hospital, Beijing, China*

Background: Ivor Lewis (Iv) and McKeown (Mc) are two commonly used minimally invasive esophagectomy. Currently, there are limited data to compare effectiveness and safety between Iv and Mc in China. **Methods:** We conduct the study based on a national collaborative prospective esophageal cancer (EC) database (designed by LinkDoc Technology Co, Ltd.).EC patients who underwent Iv or Mc esophagectomy from Jan.2010 to Jun.2017 and pathologically confirmed stage I~III with middle thoracic and lower thoracic esophagus were enrolled. Log-rank test was used in the comparison of the two surgery groups. And Cox's proportional hazard models and logistic regression were used in the factors analyses. **Results:** Total 1862 patients (1447 males and 415 females) were enrolled, mean age of 61.4.8±7.9. Among the patients, there were 97.2% squamous cell carcinoma, 1% adenocarcinoma and 1.8% others. 667 were performed with Iv esophagectomy and 1195 patients with Mc esophagectomy. Number of lymph nodes examined,mean was 14.4 ±9.02 in Iv group, compared with 21.5±11.57 in Mc group, $p< 0.05$. Recurrence rate was 12.3% in Iv group and 7.6% in Mc group, $p< 0.05$. The 5 years overall survival (OS) was 51% in Iv group and 59% in Mc group, $p< 0.05$. Multivariate analysis showed that risk factors for EC recurrence after esophagectomy include operation type (Iv vs Mc, odds ratio 1.70, CI 1.187-2.430), N stage and T stage, $p< 0.05$. Operation type (Ic vs Mc, HR 1.49, CI 1.153-1.928), N stage and T stage were hazard factors for OS in analysis of multivariate cox's proportional hazard models, $p< 0.05$. Especially, for the subgroup diagnosed as stage T3 at middle thoracic esophagus, Recurrence and OS were significantly different according to surgery type. Median blood loss was 300 mL in Iv group compared with 200 mL in Mc group, $p< 0.05$. Post-operative complications was significantly less in Iv group, $p< 0.05$. **Conclusions:** Our data showed that Mc is preferred with better lymphadenectomy, lower recurrence and improved survival compared with Iv, especially for patients diagnosed as stage T3 at middle thoracic esophagus. And Lv showed significantly less severe post-operative complications than Mc. Clinical trial information: ChiCTR1800014802.

4053 Poster Session (Board #242), Sun, 8:00 AM-11:30 AM

Final results of a phase 3 study of comparing paclitaxel plus 5-fluorouracil versus cisplatin plus 5-fluorouracil in chemoradiotherapy for locally advanced esophageal carcinoma (ESO-Shanghai 1). *First Author: Yun Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Concurrent chemoradiotherapy (CCR) with cisplatin plus 5-Fu (PF) regimen is a standard modality for locally advanced esophageal squamous cell carcinoma (ESCC) patients. This trial aimed to assess the efficacy and safety of the paclitaxel plus 5-Fu (TF) regimen versus PF regimen in CCR for ESCC patients. **Methods:** ESCC patients presenting with stage IIa to IVa were enrolled in a prospective multicenter phase 3 study. Patients were randomized to either TF or PF group. Patients in TF group were treated with 5 cycles of weekly TF (5-Fu 300 mg/m^2, civ 96h plus paclitaxel 50 mg/m^2, d1) in CCR followed by 2 cycles of monthly TF (5-FU 1800 mg/m^2, civ 72h, plus paclitaxel 175 mg/m^2 d1) in consolidation chemotherapy. Patients in PF group were treated with 2 cycles of CCR followed by 2 cycles of consolidation chemotherapy with PF (cisplatin 25 mg/m^2/d, d1-3, plus 5-Fu 1800 mg/m^2, civ 72h, q28d). The radiotherapy dose was 61.2 Gy delivered in 34 fractions. The primary end-point was the 3-yr OS. **Results:** 436 ESCC patients (217 assigned to TF group and 219 assigned to PF group) in 6 centers were recruited between April 2012 and July 2015. Median follow-up of patients who survived was 44.6 months [IQR 29.3–72.0]. The 3-yr OS was 57% in TF group and 51% in PF group (HR 0.91; 95% CI 0.69-1.18; P = 0.46). No significant differences were recorded in 3-yr DPFS or 3-yr LPFS between TF and PF groups (44.3% vs. 45.3% and 48.8% vs. 49.8%, respectively). TF group had a significant higher incidence of acute Grade 3/4 leukopenia (31.3% vs. 18.3%), dermatitis (5.1% vs. 1.4%), and pneumonitis (9.7% vs. 3.2%), and significant lower incidence of anemia (0.5% vs. 3.2%), thrombocytopenia (0.5% vs. 13.7%), fatigue (6.9% vs. 19.6%), anorexia (1.4% vs. 14.6%), nausea (1.4% vs. 14.2%), and vomiting (2.3% vs. 18.3%) than PF group ($P < 0.05$). There were 3 (1.4%) patients in TF group died of acute pneumonitis, 1 (0.5%) patient in TF group and 2 (0.9%) patients in PF group died of delayed pneumonitis. **Conclusions:** TF might be an option used in CCR in ESCC patients with a different type of side effects compared with PF, although it did not significantly prolong OS. Clinical trial information: NCT01591135.

4054 Poster Session (Board #243), Sun, 8:00 AM-11:30 AM

The activity of crizotinib in chemo-refractory MET-amplified esogastric adenocarcinomas: Results from the AcSé-crizotinib program. *First Author: Thomas Aparicio, Department of Gastroenterology, Saint Louis Hospital, Paris, France*

Background: Crizotinib (czb) is only registered for treating ALK and ROS1-translocated lung cancer. However, Czb is also a MET inhibitor. Several malignancies are characterized by MET amplification (amp). Czb activity in MET-amplified (+) tumors was explored within the French National Cancer Institute (INCa) AcSé program. This included access to tumor molecular diagnoses and an exploratory multi-tumor 2-stage design phase II trial. We herein report the results in patients (pts) with esogastric MET+ adenocarcinomas (adenoK). **Methods:** MET expression, on formalin-fixed, paraffin-embedded tumor samples, was screened in 127 centers and analyzed in 28 regional molecular genetic centers. MET+ was evaluated by FISH in tumor samples with IHC scores ≥2+. Pts with tumors showing > 6 MET copies, whatever the MET/CEN7 ratio, were eligible. Pts were treated with czb 250 mg BID. A two-stage Simon design was planned with a 90% power to detect an objective response rate (ORR) at 8 weeks (w) (CR+PR) above 30% against a 10% rate at the 10% level. The disease control rate (DCR) (CR+PR +SD) was assessed at 16 w. Responses were assessed every 8 w by RECIST v1.1. **Results:** From 08/2013 to 12/2017, MET was prospectively analyzed in 546 esogastric adenoK: amp were found in 33/546 adenoK (28/506 gastric and 5/40 esophagus). Eight pts were enrolled in the trial, median age was 62 years [44–80], WHO performance status 0 in 2 pts, 1 in 5 and 2 in 1 pt. At the cut-off date, 1 pt was still treated, 7 had stopped czb (5 PD, 2 adverse events (AEs)). Among the 7 pts evaluable for response at 8 w, we observed 3 PR and 1 SD, giving an ORR = 42.8% [6.1-79.4]. At 16 w, DCR = 50% [95% CI: 10-90] was achieved in 3/6 evaluable pts. Czb was well tolerated with only 6 grade ≥3 AEs or SAEs. The most common AEs, mainly grade 1, were anemia (87.5%), nausea (75%), hypocalcemia-edema-ASAT increase (62.5% for each), vomiting-constipation-fatigue-loss of appetite-visual disorders (50% for each). **Conclusions:** National biomarker-driven access to czb for MET+ esogastric adenoK pts is feasible. MET amp was observed in around 5% of gastric adenoK and 12% of the oesophagus adenoK. Preliminary results show Czb activity, with PR and SD, in MET+ esogastric adenoK. Clinical trial information: NCT02034981.

4055 Poster Session (Board #244), Sun, 8:00 AM-11:30 AM

PET scan-directed chemoradiation (CRT) for esophageal squamous cell carcinoma (ESCC): No benefit for salvage chemo in PET non-responders (PETnr). *First Author: Megan Greally, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pre-operative or definitive CRT is standard for locally advanced (LA) ESCC. We previously showed that PET response after induction chemo and prior to CRT and surgery strongly predicts outcomes (Cancer 118:2820; 2012). The CALGB 80803 study also revealed a benefit for changing chemo during CRT in PETnr with E adenocarcinoma (J Clin Oncol 35:1, 2017 [abstr]). **Methods:** We retrospectively reviewed all pts with LA ESCC who received induction chemo and CRT; all had PET scan pre- and post-induction chemo. Survival was calculated from date of repeat PET using Kaplan-Meier analysis and compared between groups using the log-rank test. **Results:** 113 pts were identified, median age 64, median KPS 80%, 75% had uN+ disease. 63 (56%) received induction chemo with platinum/paclitaxel, 43 (38%) with platinum/irinotecan, 6 (5%) with docetaxel/irinotecan +/- cisplatin and 1(1%) with capecitabine/oxaliplatin. 72 pts (64%) were PET responders (PETr; ³35% decrease in mSUV of tumor) and 41 (36%) were PETnr; <35% decrease). All PETr received same chemo during RT. Of PETnr, 16 continued same chemo and 25 were changed to alternate chemo during RT. Of 106 pts evaluable for clinical complete response (cCR), 88% of PETr achieved cCR vs 57% of PETnr/no chemo change vs 60% of PETnr/chemo change ($p<0.01$ for PETr vs PETnr). The cCR rate was not significantly different in the PETnr/chemo change vs PETnr/no chemo change groups (p=0.86). 31 pts had resection, 30 R0; 8 had pathologic CR (7 were PETr and 1 was a PETnr/chemo change). Median progression-free (PFS; 62.1 vs. 7.1 mos, $p<0.01$) and overall survival (OS; 72.2 vs. 17.3 mos, $p<0.01$) were significantly better for PETr vs. PETnr. Median PFS and OS for PETnr/chemo change vs. PETnr/no chemo change were 6.4 vs 8.3 mos (p=0.48) and 14.2 vs 17.2 mos (p=0.79) respectively and not significantly different. **Conclusions:** PET scan after induction chemo highly predicts for outcomes in ESCC pts who received CRT. However, PETnr pts did not benefit from changing chemo during RT, likely reflecting underlying poor biology. Next generation sequencing is ongoing. Future trials should utilize PET after induction chemo to select PETnr pts to receive experimental therapies.

4056 Poster Session (Board #245), Sun, 8:00 AM-11:30 AM

Tumor mutation burden (TMB) and immune-related adverse events (irAEs) compared to antibiotic (abx) use to predict for response to immune checkpoint inhibitors in esophagogastric cancer (EGC). *First Author: Megan Greally, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune checkpoint inhibitors (nivolumab and pembrolizumab) have clear activity in EGC. However, benefit is modest in an unselected population. TMB may be of value as a quantitive marker to identify patients (pts) with durable benefit from immunotherapy (Cancer Discov 2018 Jan;8(1): 49-58). We present updated data from an expanded cohort, including irAEs and abx use as determinants of pt outcomes. **Methods:** All pts treated with anti-CTLA-4, PD-1 or PD-L1 Abs were identified. Outcomes were correlated with TMB by MSK-IMPACT NGS panel of up to 468 genes and clinical variables, including irAEs and abx use. The third quartile of TMB was used as the cut-off. Progression-free (PFS) and overall survival (OS) were calculated from the start of immunotherapy. **Results:** Of 120 pts (110 adenoCs, 10 SCC), 90% had received ≥2 prior chemo regimens, 6 received ≥2 IO regimens. 66 (55%), 17 (14%) and 37 (31%) pts respectively received anti-PD-1, anti PD-L1 and anti-CTLA-4 plus anti-PD-1/PD-L1 Abs. The median PFS and OS were 1.8 and 5.9 mos; 2-yr OS 19%; objective response rate of 13% (n = 15, 7 PRs, 8 CRs). In IMPACT tested tumors, excluding low purity samples (n = 62), a TMB cut-off of ≥7.4 mut/Mb stratified TMB-low vs -high pts (46 vs 16), with a trend toward improved OS in the TMB-high group (27.1 vs 8.4 mos, p = 0.063). 7 of 7 dMMR pts were TMB-high. In 41 pts (34%) treated with abx during immunotherapy (and 1 month prior), there was a significant improvement in PFS (3.3 vs 1.6 mos, p = 0.04) vs those who were not; with no difference in OS (7.3 vs 4.7 mos, p = 0.23). irAEs occurred in 36 pts (30%) and were associated with improved OS (18.2 vs 3.7 mos, $p < 0.0001$), irrespective of AE grade. OS (12.7 vs 4.2 mos, p = 0.034) was improved even in pts where irAEs occurred ≤8 weeks from start of immunotherapy. The median PFS and OS in 36 pts (30%) who received chemo following progression were 4.3 and 7.7 mos. **Conclusions:** A TMB of 7.4 may serve as a cut-off to identify EGC pts more likely to benefit from immunotherapy. Abx use did not negatively impact outcomes and occurrence of irAEs was associated with improved OS. Outcomes for post-immunotherapy chemo appear promising in these heavily treated pts.

4057 Poster Session (Board #246), Sun, 8:00 AM-11:30 AM

Feasibility study of trastuzumab (T) and pertuzumab (P) added to neoadjuvant chemoradiotherapy (nCRT) in resectable HER2+ esophageal adenocarcinoma (EAC) patients (pts): The TRAP study. *First Author: Sandor Schokker, Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*

Background: Around 15% of EACs are HER2+ and treatment with T is effective in metastatic EAC. Given the success of dual neoadjuvant HER2 targeted therapy with P and T in breast cancer, we performed a phase 1B feasibility study of nCRT combined with P and T. **Methods:** HER2-positive pts (IHC 3+, or 2+ with ISH+) with resectable EAC received nCRT with carboplatin and paclitaxel (CROSS regimen), combined with 840 mg P q3w, and T in a loading dose of 4 mg/kg, followed by 2 mg/kg qw for 5 weeks (wks) and 6 mg/kg in wks 7, 10 and 13. Peak and trough serum samples were collected throughout treatment for pharmacokinetics (PK) and shed HER2 (sHER2). Cardiac safety was assessed with pre- and posttreatment MUGA scans. Primary endpoint was feasibility, defined as ≥80% completion of treatment with P and T, for which 40 pts had to be included. **Results:** We enrolled 40 pts (78% males, median age 63) of which 83% completed treatment with P and T. Reasons for non-completion were logistics (n = 3), pt request (n = 3) and death of pulmonary fibrosis during treatment (n = 1). Toxicity was similar to conventional nCRT except for rash (28%) and diarrhea grade 3 (20% of pts). Transient LVEF < 50% or decreases of ≥10% occurred in n = 4 (3 asymptomatic) without delay of surgery or cardiopulmonary complications. One pt had interval metastases preoperatively; 38 pts were operated. No unforeseen complications were reported. Thirteen pts (33%) had a pathological complete response (pCR, Mandard 1). Mandard 2, 3, 4 and 5 was seen in 8, 11, 3 and 3 pts, respectively. One year progression free survival (PFS) and overall survival (OS) were 85% and 90% (median follow up 19.4 months). PK of P was similar to prior reports in metastatic gastric cancer (all trough levels > 20 μg/ml). Median baseline sHER2 was 11.9 μg/ml; levels decreased in wk 4 (median 6.7 μg/ml) to return to baseline in wk 13 (median 10.9 μg/ml). **Conclusions:** Addition of P and T to nCRT in EAC pts is feasible and has limited additional toxicity. It shows a high pCR of 33% compared to 23% after conventional nCRT and a promising 1 year PFS and OS of 85% and 90% compared to 72% and 80% after conventional nCRT, respectively. Further biomarker research is ongoing. Clinical trial information: NCT02120911.

4058 Poster Session (Board #247), Sun, 8:00 AM-11:30 AM

Laparoscopic versus open surgery for advanced gastric cancer. *First Author: Guoxin Li, Nanfang Hospital/ Southern Medical University, Guangzhou, China*

Background: Laparoscopic distal gastrectomy for early gastric cancer is widely accepted with superiority to conventional open surgery. However, oncologic validation for advanced gastric cancer is still being debated. We conducted a multi-center, randomized, controlled trial to compare 3-year disease-free survival (DFS) rates after laparoscopic distal gastrectomy with D2 lymphadenectomy and open surgery for advanced gastric cancer. **Methods:** Between September 2012 and December 2014, we randomly assigned 1056 patients with clinical stage T2, T3, or T4a gastric cancer, without bulky nodes or distant metastases to undergo either laparoscopic or open distal gastrectomy with D2 node dissection in a 1:1 ratio. The primary end point was 3-year DFS rate. **Results:** At 3 years, the DFS rate were 76.5% in the laparoscopic group and 77.8% in the open group; the hazard ratio (HR) for recurrence was 1.069. The 3-year overall survival rates were similar in the two groups (83.1% in the laparoscopic group and 85.2% in the open group; HR for death, 1.162). The clinical recurrence types were comparable between two groups (P = 0.213). **Conclusions:** The long-term oncological outcomes of laparoscopic distal gastrectomy with D2 lymphadenectomy were non-inferior to those of the conventional open surgery for the patients with advanced gastric cancer. (CLASS-01 trial) Clinical trial information: NCT01609309.

4059 Poster Session (Board #248), Sun, 8:00 AM-11:30 AM

Capecitabine plus oxaliplatin versus capecitabine plus oxaliplatin with concurrent radiotherapy in the treatment of gastric cancer after D2 gastrectomy. *First Author: Congying Xie, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China*

Background: The role of adjuvant chemoradiotherapy (CRT) in the treatment of gastric cancer patients after D2 resection has not been defined yet. This trial was designed to compare capecitabine plus oxaliplatin (XELOX) versus XELOX combined with concurrent CRT in the treatment of gastric cancer patients after D2 gastrectomy. **Methods:** Patients with histologically confirmed gastric cancer with T3-4/N1-3 after D2 gastrectomy were enrolled and randomly assigned to XELOX for 6 cycles (CT arm) or 2 cycles XELOX plus 45 Gy radiotherapy (RT) with capecitabine concurrently, and then followed by another 4 cycles of XELOX after RT (CRT arm). The primary end point was 3-year disease-free survival (DFS), and the secondary end point was 3-year overall survival (OS). **Results:** From January 2013 to June 2017, a total of 144 Patients were protocol eligible with 74 assigned to the CT arm and 70 to the CRT arm, respectively. With a median follow up of 25.6 months, the 3-year DFS and OS rates were 76.3% and 79.6% in the CT arm, versus 72.8% and 70.9% in the CRT arm, respectively. The addition of RT did not show significant differences on the DFS (P = 0.868) and OS (P = 0.683). The rate of local recurrence-free survival and distant metastasis at 3 years were 98.5% vs. 91.7% (p = 0.281) and 18.7% vs. 18.1% (p = 0.606) for the CT and CRT arms, respectively. For patients with positive lymph nodes (84.5%), the 3-year DFS rate was 70.7% and 71.1% in the CT and CRT arms, respectively. The DFS was a bit shorter in the CT arm than in the CRT arm but without statistical difference (p = 0.920). Common grade 3/4 AEs with chemotherapy and RT were leukopenia, neutropenia, thrombocytopenia. All patients finished at least 4 cycles of XELOX with 82.1% and 75.5% patients in the CT and CRT arms finished 5 cycles of chemotherapy. **Conclusions:** No significant benefits on DFS and OS of CRT observed in the treatment of gastric cancer after D2 gastrectomy. Addition of RT did not show significant on lowering the risk of local recurrence for gastric cancer patients. Adjuvant CRT needs further investigation with larger populations for gastric cancers patients after D2 gastrectomy. Clinical trial information: NCT01711242.

4060 Poster Session (Board #249), Sun, 8:00 AM-11:30 AM

Quality of life in the CRITICS study, a multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer. *First Author: Romy Van Amelsfoort, The Netherlands Cancer Institute Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Patient-reported outcome is an important objective in clinical trials, as it addresses the impact of the disease and treatment on health-related quality of life (HRQOL). In the multicenter randomized phase III CRITICS study no significant difference in overall survival was found between postoperative chemotherapy and chemoradiotherapy after neo-adjuvant chemotherapy and D2 surgery (5-year OS 42% vs 40%). The CRITICS study investigated health-related quality of life in both treatment groups as one of the secondary objectives. **Methods:** Patient-reported outcome questionnaires were completed at baseline, after preoperative chemotherapy, after surgery, after postoperative chemotherapy (CT) or chemoradiotherapy (CRT) and during follow-up at 12 months after the end of postoperative treatment for 788 patients with adenocarcinoma of the stomach. Cancer-related quality of life was assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). A QLQ-C30 summary score at each time point was calculated as the mean of the combined 13 QLQ-C30 scale scores (max score 100; financial impact and global quality of life scale scores excluded). Linear mixed-modeling was applied to assess differences in the QLQ-C30 summary score between the CT and CRT group, accounting for missing values during follow-up. **Results:** 645 patients out of the 788 patients had at least one evaluable questionnaire. The number of evaluable questionnaires was comparable between the CT and CRT groups. Evolution of QLQ-C30 summary scores over time was non-linear with baseline scores of 86 vs 84, lowest scores after surgery of 77 vs 75 and recovery of the scores to 83 vs 80 after 12 months of follow-up. No significant differences in QLQ-C30 summary scores over time were observed between the CT and CRT group (p = 0.567). **Conclusions:** In the CRITICS study HRQOL summary scores showed no differences over time between the CT and the CRT group. Besides HRQOL, pathological T- and N-stage, resection margin status and histological type contribute to the optimal choice of treatment. Clinical trial information: NCT00407186.

4061 Poster Session (Board #250), Sun, 8:00 AM-11:30 AM

Selumetinib plus docetaxel as second-line chemotherapy in KRAS mutant, KRAS amplified or MEK signatured gastric cancer patients: First arm of the umbrella trial in GC though the molecular screening, VIKTORY trial. *First Author: Jeeyun Lee, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)*

Background: This trial was a phase II study with selumetinib (AZD6244)/ docetaxel as second-line treatment for metastatic GC patients with MEK signature or RAS gene alterations as part of the GC umbrella trial, guided through the molecular screening, the VIKTORY trial (NCT#02299648). **Methods:** Selumetinib was administered orally 75mg twice a day continuously. Docetaxel was administered as an IV infusion over 1 hour at 60 mg/m2 every 3 week of a 21 days schedule. The primary objective was to investigate response rate (RR) and secondary objectives were to perform pre-planned analysis using ctDNA and tumors to identify an optimal biomarker for selumetinib. **Results:** Twenty seven patients who were identified through the VIKTORY screening to harbor KRAS mutation, KRAS amplification or MEK signature were enrolled onto the study. Of 27 patients, 12 patients had GC harboring KRAS mutation and two KRAS amplification. The remaining 13 patients were KRAS wild type with either low MEK signature (N = 7) or high MEK signature (N = 6). Only one of 12 KRAS mutant GC had high MEK signature. Of 25 patients who received the study drug, there were 7 partial responses (PRs), 8 stable diseases (SDs), 6 progressive diseases (PDs) and 4 non-evaluable diseases. The overall RR for the study combination was 28.0% (95 CI, 0.12 – 0.49). The most commonly observed any grade adverse events (AEs) were skin rash (7.4%) but no grade 3 or 4 skin rash. The second common AE was diarrhea (5.5%) which was all grade 1/2. In biomarker analysis, the two patients with had typical KRAS mutation (G12) or KRAS amplification with high MEKsignature achieved a PR from selumetinib/docetaxel . However, three with atypical KRAS mutation (i.e. A146P, Q61R, Q61H) with low/intermediate MEK signature showed PD to the combination therapy. **Conclusions:** Selumetinib plus docetaxel as 2nd line therapy revealed the useful efficacy and tolerable safety in GC patients with MEK signature or RAS gene alterations. Especially, the specific subset of patients with had typical KRAS mutation or KRAS amplification with high MEK signature were likely to benefit from selumetinib/docetaxel. Clinical trial information: NCT02448290.

4062 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

Pembrolizumab (pembro) vs paclitaxel (PTX) for previously treated advanced gastric or gastroesophageal junction (G/GEJ) cancer: Phase 3 KEYNOTE-061 trial. *First Author: Charles S. Fuchs, Smilow Cancer Hospital, Yale New Haven Health, New Haven, CT*

Background: Pembro has shown promising antitumor activity in patients (pts) with pretreated G/GEJ cancer. KEYNOTE-061 (NCT02370498) was a global phase 3 study of pembro vs PTX for previously treated advanced G/GEJ adenocarcinoma that progressed after first-line chemo containing platinum and fluoropyrimidine. **Methods:** Eligible pts were randomized to pembro 200 mg Q3W or standard-dose PTX. Randomization was stratified by geographic region, TTP on first-line therapy, and PD-L1 combined positive score (CPS). Primary end points were OS (efficacy boundary, one-sided $P = .0135$) and PFS in the CPS ≥ 1 population. **Results:** 395/592 pts enrolled had PD-L1 CPS ≥ 1: 196 assigned to pembro, 199 to PTX. After median follow-up of 8 mo, 7.8% of pts completed or remained on pembro vs 0% on PTX. Median OS was 9.1 mo with pembro vs 8.3 mo with PTX (HR 0.82, one-sided $P = .042$) (Table). 12-mo OS rates were 39.8% vs 27.1%; 18-mo rates were 25.7% vs 14.8%. There was no difference in PFS or ORR, but pembro responses were more durable (Table). Pembro treatment effect was more evident in pts with ECOG PS 0 (HR 0.69; 95% CI 0.49-0.97) or GEJ tumors (HR 0.61; 95% CI 0.41-0.90). In post-hoc analysis, the pembro treatment effect for OS was greater for CPS ≥ 5 (HR 0.73; 95% CI 0.52-1.03) and ≥ 10 (HR 0.64; 95% CI 0.41-1.02). In all pts, grade 3-5 drug-related AE incidence was 14.3% with pembro vs 34.8% with PTX; 3.1% vs 5.4% discontinued due to drug-related AEs. **Conclusions:** Pembro reduced the risk of death by 18% vs PTX in pts with previously treated G/GEJ cancer and PD-L1 CPS ≥ 1, although this difference was not statistically significant. Pembro had a better safety profile than PTX. Pembro treatment effect was more evident in pts with ECOG PS 0 and with increasing PD-L1 expression. Trials of pembro in G/GEJ cancer are ongoing. Clinical trial information: NCT02370498.

	Pembro N = 196		PTX N = 199
OS			
Median (95% CI), mo	9.1 (6.2-10.7)		8.3 (7.6-9.0)
HR (95% CI)		0.82 (0.66-1.03)	
P		.042	
PFS[a]			
Median (95% CI), mo	1.5 (1.4-2.0)		4.1 (3.1-4.2)
HR (95% CI)		1.27 (1.03-1.57)	
P		.98	
ORR,[a] % (95% CI)	15.8 (11.0-21.7)		13.6 (9.1-19.1)
DOR,[a] median (range)	18.0 (1.4+ to 26.0+)		5.2 (1.3+ to 16.8)
≥12 mo, %	59.5		29.5

[a]Assessed per RECIST v1.1 by blinded, independent central review.

4063 Poster Session (Board #252), Sun, 8:00 AM-11:30 AM

Co-existing alterations in cell-cycle pathway genes and impact on benefit from trastuzumab in advanced esophagogastric cancers (EGC): Analysis of 527 *Her2*-amplified cases. *First Author: Joseph Chao, City of Hope, Duarte, CA*

Background: The addition of targeted therapies, including trastuzumab, has resulted in limited benefit in EGC. The response rate for trastuzumab in combination with chemotherapy is under 50% in Her2 amplified EGC, reflecting a molecularly heterogeneous disease. The genomic context of Her2 amplification may impact trastuzumab responsiveness. **Methods:** We analyzed clinical samples from EGC patients using hybrid-capture based comprehensive genomic profiling (CGP). Pre-specified literature review was used to determine genomic alterations (GA) associated with de-novo trastuzumab resistance. Clinicopathologic features and outcomes data were abstracted, and descriptive statistics used to examine relationships between GA and outcomes. **Results:** From 2,245 GEJ adenocarcinomas and 1,883 gastric adenocarcinomas (GC) we identified 395 *Her2*-amplified GEJ (18%) and 132 *Her2*-amplified (Her2amp) GC (7.0%) cases. Median *Her2* copy number was 19 in GEJ and 16 in GC samples. *PIK3CA* GA and *MET* amp were observed in ~9% and ~5% of both *Her2*amp and non- *Her2*amp EGC cases; however, co-amplification of cell-cycle mediators *CDK6* and *CCCNE1* were enriched in *Her2*amp cases (Table). *MYC* amp and deleterious *SMAD4* GA were enriched in cases with *Her2*amp. In cases with > 100 estimated *Her2* copies, *PIK3CA* GA were significantly less frequent than cases with 6-99 copies (2.3% vs. 9.8%, P = 0.04). All *Her2*amp cases were microsatellite stable. A clinically annotated *Her2*amp cohort will be presented. **Conclusions:** GA predicted to decrease trastuzumab sensitivity exist in a significant portion of *Her2*amp EGC, although not all are enriched relative to non-*Her2*amp cases. Baseline tumoral heterogeneity and genomic context are anticipated to modify outcome and prospective stratification will be important to optimize therapies.

	Her2 Amp			Non-*Her2*amp	
	All cases (n = 527)	GEJ (n = 395)	GC (n = 132)	All cases (n = 3,601)	*P* value (All cases)
***PIK3CA* GA**	8.5%	9.1%	6.8%	9.5%	0.52
***CDK6* amp**	11%	9.6%	14%	6.8%	0.002
***CCNE1* amp**	19%	20%	17%	7.1%	< 0.001
***CCND1* amp**	5.3%	5.8%	3.8%	7.7%	0.07
***MET* amp**	3.8%	3.3%	5.3%	4.7%	0.39
***MYC* amp**	16%	15%	17%	9.8%	< 0.001
CDKN2A* GA	22%	25%	14%	19%	0.21
SMAD4* GA	9.7%	10%	8.3%	5.5%	< 0.001

4064 Poster Session (Board #253), Sun, 8:00 AM-11:30 AM

Diversity of first-line palliative systemic treatments for esophagogastric cancer patients with synchronous metastases: A real world evidence study. *First Author: Willemieke P.M. Dijksterhuis, Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands*

Background: Optimal palliative systemic treatment for metastatic esophagogastric cancer is not well defined, causing variation in treatment. Aim of this study was to explore diversity in first-line systemic treatment in metastatic esophagogastric cancer patients in a real world setting and assess the effect on overall survival (OS) and progression-free survival (PFS). **Methods:** In a retrospective cohort study (2010-2016), esophagogastric cancer patients (n= 2295) with synchronous metastases treated with systemic therapy were included. Systemic therapy was divided in monotherapy, doublets, triplets (all without trastuzumab), and regimens with trastuzumab. Kaplan-Meier curves and Cox proportional hazards regression, with adjustment for age, gender, tumor and metastatic locations, year of diagnosis and performance status, was used to analyze OS and PFS (PFS only available for 2010-2014 patients, n= 1392). **Results:** Up to 69 different systemic treatment regimens were administered, with a median OS of 8.7 and PFS of 4.8 months. Nearly half of patients (48.2%) were treated with doublet therapy, while 752 patients (32.5%) received triplet and 230 (10.0%) monotherapy (Table 1). Median survival was highest in patients with trastuzumab. For patients not treated with trastuzumab, triplet therapy did not show difference in survival compared to doublet therapy. **Conclusions:** Esophagogastric cancer patients with synchronous metastases are treated with a wide variety of palliative systemic treatment. In our cohort we found that patients treated with a trastuzumab regimen had the best survival, and that doublet therapy provided similar overall and progression-free survival compared to triplet chemotherapy.

	Overall survival (n= 2295)				Progression-free survival (n= 1392)			
First-line palliative treatment	**%**	**Median OS (months)**	**Adjusted HR**	**95% HR CI**	**%**	**Median PFS (months)**	**Adjusted HR**	**95% HR CI**
Monotherapy	10.0%	5.8	1.51	1.29-1.77	12.4%	2.8	1.37	1.14-1.65
Doublet	48.2%	9.2	1.00	-	42.2%	4.7	1.00	-
Triplet	32.5%	8.7	0.98	0.89-1.12	39.4%	5.3	0.89	0.77-1.02
Trastuzumab	7.0%	12.5	0.60	0.49-0.73	4.7%	7.6	0.58	0.44-0.77
Not specified	2.3%	9.0	1.22	0.86-1.73	1.4%	7.3	0.83	0.47-1.45

4065 Poster Session (Board #254), Sun, 8:00 AM-11:30 AM

Investigation of PD-L1 expression and response to pembrolizumab (pembro) in gastric cancer (GC) and cervical cancer (CC) using combined positive score (CPS) and tumor proportion score (TPS). *First Author: Karina Kulangara, Dako North America, Agilent Technologies, Carpinteria, CA*

Background: TPS, the percentage of viable tumor cells with partial or complete membrane staining at any intensity, has been invaluable for assessing PD-L1 expression in non–small cell lung cancer (NSCLC) and identifying patients (pts) likely to respond to anti-PD–1/PD-L1 therapy. However, TPS has limited utility beyond NSCLC. We investigated the predictive value of TPS and CPS and their association with response to pembro in pts with GC and CC. **Methods:** Tumor samples from pts with previously treated GC (KEYNOTE-059, NCT02335411) or CC (KEYNOTE-158, NCT02628067) were analyzed for PD-L1 expression per an investigational-use-only-labeled version of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). Response was assessed per RECIST v1.1 by independent review. External reproducibility of CPS, the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100, was assessed. **Results:** Response, prevalence, positive predictive value (PPV), and negative predictive value (NPV) for CPS and TPS at cutoffs of 1 (TPS1, CPS1) and 10 (TPS10, CPS10) are shown in the table. Response to pembro was significantly associated with CPS ($P = 0.002$) but not TPS ($P = 0.224$) in GC, whereas response to pembro was significantly associated with CPS ($P = 0.008$) and TPS ($P = 0.023$) in CC. Intersite and interobserver overall agreement assessments of external reproducibility for CPS were 92.0% (95% CI, 87.4-96.3) and 96.6% (95% CI, 94.0-98.7), respectively, in GC and 95.0% (95% CI, 90.3-99.2) and 99.7% (95% CI, 99.7-100.0), respectively, in CC. **Conclusions:** CPS is a robust, reproducible scoring method that identified more responders than did TPS in GC and CC. Further investigation of CPS in cancers beyond NSCLC is warranted. Clinical trial information: NCT02335411 and NCT02628067.

Scoring and Cutoff	Responders/Total n/N			Prevalence of PD-L1 Expression, %	PPV, %	NPV, %	Odds ratio for Tumor Response
	All Patients, N	PD-L1 Positive	PD-L1 Negative				
Gastric cancer							
CPS1	257	24/148	7/109	58	16	94	2.8
TPS1		5/32	26/225	12	16	88	1.4
Cervical cancer							
CPS1	96	13/81	0/15	84	16	100	∞
TPS1		10/50	3/46	52	20	93	3.6
CPS10		10/45	3/51	47	22	94	4.6
TPS10		6/26	7/70	27	23	90	2.7

4066 Poster Session (Board #255), Sun, 8:00 AM-11:30 AM

Comparison of bimodality versus trimodality therapy for esophageal or gastroesophageal junction (GEJ) cancer: Experience from the Princess Margaret Cancer Centre. *First Author: Akina Natori, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: There are no phase 3 trials comparing definitive chemoradiation (bimodality) vs. perioperative chemoradiation (trimodality) for locoregional esophageal/GEJ cancer. **Methods:** A retrospective analysis (2011-2016) compared bimodality and trimodality therapy in patients (pts) with locoregional esophageal/GEJ cancer treated with curative intent. Overall survival (OS) and disease-free survival (DFS) were calculated from the date of diagnosis. Uni- and multivariable Cox proportional hazards regression adjusted for patient and disease factors. **Results:** Of 141 patients, 107 (76%) were male. Mean ages were 66.7 $\pm$ 12.4 years (bimodality; N = 57) and 58.6 $\pm$ 11.3 years (trimodality; N = 84). For bimodality pts, 49% had adenocarcinoma (adeno) and 51% had squamous cell carcinoma (SCC). For trimodality pts, 76% had adeno and 24% had SCC. Bimodality pts received a higher radiation dose compared to trimodality pts (59.4 $\pm$ 7.2 vs. 44.9 $\pm$ 5.8 Gy). We found that trimodality therapy significantly improved OS and DFS compared to bimodality therapy (4-year OS: 40% vs. 31%, HR 0.56, 95%CI 0.36-0.87, p = 0.008; 4-year DFS: 33% vs. 23%, HR 0.60, 95%CI 0.40-0.90, p = 0.01). This difference was confined to the subgroup with adeno histology (OS: HR 0.28, 95%CI 0.16-0.47, $p < 0.001$; DFS: HR 0.26, 95%CI 0.16-0.43, $p < 0.001$). In the SCC subgroup, OS and DFS were similar (OS: HR 1.30, 95%CI 0.48-2.64, p = 0.77; DFS: HR 0.91, 95%CI 0.43-1.94, p = 0.82). Using multivariable regression with AIC backward selection, the only retained prognostic factors were treatment modality ($p < 0.001$) and histology (p = 0.002). **Conclusions:** Our findings support preferential use of trimodality therapy for pts with adeno histology given superior OS and DFS, whereas bimodality and trimodality therapy appeared comparable in pts with SCC histology. Pending confirmation in a larger series with longer follow-up, these findings suggest differential treatment algorithms for locoregional esophageal and GEJ cancer based on tumor histology.

4067 Poster Session (Board #256), Sun, 8:00 AM-11:30 AM

Phase III study of intraperitoneal/intravenous adjuvant chemotherapy compared intravenous adjuvant chemotherapy in patients with stage III gastric cancer. *First Author: Yang Yang, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University and Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: Peritoneal metastasis is detected as any part of the metastasis/recurrence pattern in most stage III patients after radical surgery and appears to be the most life-threatening type of metastasis in patients with advanced gastric cancer. Previous studies have suggested that the molecular detection of cancer-specific carcinoembryonic antigen (CEA) mRNA levels in the peritoneal lavage has superior value for postoperative peritoneal recurrence in patients with advanced gastric cancer. The efficacy of intraperitoneal (IP) chemotherapy has been shown in gastric cancer patients with peritoneal metastasis. **Methods:** Eligibility criteria included pathologically confirmed stage III gastric adenocarcinoma after radical surgery, and no prior chemotherapy. Patients were first divided into CEA-positive group and CEA-negative group according to the CEA mRNA lever in the peritoneal lavage, and then in each group patients were randomized 1:1 to intraperitoneal (IP) arm and intravenous (IV) arm. Patients in IP arm received 2 cycles intraperitoneal docetaxel with oral S-1 and 4 cycles intravenous docetaxel with oral S-1, while patients in IV arm received 6 cycles intravenous docetaxel with oral S-1. The primary endpoint was 1-year disease-free survival rate (1-year DFS rate). Secondary endpoints were disease-free survival, overall survival, and safety. **Result:** Between April 2015 and June 2016, 161 patients were enrolled and 158 patients included in the efficacy analysis. 65 patients had positive CEA mRNA in peritoneal lavage and 93 had negative CEA mRNA. Baseline patient characteristics were balanced between IP arm and IV arm in both CEA-positive group and CEA-negative group. The 1-year DFS rate for CEA-positive group and CEA-negative group were 41% and 89%, respectively ($p < 0.01$). In CEA-negative group, the 1-year DFS rate for IP arm and IV arm were 86% and 89%, respective (P = 0.720). In CEA-positive group, the 1-year DFS rate for IP arm and IV arm were 66% and 41%, respective (P = 0.035). Both regimens were tolerable. **Conclusion:** The primary analysis showed the statistical superiority and clinical efficacy of the multi-route (intraperitoneal/intravenous/oral) regimen for patients with positive CEA mRNA in peritoneal lavage. It suggested clinical efficacy. Clinical trial information: ChiCTR-IPR-15006202.

4068 Poster Session (Board #257), Sun, 8:00 AM-11:30 AM

Frequency of overexpression of HER3 and prognostic consequences in European patients with early gastric cancer. *First Author: Nieves Martinez Lago, Hospital Clinico de Santiago de Compostela, Santiago De Compostela, Spain*

Background: HER2 status is a predictive biomarker to response to trastuzumab in metastatic gastric adenocarcinomas. However, relatively little is known about the role of HER2 and HER3 in the non-metastatic disease in European population. **Methods:** Immunohistochemical expression of HER2 was analyzed using DAKO-HercepTest™ and gene amplification using DAKO-DuoCISH kit; both were scored according to published criteria. HER3 expresión was analyzed using HER3 clon DAK-H3-ICHER3 HER2 patients with 0-1+ were classified as HER2 negative, patients with 2+ and negative DuoCISH as equivocal and 3+ or 2+ with positive DuoCISH as positive. HER3 pts were classified as negative if 0-1+ or positive 2-3+ by two independent observers. Six subtypes according to HER2 and HER3 status were defined. Relationship between this classification and the clinicopathological characteristics and survival was analyzed retrospectively. **Results:** 106 pts diagnosed between Jan-2007 and Jun-2014 were analyzed. Subtype distribution was: HER2-HER3 (-) (56.6%), HER2 equivocal/HER3 (–) 9 pts (8.5%), HER2 (-) HER3 (+) (15.1%), HER2 equivocal HER3 (+) (6.6%), HER2 (+) HER3 (-) (7.5%) and HER2 (+) HER3 (+) (5.7%). HER2 had a significant association with HER3 (p = 0.018). Strong or moderate HER2 expression was associated with intestinal differentiation (p = 0.020) while tumors with strong or moderate HER2 expression or high HER3 expression were associated with lower grade (p = 0.050). Patients with low expression of HER2 and HER3 had a better specific overall survival ($> 85\%$) than those with HER3 overexpression (66.7-68.6%). Patients with strong or moderate HER2 expression without HER3 expression tumors had the worse survival (50%). **Conclusions:** Our algorithm based in HER2 and HER3 status proposes a classification in 6 groups with clinicopathologic and prognostic correlates. Overexpression of HER3 is a frequent phenomenon in early gastric cancer that modulates the adverse prognosis associated with HER2 overexpression. Patients with HER3 overexpression have an intermediate prognosis between patients with isolated HER2 overexpression and those who lack both drivers.

4069 Poster Session (Board #258), Sun, 8:00 AM-11:30 AM

Circulating tumor DNA dynamics in resectable gastric cancer. *First Author: Alessandro Leal, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: There is an unmet need for predictive biomarkers of clinical outcomes in resectable gastric cancer (RGC) treated with perioperative chemotherapy. We have used targeted error correction sequencing (TEC-Seq) to analyze 58 driver genes in cell-free circulating tumor DNA (ctDNA) from patients enrolled in the CRITICS study (NCT00407186). **Methods:** We prospectively isolated cell-free DNA (cfDNA) from plasma of 115 patients with stage Ib-IVa RGC enrolled in a phase III trial of neoadjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy. Samples were collected prior to neoadjuvant treatment (baseline), as well as prior to and after partial or total gastrectomy. Pathologic responses to neoadjuvant chemotherapy were assessed using tumor regression grade (TRG). Tumor-derived alterations were analyzed using TEC-Seq at the indicated timepoints. **Results:** Patients had a median follow-up of over 60 months. Initial analyses of 84 plasma samples from 52 patients revealed median levels of cfDNA of 9.8 ng/ml (0.8-123.0). We detected 259 somatic mutations in 34 genes. Patients with tubular adenocarcinoma had higher ctDNA concentrations than signet-ring cell carcinoma at baseline, with median mutant allele fractions (MAFs) of 0.25% vs. 0.16%, respectively ($P < 0.001$). ctDNA levels were reduced after neoadjuvant chemotherapy, with MAFs declining from 0.22% to 0.15% ($P < 0.001$). TRG 1-3 responses were associated with longer median overall survival (OS) (not reached (NR) *vs.* 39.4 months, HR = 0.23; 95% CI = 0.06-0.96, $P = 0.04$) and event-free survival (EFS) (NR *vs.* 33.8 months, HR = 0.34; 95% CI = 0.14-0.96, $P = 0.02$). We observed a trend for longer OS and EFS among patients with detectable ctDNA at baseline who were treated with perioperative chemotherapy (median OS NR *vs.* 37.4 months, HR = 0.39; 95% CI = 0.12 to 1.25, $P = 0.1$; median EFS NR *vs.* 30 months, HR = 0.53; CI 95% 0.18-1.6, $P = 0.2$, respectively). **Conclusions:** Our study shows that ctDNA levels differ between histologic subtypes of gastric cancer. The presence of detectable ctDNA at baseline may provide a predictive real-time biomarker of neoadjuvant chemotherapy benefit in patients with resectable disease. Additional ctDNA analyses at all timepoints will be presented. Clinical trial information: NCT00407186.

4070 Poster Session (Board #259), Sun, 8:00 AM-11:30 AM

Induction chemoradiotherapy for esophageal cancer: Comparing CROSS regimen with cisplatin/5-FU. *First Author: Abraham Geller, Harvard Medical School, Boston, MA*

Background: While trimodal therapy with neoadjuvant carboplatin/paclitaxel (CP) has demonstrated superiority over surgery alone for treatment of locally advanced esophageal cancer (LAEC), its superiority to alternative regimens is yet unproven. Here we directly compare CP against cisplatin/5-FU (CF), the historical standard, as a component of trimodal therapy for LAEC. **Methods:** Patients receiving trimodal therapy with either CP or CF for LAEC at a single institution from 2002 to 2017 were included in this retrospective study. Clinical data, treatment regimen, and tumor response were obtained from medical records. The primary outcome was pathologic complete response (pCR). Secondary outcomes were overall (OS) and diseasefree survival (DFS), calculated from the date of surgery until death (OS & DFS) or first recurrence (DFS only). Primary outcomes were measured with logistic regression; survival was estimated with KaplanMeier and Cox Proportional Hazards models. Patient characteristics were compared with Student s T and chi square tests. **Results:** 326 patients were included in this study. 187 patients (57%) received CP; 139 patients (43%) received CF. Mean follow-up was 36 months. The CP group was older (mean age 64 vs. 62, $P < .01$) and had a higher rate of hypertension (49% vs. 35%, P = .02) than the CF group. Distribution of tumor stages was similar between groups (P = .3). CF was associated with improved pCR compared to CP in both univariate (OR 1.8, P = .02) and multivariate (OR 2.2, P = .01) analysis. CF showed improved median OS compared to CP (42 vs. 29 months, P = .04), and trended toward improved DFS (27 vs. 17 months, P = .08). In multivariate analysis controlling for age, performance status, and comorbidities, CF was associated with improved OS (HR .68, P = .03) and DFS (HR .67, P = .02) compared to CP. **Conclusions:** Trimodal therapy with CP has become the standard of care for curative treatment of LAEC, yet most studies compare it against surgery alone rather than trimodal therapy with an alternative regimen. Here we directly compare CP to the historical standard regimen (CF), finding that CP is associated with worse tumor response and survival. These findings warrant further investigation with prospective studies.

4071 Poster Session (Board #260), Sun, 8:00 AM-11:30 AM

Translating molecular subtypes of gastric and gastroesophageal junction cancer (GC and GEJC) to the metastatic (met) setting: Prevalence and outcome dataTranslating molecular subtypes of gastric and gastroesophageal junction cancer (GC and GEJC) to the metastatic (met) setting: prevalence and outcome data. *First Author: Itziar Gardeazabal, Clinica Universidad de Navarra, Pamplona, Spaine*

Background: GC is the third cause of cancer death worldwide. Treatment options are limited and a molecular classification on top of HER2 may help to guide therapy. To date, the reported molecular classifications are based on localized tumors with scarce clinical follow-up. We report the first comprehensive tumor profiling of met GC/GEJC. **Methods:** 171 tumor samples from patients (pts) treated at Vall d'Hebron Institute of Oncology (2010–17) were analyzed by next generation sequencing, HER2 status by immunohistochemistry (IHC) and in situ hybridization (ISH), microsatellite instability (MSI) by IHC and Epstein-Barr virus (EBV) by ISH. Results were correlated with histology and clinical variables. **Results:** Median age was 60 years, 70% men, 22% GEJC. At diagnosis, 63% pts had only 1 met site (43% lymph nodes, 40% peritoneum, 33% liver); 41% diffuse and 40% intestinal subtype. TP53mut was found in 60%, equally in diffuse and intestinal subtypes. Molecular subtypes were defined as Chromosomal Instability TP53mut (CIN), CIN_HER2- (23%) and CIN_HER2+ (23%); no_CIN or TP53wt (19%); MSI (8%) and EBV (3%; 1 East-Europe pt, 2 Spanish pts with lymphoepitelioma-like histology). All subtypes equally distributed along the stomach and GEJ (24% had missing TP53mut status but were HER2, MSI and EBV neg). CIN subtype was associated with liver met (p = 0.004) and non_CIN with peritoneum met (p = 0.025). The median overall survival (mOS) was 24.2 months (m). MSI pts (1 out of 8 received immunotherapy) had lower mOS (9.83m v 22.2m, p = 0.003). None of the other molecular subtypes including CIN_HER2+ was prognostic for mOS. **Conclusions:** To our knowledge, this is the first broad molecular report of met GC/GEJC with clinical annotation. The molecular epidemiology in met disease differs from the previous classifications of localized GC/GEJC. We identify MSI as a poor prognostic factor while HER2+ did not impact on outcome. EBV positivity was predominantly found in rare histologies and East-Europe pts.

4073 Poster Session (Board #262), Sun, 8:00 AM-11:30 AM

Is cytoreductive surgery and hyperthermic intraperitonealchemotherapy reasonable treatment for gastric signet-ring cell adenocarcinoma and linitis plastica with peritoneal metastasis? CYTO-*CHIP* study—Ancillary results. *First Author: Pierre Emmanuel Bonnot, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Pierre-Bénite, France*

Background: Incidence of gastric signet-ring cell adenocarcinoma (SRCa) is increasing. Linitis plastica (LP) is its typical presentation. SRCa are associated with less chemosensitivity and more peritoneal metastasis (PM). Most consider PM from a gastric SRCa as an end-stage disease. Cytoreductive surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) are highly debated in those indications. **Methods:** 277 patients treated for gastric cancer with PM by CRS with or without HIPEC in 19 French centers from 1989 to 2014 were included. Diagnosis of an SRCa was based on the presence of isolated carcinoma cells containing mucin. Purpose: to evaluate the impact of CRS and HIPEC in patients with PM from SRCa compared with those with PM from non-SRCa. **Results:** 188 patients had an SRCa with 55.1 % of LP. One tumor was a LP in the 89 patients with a non-SRCa. Patients with SRCa were more frequently female and younger, with more diffuse PM, undifferentiated and pN3 tumors. There was no difference in perioperative treatments. 124 (66%) patients in the SRCa group and 56 (62.9%) in the non-SRCa group underwent an HIPEC. Median Peritoneal Cancer Index (PCI) was higher in HIPEC sub-groups (SRCa: 7 *v* 2; non-SRCa: 5 *v* 1). PM from SRCa was associated with worse survival from surgery. After CRS, with or without HIPEC, 3-year OS was 14% in the SRCa *v* 38.4% in the non-SRCa ($P = < .001$). In the SRCa group, HIPEC was associated with better survival on multivariate analysis than CRS alone (median OS: 16.3 *v* 11 months, HR, 0.526; 95% CI, 0.34- 0.81; $P = .003$). LP, tumor grade, PCI and adjuvant treatment were independent prognostic factors. In the non-SRCa group, effect of HIPEC was more significant with 3 and 5-year OS of 50.1% and 45.4 *v* 17 % and 17 % (P = .004). ASA score, PCI and nodal status were independent prognostic factors. **Conclusions:** PM from gastric SRCa or non-SRCa have distinct prognosis. HIPEC seems a valuable option therapy for resectable PM from SRCa. Concerning PM from non-SRCa, this study is currently the best evidence that HIPEC can offer similar survival rates to non-metastatic tumors on selected patients. *NCT:03253939.*

4074 Poster Session (Board #263), Sun, 8:00 AM-11:30 AM

Safety and clinical activity of 1L atezolizumab + bevacizumab in a phase Ib study in hepatocellular carcinoma (HCC). *First Author: Stacey Stein, Yale School of Medicine, New Haven, CT*

Background: Advanced HCC is a lethal cancer with a high unmet medical need. Single-agent immunotherapy with PD-L1/PD-1 blockade or treatment (Tx) with anti-angiogenic bevacizumab (bev; anti-VEGF) has shown modest activity in HCC. We hypothesized that the combination of atezolizumab (atezo; anti–PD-L1) + bev results in a greater clinical benefit due to the additional immunomodulatory effects of bev (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and Tregs in tumors), which create a more favorable tumor microenvironment that potentiates the efficacy of atezo. **Methods:** Patients (pts) with unresectable or metastatic HCC who were naive to systemic Tx were enrolled in a Phase Ib study cohort (NCT02715531). Pts received atezo (1200 mg) + bev (15 mg/kg) IV every 3 weeks until loss of clinical benefit or unacceptable toxicity. The primary objective was to assess the safety and tolerability of the combination. Secondary efficacy endpoints included ORR, PFS, DOR and time to progression (TTP) per RECIST v1.1; and OS. **Results:** As of the data cutoff (October 24, 2017), 26 pts were evaluable for safety. Tx-related all-grade AEs occurred in 21 pts (81%). Tx-related grade 3-4 AEs were seen in 9 pts (35%), most commonly hypertension (n = 5 [19%]). No grade 5 AEs were observed. Two pts (8%) experienced 3 Tx-related grade 3 serious AEs (autoimmune encephalitis, mental status change and intra-abdominal hemorrhage). Immune-related AEs requiring corticosteroid Tx occurred in 3 pts (12%). Among 21 efficacy-evaluable pts (minimum follow-up, 16 wk; median survival follow-up, 8.3 mo), confirmed partial responses occurred in 13 pts (62%) regardless of HCC etiology, region (Asia or US), baseline a-fetoprotein levels ($\geq$ or $<$ 400 ng/mL) or extrahepatic spread of tumor. The median estimates for PFS, DOR, TTP and OS have not yet been reached. **Conclusions:** The combination of atezo + bev is safe and well tolerated; no new safety signals were identified beyond the established safety profile for each agent. The confirmed response rate of 62% suggests that atezo + bev in combination has synergistic clinical activity. Expansion of this HCC cohort and evaluation of atezo + bev in a Phase III study are under way. Clinical trial information: NCT02715531.

4075 Poster Session (Board #264), Sun, 8:00 AM-11:30 AM

Anti-programmed death-1 antibody SHR-1210 (S) combined with apatinib (A) for advanced hepatocellular carcinoma (HCC), gastric cancer (GC) or esophagogastric junction (EGJ) cancer refractory to standard therapy: A phase 1 trial. *First Author: Jian-Ming Xu, Cancer Center, 307 Hospital, Academy of Military Medical Sciences, Beijing, China*

Background: A phase 1 (P1) study to assess the safety and efficacy of combination of S, a fully human IgG4 monoclonal antibody against PD-1 with PD-L1/PD-L2 plus Apatinib (A), a VEGFR2 inhibitor in patients (pts) with advanced HCC, GC, EGJ cancer. **Methods:** In P 1a dose escalation, pts received A (125, 250, 500mg, QD, 5 pts per cohort) and S (200 mg, Q2W) until unacceptable toxicity, disease progression. In phase 1b cohort expansion, pts received A at recommended P2 dose (RP2D) + S (200 mg, Q2W). Response was evaluated by RECIST v1.1. **Results:** At the cut-off data (Feb. 2. 2018), 42 pts (P 1a, n = 15; P 1b, n = 27) were enrolled. Median prior lines of therapy in HCC and GC were 1 and 2, respectively. In P1a stage, 3 DLTs (all grade 3 pneumonia) were observed in A 500mg cohort. The RP2D was A 250mg + S. In P 1b stage, the median treatment duration was 19 wks (range, 2-57 wks). 19 pts (58%) had $\geq$ grade 3 treatment-related adverse events (TRAEs). The $\geq$10% grade 3 TRAEs were hypertension (18%), increased AST (15%) and ALT (12%). These AEs were manageable, only 1 pt discontinued treatment due to TR grade 3 hyperbilirubinemia. There were no TR- deaths. The ORR and DCR in 36 evaluable pts in all 3 cohorts were 30.6% (n = 11) and 83.3% (n = 30), respectively. All 11 responses occurred in A 125mg (n = 1) and 250mg (n = 10) cohorts. Among 18 HCC pts (14 evaluable: A 125mg cohort, n = 4; A 250mg cohort, n = 9, A 500mg cohort, n = 1), all infected with HBV. The ORR and DCR were 50.0% and 85.7%, respectively. Notably, 2 pts in A 125mg cohort had initial SD at best response, and achieved PR after escalating A dose to 250 mg, therefore the ORR at A 250 mg dose level was 54.5% (6/11). The median progression-free survival (PFS) was not reached. All 7 pts with PR were still on treatment, 5 lasted for 47 weeks+. Of 24 GC or EGJ cancer pts (22 evaluable: A cohort, 250mg n = 20; 500mg, n = 2), the ORR in A 250mg cohort was 20.0% and DCR was 80.0%. The median PFS was 3.0 months. **Conclusions:** S + A at RP2D demonstrated manageable toxicity in HCC, GC or EGJ cancer pts. Particularly encouraging clinical activity (PR rate 54.5%) was observed in pts with pretreated, advanced HCC. Clinical trial information: NCT02942329.

4076 Poster Session (Board #265), Sun, 8:00 AM-11:30 AM

A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). *First Author: Masafumi Ikeda, National Cancer Center Hospital East, Kashiwa, Japan*

Background: LEN is a multikinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFRα, RET, and KIT that showed noninferiority with respect to overall survival (OS) compared with sorafenib in the first-line treatment of pts with uHCC in a phase (Ph) 3 trial (REFLECT). PEM is an anti-PD-1 monoclonal antibody that has shown promising activity in HCC. An ongoing Ph 1b study of LEN + PEM has shown promising activity in several solid tumor types. We report preliminary results from a Ph1b trial of LEN + PEM in pts with uHCC. **Methods:** In this open-label, multicenter study, pts with uHCC, BCLC stage B (not eligible for transarterial chemoembolization) or C, Child-Pugh class A, and ECOG PS $\leq$ 1 received LEN (body weight $\geq$ 60 kg: 12 mg/day; $<$ 60 kg: 8 mg/day) daily and 200 mg PEM IV once every 3 wks. Tolerability was evaluated by assessing dose-limiting toxicities (DLTs) during the first cycle in pts who were ineligible for other therapies (3+3 design; Part 1). Once tolerability of the combination was confirmed, additional pts with no prior systemic therapy for uHCC were enrolled (Part 2). The primary endpoint was safety. Secondary and exploratory endpoints included OS, and objective response rate, progression-free survival, and time to progression using modified RECIST (mRECIST). Tumor assessments of complete or partial responses (CR or PR) were confirmed $\geq$ 4 weeks after initial response. **Results:** As of December 1, 2017, 18 pts had received LEN + PEM (Part 1: n = 6; Part 2: n = 12). Pts had BCLC stage B (n = 6) or C (n = 12), Child-Pugh scores of 5 (n = 14) or 6 (n = 4), and 4 pts (22%) had received prior sorafenib. No DLTs were reported in Part 1. All 18 pts remained on study. TEAEs occurred in 17 pts (94%); the most common TEAEs were decreased appetite and hypertension (56% each). No new safety signals were identified. Efficacy outcomes are reported in the Table. At data cutoff, tumor reduction from baseline was observed in all evaluable pts except one. **Conclusions:** LEN + PEM was well tolerated with encouraging anti-tumor activity in pts with uHCC. Clinical trial information: NCT03006926.

	Part 1 (n = 6)	Part 2 (n = 7)	Total (n = 13)
Best Overall Response, n (%)			
PR*	4 (67)	2 (29)	6 (46)
Stable Disease	2 (33)	4 (57)	6 (46)
Progressive Disease	0 (0)	0 (0)	0 (0)
Not Evaluable	0 (0)	1 (14)	1 (8)

*3 PRs confirmed.

4077 Poster Session (Board #266), Sun, 8:00 AM-11:30 AM

A multicenter, single arm phase II trial of a small molecule immune-modulator icaritin: Safety, overall survival, immune dynamics, and PD-L1 expression in advanced hepatocellular carcinoma. *First Author: Yan Sun, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: HCC was characterized with high heterogeneity and immune "tolerogenic". Despite of immune checkpoint inhibitors have demonstrated promising results with improved overall survival, a significant fraction of advanced HCC patients are still left with limited treatment options and poor survival. The purpose of this study is to determine the safety, clinical activity and immune dynamic biomarkers of a small molecule icaritin, IL-6/STAT3 immune-modulator in advanced HCC. **Methods:** Major eligibility criteria include histologically confirmed unresectable HCC patients with Child-Pugh Class A or B liver function. Total of 70 advanced HCC patients were enrolled and administrated with 600 mg b.i.d. Primary endpoints were TTP, secondary endpoints were safety, OS, and DCR. Local disease control was defined as no progressive disease (PD) by RECIST. Kaplan-Meier analysis was utilized for OS assessment. Immune dynamic of NLR, IL-6 and baseline PD-L1 expression of immune cells was evaluated, retrospectively. **Results:** There was no $\geq$grade III drug related AE observed in all enrolled 70 advanced HCC patients. Objective response evaluation in per-protocol population showed PR (1.6%), SD (32.8%) and PD (59.0%) and median overall survival (OS) 254day (95% CI, 172-296). DCR was achieved 34.4% (95% CI, 22.7-47.7%); Median OS for the PD-L1-positive (n = 9) and negative (n = 24) subgroups were 389 (95% CI, 80-522) vs. 286.5days (95%CI, 135-482), for IL-6-advantage (n = 24) and disadvantage (n = 16) subgroups were 366.5 (95% CI, 277-566) vs. 157days (95% CI, 125-254), for NLR-advantage (n = 27) and disadvantage (n = 23) subgroups were 295(95% CI, 235-509) vs. 178days (95% CI, 135-296), respectively. **Conclusions:** Icaritin has demonstrated its favorable clinical safety and immune-modulation clinical efficacy. The improved OS was implicated in the subgroups of advanced HCC patients including PD-L1-positive immune cell expression. Both safety and immune-response efficacy are warranted for the phase III trial. Clinical trial information: NCT01972672.

4078 Poster Session (Board #267), Sun, 8:00 AM-11:30 AM

Phase I dose-finding study of OPB-111077, a novel STAT3 inhibitor, in patients with advanced hepatocellular carcinoma. *First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of (South), Korea*

Background: The signal transducer and activator of transcription 3 (STAT3) signaling pathway might be a promising therapeutic target for hepatocellular carcinoma (HCC). **Methods:** This study was a multicenter, open-label, non-comparative, dose escalating phase I study of OPB-111077, an oral STAT3 inhibitor, in patients with advanced HCC who failed on sorafenib. Continuous dosing (daily administration: 50 mg to 400 mg) and intermittent dosing (4-days on/3-days off administration: 300 mg to 900 mg) regimens were evaluated and the dose-limiting toxicities (DLTs), maximal tolerated dose (MTD), and recommended dose (RD) were the primary endpoints. **Results:** A total of 33 patients (19 for continuous dosing and 14 for intermittent dosing) were enrolled. One patient experienced a DLT with grade 3 dizziness, but the MTD was identified in neither the continuous nor the intermittent dosing cohorts. The RDs were determined to be 250 mg for the continuous dosing regimen and 600 mg for the intermittent dosing regimen. There was no treatment-related death; 6 patients (18%) had grade 3-4 toxicities including thrombocytopenia (6%), fatigue (3%), and dizziness (3%). No patients achieved complete or partial responses and the median progression-free survival was 1.4 months (95% confidence interval, 0.8-2.8). **Conclusions:** OPB-11107 was well tolerated in patients with advanced HCC after sorafenib failure, but only showed limited preliminary efficacy outcomes. Further investigation of the role of the STAT3 signaling pathway in HCC and the development of biomarkers for STAT3 inhibitors are warranted. Clinical trial information: NCT01942083.

4079 Poster Session (Board #268), Sun, 8:00 AM-11:30 AM

Phase Ib study of binimetinib (MEK162) in combination with capecitabine in gemcitabine-pretreated advanced biliary tract cancer. *First Author: Jin Won Kim, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of (South), Korea*

Background: In biliary tract cancer (BTC), RAS/RAF/MEK/ERK pathway is known to be activated in up to 20-40%. Binimetinib (MEK162) is allosteric MEK1/2 inhibitor, which shows preclinical activity in BTC. Interestingly, MEK inhibitor and 5-FU shows synergistic effects in BTC cells. With that, we conducted phase Ib study of binimetinib and capecitabine in gemcitabine-pretreated BTC patients. **Methods:** This study consists of dose escalation (DE) part and expansion (EX) part. Binimetinib (B) and capecitabine (C) were dosed twice daily, 2 weeks/1 week on/off. In DE part, 3 dose levels (DL) were tested (DL1: B 15mg, C 1000 mg/m^2; DL2: B 30mg, C 1000 mg/m^2; DL 3: B 30mg, C 1250 mg/m^2) with 3+3 design. The primary end point was maximum tolerated dose in DE part and 3 month-progression free survival (PFS) rate (3m-PFSR) in EX part. **Results:** In DE part, 9 patients (3 per DL) were recruited and there was no dose limiting toxicity up to DL3. Recommended phase 2 dose (RP2D) was determined as DL3. In EX part, 25 patients were enrolled. Median age was 63 years old (range 48-73). Primary tumor origins were gallbladder (29.4%), intrahepatic (29.4%), extrahepatic (26.5%), and ampulla of vater (14.7%). 25 (73.5%) and 9 patients (26.5%) were 2nd-line and 3rd-line setting, respectively. Of 34 evaluable patients, 6 (17.6%) and 20 patients (58.8%) showed partial response and stable disease (SD). Response rate and disease control rate were 17.6% (95% CI, 4.8 - 30.4) and 76.5% (95% CI, 62.1 - 90.7). Median PFS and overall survival (OS) were 3.9 m (95% CI, 3.0 - 4.8) and 8.0 m (95% CI, 4.9 - 11.1). 3m-PFSR was 61.3%. 60% of patients with SD showed prolonged SD ($>$ 12 weeks). In biomarker study, RAS/RAF/MEK/ERK pathway activated patients showed longer PFS (5.4 m vs 2.6 m, p = 0.031) and OS (10.8 m vs 5.3 m, p = 0.011) than non-activated patients. Most of adverse events were grade 1/2 and manageable with G3 anemia (11.8%) and G3 fatigue (5.9%). **Conclusions:** RP2D of binimetinib and capecitabine combination is binimetinib 30mg, capecitabine 1250 mg/m^2, twice daily, 2 weeks on/1 week off. This combination shows acceptable tolerability and promising antitumor efficacy, especially in RAS/RAF/MEK/ERK pathway activated BTC patients. Clinical trial information: NCT02773459.

4080 Poster Session (Board #269), Sun, 8:00 AM-11:30 AM

Phase II trial of sorafenib plus doxorubicin (SD) in patients (Pts) with advanced hepatocellular carcinoma (HCC) after progression of disease (PD) on sorafenib (S). *First Author: Imane H. El Dika, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: SD may synergistically improve outcome after PD on S by promoting ASK-1 mediated apoptosis through RAF-1 inhibition. In a prior retrospective analysis of 14 pts who in the lack of other choices of therapy received SD after PD on S, progression free survival (PFS) and overall survival (OS) were 3.4 and 10.1 months (m) respectively **Methods:** A non-randomized, open label, single institution, single arm phase II study of SD in pts with histologically confirmed advanced HCC. Eligibility: RECIST 1.1 radiologic PD on S, ECOG 0-1, Child-Pugh A, and adequate major organ function. Therapy: S 400mg twice a day (once a day if bilirubin (B) $\geq$1.3mg/dl $\leq$3mg/dl) and D 60mg/m2 (30mg/m2 if B $\geq$1.3 mg/dl $\leq$3mg/dl) on day 1 of 3-week cycle. Cross-sectional imaging was performed every 3 cycles. The primary endpoint was OS at 6m (OS6), based on Simon two-stage design, unacceptable OS6 50%, acceptable OS6 72%, type I and II errors 5 and 15% respectively. Secondary endpoints included PFS, OS, response rate by RECIST 1.1, and associations between duration of prior S and OS and PFS. Baseline and on-treatment biopsies evaluated ASK-1 and p-ERK expression levels (separate report) **Results:** N = 30 pts enrolled. The majority were male (86%), median age 64 years (range 24-82), 16 pts had hepatitis (53%). OS6 was 76.6% [95%CI: 57.2-88.1%]. Median doses of D and S were 94mg and 380mg respectively. OS was 8.6 [95%CI: 7.3-12] m, and PFS was 3.6 [95%CI: 2.4-4.4] m. There were 3 (10.7%) partial responses and 17 (60.7%) stable disease. Median duration of prior S treatment was 3.3 [range: 0.9-27] m. Neither OS nor PFS were associated with previous S duration (p value 0.11 and 0.15 respectively). Grade 3-4 adverse events occurring in $\geq$ 10% of pts: neutropenia (16%), febrile neutropenia (10%), lymphopenia (43%), anemia (10%), thrombocytopenia (10%), elevated AST (23%) and ALT (10%), hypophosphatemia (10%), and fatigue (10%). There was no treatment related death. **Conclusions:** Despite the study meeting its primary endpoint, SD resulted in significant toxicity and a median OS of 8.6 m. Based on front-line evaluation of SD and the results reported herein, further development of SD in HCC is not warranted Clinical trial information: NCT01840592.

4081 Poster Session (Board #270), Sun, 8:00 AM-11:30 AM

A phase II study of ramucirumab for advanced, pre-treated biliary cancers. *First Author: Jonathan Mizrahi, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Biliary cancers (BC) have no clear second-line therapy in advanced disease after progression on standard of care gemcitabine and cisplatin. Angiogenesis has been shown to be a potential target for BC, and ramucirumab, FDA-approved for treatment of advanced gastric, lung and colon cancer, is a novel monoclonal antibody that targets VEGFR2 to inhibit tumor-induced angiogenesis. **Methods:** We conducted a single arm, phase 2 single center study. Eligibility criteria included patients (pts) with advanced BC, ECOG PS 0 or 1, who had received at least 1 prior regimen containing gemcitabine. Pts were treated with IV ramucirumab at a dose of 8 mg/kg every 2 weeks, and restaging imaging was performed every 8 weeks until progression. The primary endpoint was progression free survival (PFS). Secondary endpoints included overall response rate (ORR), disease control rate (DCR), overall survival (OS) and toxicity (tox) of ramucirumab. Exploratory endpoints included correlating baseline gene expression profile and pre- and post-therapy CT imaging features with tumor response. **Results:** 43 of a planned 50 pts were enrolled, 42 receiving treatment. The cohort had a median age of 59.9 yrs (range 42-77), ECOG PS 0/1 (16/26), male/female (20/22), intrahepatic cholangiocarcinoma/extrahepatic/gallbladder (23/9/10), median prior therapies = 1 (range 1 to 5). Pts received a median number of 6 cycles. There were 9 (21%) grade 3 tox including anorexia, dehydration, hypertension, hyponatremia, proteinuria and vomiting. No grade 4 tox were observed, and no pts were taken off study due to tox. 5 pts required dose reductions. After a median follow-up of 3.44 months, the median PFS and OS were 2.73 months (95% CI: 1.91-8.03) and 6.31 months (95% CI: 4.7 – not reached). Of 34 pts evaluable for response, ORR = 0% and DCR = 44%, with 6 pts on treatment for $>$ 24 weeks. Analysis of the correlative endpoints is ongoing. **Conclusions:** Ramucirumab as a single agent was well-tolerated and resulted in a PFS similar to that achieved with more toxic chemotherapy regimens used in the refractory setting. Furthermore, a minority of ramucirumab-treated patients (13%) experienced prolonged PFS $>$ 24 weeks, warranting further investigation of this agent in refractory BC. Clinical trial information: NCT02520141.

4082 Poster Session (Board #271), Sun, 8:00 AM-11:30 AM

Multi institutional phase II trial of single agent regorafenib in refractory advanced biliary cancers. *First Author: Richard D. Kim, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: There is currently an unmet medical need for patients with advanced biliary cancer (BC) who have failed one prior gemcitabine based systemic therapy.Regorafenib is an oral multi-kinase inhibitor that targets both receptor tyrosine kinases (RTKs), as well as the tumor cell proliferation/survival signaling pathway kinases (RAS/RAF/MEK/ERK). **Methods:** Pts with histologically proven BC who progressed on at least one line of systemic therapy received regorafenib 160 mg daily 21 days on 7 days off in a 28 days cycle. The single arm design was used to access 6 month overall survival (OS) as a primary endpoint. The study tested the null hypothesis of $\leq$30% of OS at 6 month against the alternative of $\geq$50% of OS at 6 month (HR = 0.578). With one-sided α of 10% and 86% power, the experimental treatment was deemed to have good activity if $\geq$14 out of 32 evaluable patients (43.8%) survive 6 months or longer. The secondary objectives included median OS, RR and PFS. **Results:** Thirty nine pts received at least 1 dose of regorafenib of whom 32 pts were evaluable for efficacy. Twenty pts failed 1 line of therapy and 12 pts failed two lines of therapy. Median age was 62 (range: 27-88) years and the primary sites of tumor were intrahepatic cholangiocarcinoma (68.8%), extrahepatic (18.8%), and gallbladder (12.5%). Pts were considered evaluable for efficacy if patients received more than 1 cycle of regorafenib. Seven pts were not evaluable because one pt withdrew consent, 5 pts expired due to clinical progression within a month and 1 pt due to toxicity. For 32 evaluable pts, 6 month OS was 50.9% (95% CI: 32.1%-67.0%), 12 month OS was 35% (95% CI 16.2-53.7) and 18 month OS was 35% (95% CI 16.2-53.7). Median PFS was 3.7 months (95% CI: 2.3-5.5) and median OS was 9.9 months (95% CI: 3.7-20.1). PR was achieved in 2 (6.2%) pts, SD in 18 (56.2%) pts with DCR of 62.4%. The overall toxicity profile was as expected with grade 3/4 AE of 71.8%. The most common adverse events were fatigue (56.4%) and hypertension (53.8%). Dose modification was required in 49% of the patients. Plasma samples were collected in all pts with planned correlative studies underway. **Conclusions:** The primary endpoint was met in this study. Further randomized trials are warranted to confirm the efficacy Clinical trial information: NCT02115542.

4083 Poster Session (Board #272), Sun, 8:00 AM-11:30 AM

Phase 1B study of enzalutamide (ENZA) with or without sorafenib (SORA) in patients (pts) with advanced hepatocellular carcinoma (HCC). *First Author: James J. Harding, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Preclinical models indicate that androgen receptor (AR) interference with ENZA is deleterious to HCC; however, ENZA also activates feedback circuitry that may be overcome with the addition of SORA. **Methods:** This is a multicenter, National Comprehensive Cancer Network funded, phase 1B study of ENZA $\pm$ SORA unresectable/metastatic HCC pts (NCT02642913). In PART 1 of the study, a 3 + 3 dose de-escalation design with expansion cohort was used to establish the safety and ENZA recommended phase 2 dose (RP2D). In PART 2, a 3 + 3 dose escalation was used to establish the safety and RP2D of ENZA + SORA. Secondary objectives included response rate (RR) by RECIST 1.1, pharmacokinetics (PK), progression-free (PFS) and overall survival (OS). Correlative analyses included AR determination by immunohistochemistry and enumeration of pretreatment and on-treatment high definition circulating tumor cells (HD-CTCs). **Results:** 16 pts received ENZA 160mg QD on PART 1—median age 70/75% male/19% hepatitis B virus (HBV)/13% hepatitis C virus (HCV)/ 100% Child Pugh A/100% failed prior SORA. No dose limiting toxicity (DLTs) occurred and drug-related Grade 3 AEs were rare—hypertension (1), hyperglycemia (1), transaminitis (1), and electrolyte abnormalities (1). No objective responses were observed. 8/16 (53.3%) pts had stable disease (SD). Median PFS and OS were 1.8 and 9.4 months. 12 pts received ENZA 160mg QD with SORA 400mg QD or BID in PART 2—median age 72/83% male/8.3% HBV/33% HCV/100% Child Pugh A/100% treatment naïve. No DLTs were observed and drug-related Grade 3 AEs included hypertension (2), headache (1) and hypophosphatemia (1). No objective responses were observed. 7/12 (64%) pts had SD. AR was detected in 16/21 (76%) tumor samples and did not associate with RR (p = 0.61). ENZA enhanced the metabolism of SORA leading to a 60% reduction of SORA area under the curve $(AUC)_{0\text{-}8hr}$ at steady state. HD-CTCs were detected in 11/32 (34.3%) samples, and in 13 paired samples, treatment did not affect CTC concentrations (p = 0.9). **Conclusions:** Despite an adequate safety profile, ENZA has no single agent activity in AR (+) or (-) HCCs. ENZA + SORA development is limited by drug-drug interactions. Clinical trial information: NCT02642913.

4084 Poster Session (Board #273), Sun, 8:00 AM-11:30 AM

Selumetinib (Sel) and cisplatin/gemcitabine (CisGem) for advanced biliary tract cancer (BTC): A randomized trial. *First Author: Mark Doherty, Odette Cancer Centre at Sunnybrook Health Sciences Centre, University Health Network, Toronto, ON, Canada*

Background: Sel (AZD6244, ARR142886) is an oral MEK inhibitor, with preclinical evidence of synergy with Gem in BTC. CisGem is standard first-line treatment for advanced BTC. This trial assessed the efficacy of Sel in continuous or sequential combination with CisGem in first-line advanced BTC. **Methods:** This randomized multicentre phase II trial (NCT02151084) enrolled patients (pts) with advanced cholangiocarcinoma (CC) or gallbladder cancer (GBC). CisGem was given at standard doses. Sel started at 75mg BID, daily (continuous – Arm A) or day 1-5, 8-19 every 21 days (sequential – Arm B). Arm C was CisGem alone. Sel starting dose was reduced to 50mg BID for toxicity concerns after 32 enrolled pts (protocol amendment). Primary endpoint was % change in RECIST tumor size of 48 evaluable pts: Arm A or B vs Arm C at 10 wks. Secondary endpoints: PFS, OS, ORR, disease control rate (DCR) and toxicity. **Results:** 57 pts were enrolled: 29 female; 22 intrahepatic CC, 16 extrahepatic CC and 19 GBC. Baseline characteristics were similar across arms. Mean change in tumor size was not significantly different between either Sel arm and the control arm (Arm A p = 0.37, Arm B p = 0.53 [Table]). There were no significant differences in other efficacy endpoints. Toxicities appeared more frequent in Arm A; dose intensity of Gem and Sel were lower. More pts in Arms A and B stopped treatment due to toxicity than Arm C. **Conclusions:** Adding Sel to CisGem failed to improve tumor response at 10 wks, or prolong survival, but added toxicity and led to lower dose intensity. Exploration of biomarkers may identify a group deriving benefit, but it should not be studied further in unselected BTC. Clinical trial information: NCT02151084.

	Arm A (N = 19)	Arm B (N = 19)	Arm C (N = 19)	overall p-value
Mean % change in tumor size at 10 wks (95% CI)	-7.3 (-24.3,+9.7)	-16.3 (-26.2,-6.4)	-13.2 (-25.2,-1.3)	0.80
ORR (%)	36	29	29	0.91
DCR (%)	86	88	88	0.95
Median PFS (months)	6.0	6.6	6.4	0.58
Median OS (months)	10.9	14.8	12.7	0.76
Treatment discontinuation reason				
Disease progression	7	7	13	
Toxicity	4	6	0	
Death	0	0	2	
Withdrawn consent	1	3	1	
Non-protocol surgery	0	1	0	
Toxicity Events (Grade [G])				
G 3	63	52	40	
G 4	8	13	10	
G 5	2	1	0	
Non-hematologic G3-5	55	34	34	
Relative Dose Intensity C1-3, %				
Cis	92.2	94.5	93.2	0.21
Gem	85.7	93.8	94.1	0.10
Sel	74.1	85.6	-	0.28

4085 Poster Session (Board #274), Sun, 8:00 AM-11:30 AM

ADI-PEG 20 and FOLFOX6: A phase 1 study in pts (pts) with advanced hepatocellular carcinoma (HCC). *First Author: James J. Harding, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Arginine depletion interferes with pyrimidine metabolism as well as DNA damage repair pathways, and preclinical data indicate that pairing pegylated arginine deaminase (ADI-PEG 20) with fluoropyrimidines or platinum enhances cytotoxicity *in vitro* and *in vivo* in arginine auxotrophs. **Methods:** An open-label phase 1 trial of ADI-PEG 20 and FOLFOX6 for treatment-refractory HCC and other advanced gastrointestinal (GI) tumors was based on a 3 + 3 dose escalation design. The primary objectives were to define, safety, tolerability, and the recommended phase 2 dose (RP2D). An HCC expansion cohort was used to define best overall response rate (ORR). Secondary objectives included progression-free survival (PFS), overall survival (OS), and exploration of pharmacodynamics and immunogenicity. Eligible patients were treated with intravenous FOLFOX6 biweekly at standard doses and ADI-PEG 20 intramuscularly weekly at 18 (Cohort 1) or 36 mg/m^2 (Cohort 2 and RP2D expansion). **Results:** 27 pts enrolled—23 advanced HCC (and 4 other GI). HCC cohort: median age 64 (44-77) years old/70% male/100% Child Pugh A/57% non-viral/70% extrahepatic disease/39% portal vein involvement/43% $\geq$ 2 lines of treatment. No dose-limiting toxicities were observed and the RP2D for ADI-PEG 20 was 36 mg/m^2 weekly with FOLFOX6. Common adverse events (AEs) any grade: thrombocytopenia, neutropenia, leukopenia, anemia, and fatigue. Among 23 HCC pts, the most frequent treatment related Grade $\geq$ 3 AEs were neutropenia (47.8%), thrombocytopenia (34.7%), leukopenia (21.7%), anemia (21.7%), and lymphopenia (17.4%). The ORR for 23 HCC pts was 21.7% (95% CI: 95 7.5-43.7). Median PFS and OS were 7.3 and 14.5 months. Arginine levels (Mean $\pm$ SEM, baseline 81.7 $\pm$ 8.2, week 1 0.8 $\pm$ 0.2μM) were depleted with therapy despite the emergence of low levels of anti-ADI-PEG 20 antibodies. The degree of arginine depletion, presence of antibodies, and archived tumoral argininosuccinate synthetase-1 levels did not correlate with response. **Conclusions:** Concurrent ADI-PEG-20 and FOLFOX6 is safe with favorable efficacy compared to historic controls. The HCC cohort has been expanded further into a phase II study of the combination in the third-line. Clinical trial information: NCT02102022.

4086 Poster Session (Board #275), Sun, 8:00 AM-11:30 AM

Phase II study of pembrolizumab in advanced, unresectable hepatocellular carcinoma. *First Author: Lynn G. Feun, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL*

Background: Recently, checkpoint inhibitors have shown modest activity in patients (pts) with advanced, unresectable hepatocellular carcinoma (HCC). In multicenter trials with nivolumab and pembrolizumab, the response rates have been reported to be 14% and 16%, respectively. We report a prospective single-institution investigator-initiated clinical/translational study of pembrolizumab in advanced HCC. **Methods:** A phase II trial is ongoing, with pembrolizumab administered at a fixed dose of 200 mg iv every 3 weeks for advanced HCC patients who may have progressed on, were intolerant of, or refused sorafenib. CT or MRI scans were performed after every 3 doses. RECIST 1.1 was used to assess response. Time to tumor progression (TTP) and overall survival (OS) were estimated by Kaplan-Meier method. Median TTP and median OS were estimated along with the corresponding 95% confidence interval. **Results:** Twenty six patients have been treated and 21 were evaluable for response at this time. Ten of the 21 patients had prior sorafenib. Seven had hepatitis C and 1 had hepatitis B. Sixteen had extrahepatic metastases. The median TTP was 3 months(95%CI:2-7) and median OS was 14 months(95%CI: 3- not estimable). In terms of response, one had complete response and 6 had partial response (PR) for overall response rate of 33%. Two others had stable disease. TTP for responding pts were 6+, 7, 8, 8,9, 9+, and 14 + months with 3 having ongoing responses. Five of these 7 had extrahepatic metastases which responded to treatment. Four of 7 had prior sorafenib. Drug-related toxicity included: hypothyroidism (4 patients) grade 4 neutropenia (1) and reversible, temporary elevation of liver function tests (grade 3 in 3 pts). Other grade 1-2 toxicities included: diarrhea (4), skin rash (5) and fatigue (2). Correlative studies including hepatitis B and C titers, IL1B, IL12, IL18, IL6, TGF beta, gamma interferon, and PD-L1/PD-1 staining are ongoing and will be presented. **Conclusions:** Pembrolizumab has activity in advanced HCC patients, including those with extrahepatic metastases. Toxicity was generally well tolerated and reversible. A set of immunological markers as well as PD-L1/PD-1 staining is being investigated as possible indicator for response. Clinical trial information: NCT02658019.

4087 Poster Session (Board #276), Sun, 8:00 AM-11:30 AM

Phase 2 trial of pembrolizumab (PEM) plus granulocyte macrophage colony stimulating factor (GM-CSF) in advanced biliary cancers (ABC): Clinical outcomes and biomarker analyses. *First Author: Robin Kate Kelley, University of California San Francisco, San Francisco, CA*

Background: The efficacy of immune checkpoint inhibition (CPI) has not been established in ABC. The combination of CPI plus the myeloid cytokine GM-CSF was safe with prolonged overall survival (OS) compared to CPI monotherapy in melanoma. This phase 2 trial evaluates the safety, efficacy, and biomarkers of PEM in combination with 2 cycles of low dose induction GM-CSF in ABC (NCT02703714). **Methods:** Design: Simon's 2-stage. Key eligibility: ABC after $\geq$ 1 standard therapy, no prior CPI, bilirubin $\leq$ 1.5xULN. Treatment: PEM 200 mg IV Q3 weeks plus GM-CSF 250 μg SC days 1-14 Q3 weeks for 2 cycles. Endpoints: 1°: Overall response rate (ORR) by RECIST 1.1 with H_0 5% vs. H_1 20%. Key 2°: Safety, progression-free survival at 6 months (PFS6), OS, tumor PD-L1 expression. Exploratory: CA 19-9 levels, tumor microsatellite (in)stability (MSI, MSS), tumor mutation burden (TMB), tumor and peripheral immune cell profiling. **Results:** Accrual has completed with 27 patients enrolled 5/2016-9/2017: Stage 1/2 9/18; F/M 13/14; median age 61; intra-/extra-hepatic 74%/26%; stage IVA/B 85%, II/III 15%; median prior therapies 2 (range 1-6); MSI/MSS/unknown 1/19/7; TMB high+int./low/unknown 5/11/11. Adverse events (AE): Related $\geq$ grade (Gr)3 AE in 2 (7%) (1 each immune-related (ir)AE of Gr4 diabetes mellitus and Gr3 fever); irAE requiring steroids in 3 (11%); endocrine irAE in 8 (30%). Disposition: 20 pts discontinued for PD, 1 for Gr2 irAE neuropathy/arthralgia, 1 for unrelated AE; 5 remain on treatment. Median cycles: 6 cycles (range 2-28+). ORR: Confirmed partial response (cPR) in 5 (19%) (95% CI: 3-34%) (1 MSI, 4 MSS); cPR or stable disease (SD) $\geq$ 6 months in 9 (33%). PFS6: 35% (95% CI: 15-54%); median OS: not reached. Endocrine irAE, CA 19-9 changes $\geq$ 50%, hepatitis C virus (HCV), and TMB were associated with efficacy in univariate analyses. PD-L1+ in $\geq$ 1% cells was present in 3/10 (30%) pre-treatment samples but was not associated with ORR or PFS6; additional PD-L1 results are pending. **Conclusions:** PEM plus induction GM-CSF is safe and well-tolerated in ABC. Prolonged responses and PFS in MSS ABC along with candidate biomarkers warrant further study in larger sample. Clinical trial information: NCT02703714).

4088 Poster Session (Board #277), Sun, 8:00 AM-11:30 AM

Outcomes in patients (pts) who had received sorafenib (S) as the only prior systemic therapy in the phase 3 CELESTIAL trial of cabozantinib (C) versus placebo (P) in advanced hepatocellular carcinoma (HCC). *First Author: Robin Kate Kelley, University of California San Francisco, San Francisco, CA*

Background: C inhibits tyrosine kinases including MET, VEGFR, and AXL. In the CELESTIAL trial, C improved overall survival (OS) and progression-free survival (PFS) compared with P in pts with advanced HCC after 1 or 2 prior lines of systemic therapy including S. Overall, median OS was 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049), and median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; p $<$ 0.0001). Here, outcomes were analyzed for pts who had received S as the only prior systemic therapy. **Methods:** In the overall study, 707 pts were randomized 2:1 to receive C (60 mg qd) or P stratified by disease etiology, geographic region, and extent of disease. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, and ECOG PS $\leq$1. Pts must have received prior S and could have received up to two lines of prior systemic therapy for HCC. Outcomes were analyzed for pts who received only prior S based on duration of prior S ($<$ 3 mo, 3 to $<$ 6 mo, and $\geq$6 mo). **Results:** Out of the 495 pts who received only prior S, 136 (27%) received prior S for $<$ 3 mo, 141 (28%) for 3 to $<$ 6 mo, and 217 (44%) for $\geq$6 mo. OS and PFS were improved for C vs P in pts who had received only prior S; median OS was 11.3 mo for C vs 7.2 mo for P (HR 0.70), and median PFS was 5.5 mo for C vs 1.9 mo for P (HR 0.40). Results for OS and PFS also favored C for subgroups based on duration of prior S (Table). Median OS was generally longer for pts who received prior S for longer durations in both treatment arms. Grade 3/4 adverse events in subgroups were similar to those observed in the overall population in both arms. **Conclusions:** C improved OS and PFS vs P in pts with advanced HCC who had received S as the only prior systemic therapy irrespective of the duration of prior S treatment. Clinical trial information: NCT01908426.

	Prior S Only		Duration of Prior S					
			< 3 mo		3 to < 6 mo		≥6 mo	
	C (N = 331)	P (N = 164)	C (N = 89)	P (N = 47)	C (N = 98)	P (N = 43)	C (N = 143)	P (N = 74)
Median OS, mo	11.3	7.2	8.9	6.9	11.5	6.5	12.3	9.2
OS HR (95% CI)	0.70 (0.55–0.88)*		0.72 (0.47–1.10)		0.65 (0.43–1.00)		0.82 (0.58–1.16)	
Median PFS, mo	5.5	1.9	3.8	1.8	5.4	1.9	5.7	1.9
PFS HR (95% CI)	0.40 (0.32–0.50)*		0.35 (0.23–0.52)		0.37 (0.25–0.56)		0.48 (0.35–0.67)	

*Stratified; all other HRs are unstratified.

4089 Poster Session (Board #278), Sun, 8:00 AM-11:30 AM

Real-time circulating tumor DNA profiling of advanced cholangiocarcinoma (CCA). *First Author: Kabir Mody, Mayo Clinic, Jacksonville, FL*

Background: Cholangiocarcinoma (CCA) has limited treatment options. Genomic analyses have led to development of targeted therapies now in several clinical trials, and may enable the discovery of new treatment options. However, biopsy often yields limited tissue, thus hampering tissue-based profiling opportunities. Data regarding circulating tumor DNA (ctDNA) plasma analysis in CCA during real time clinical practice is limited. **Methods:** We performed ctDNA NGS analysis in patients with advanced CCA (January 2015 – December 2017). ctDNA analysis was performed using Guardant 360, which detects single nucleotide variants, amplifications, fusions, and specific insertion/deletion mutations in up to 73 different genes. Seventeen samples were performed on previous panel versions (3 on a 54-gene, 1 on a 68-gene, and 13 on a 70-gene panel) The mutant allele fraction (MAF) for detected alterations was calculated relative to wild type in ctDNA. Actionability was defined as possible treatments within OncoKB levels I-IV and R1. The study was conducted in accordance with Mayo Clinic Institutional Review Board requirements. **Results:** Among 104 patients and 115 total samples, ctDNA NGS revealed at least one genomic alteration (excluding variants of uncertain significance (VUS) and synonymous mutations) in 80 patients (77%). Median number of alterations per patient was 3 [range, 1-15], with a median mutant allele fraction of 0.42% (range, 0.1% - 94.2%). The total number of unique alterations was 389, with the most commonly altered genes being: *TP53* (84 alterations, 22%), followed by *KRAS* (34 alterations, 9%), *FGFR2* (31 alterations, 8%), *ARID1A* (20 alterations, 5%), APC and PIK3CA (16 alterations each, 4%). Amplifications were noted in 14 genes, including BRAF, CCND1, CCND2, CCNE1, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, MET, MYC, PDGFRA, and PIK3CA. Fusions of FGFR2 were seen in 3 cases. Potentially actionable alterations were seen in 63 of the 104 patients (61%). **Conclusions:** ctDNA plasma profiling of patients with advanced CCA is a feasible alternative method to gather comprehensive genomic data. Further study of responses to ctDNA NGS-guided over tissue-guided targeted therapy is needed to define the best means to optimize outcomes in CCA.

4090 Poster Session (Board #279), Sun, 8:00 AM-11:30 AM

Outcomes based on age in the phase 3 CELESTIAL trial of cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC). *First Author: Lorenza Rimassa, Humanitas Clinical and Research Center, Rozzano, Italy*

Background: The incidence of HCC generally increases with age, although the age of onset varies depending on disease etiology and geographic region (Yang, Nat Rev Gastroenterol Hepatol 2010). In the phase 3 CELESTIAL trial (NCT01908426), C, an inhibitor of MET, VEGF receptors, and AXL, improved overall survival (OS) and progression-free survival (PFS) compared with P in pts with previously-treated advanced HCC. Overall, median OS was 10.2 mo for C vs 8.0 mo for P (HR 0.76, 95% CI 0.63–0.92; p = 0.0049), and median PFS was 5.2 mo for C vs 1.9 mo for P (HR 0.44, 95% CI 0.36–0.52; p < 0.0001). Here, we evaluate clinical outcomes based on age in the CELESTIAL trial. **Methods:** 707 pts were randomized 2:1 to receive C (60 mg qd) or P. Eligible pts had pathologic diagnosis of HCC, Child-Pugh score A, ECOG PS ≤1, and must have received prior sorafenib. Randomization was stratified by disease etiology, geographic region, and extent of disease. Outcomes were analyzed for subgroups based on age (< 65 years and ≥65 years). **Results:** Median age at baseline was 64 years; 51% of pts were < 65 years old. Etiology of HBV was more frequent in pts < 65 years vs ≥65 years old (52% vs 22%), while etiology of HCV occurred at a similar frequency in both age groups (24%). Asian race and enrollment in Asia were more frequent in pts < 65 years vs ≥65 years old (46% vs 21% Asian race; 35% vs 14% enrolled in Asia). Median OS was 9.6 mo for C vs 7.7 mo for P (HR 0.81, 95% CI 0.62–1.05) for pts < 65 years old and 11.1 mo for C vs 8.3 mo for P (HR 0.74, 95% CI 0.56–0.97) for pts ≥65 years old. Median PFS was 5.0 mo for C vs 1.9 mo for P (HR 0.45, 95% CI 0.35–0.57) for pts < 65 years old and 5.4 mo for C vs 2.0 mo for P (HR 0.46, 95% CI 0.35–0.59) for pts ≥65 years old. The discontinuation rate due to treatment-related adverse events in the C group was lower in pts < 65 years vs ≥65 years old (11% vs 22%), while the percentage of pts with any dose reduction (61% vs 64%) and the median average daily dose of C (37 mg vs 34 mg) were similar in both age groups. The most common grade 3/4 adverse events in both age groups were consistent with those in the overall population. **Conclusions:** C improved OS and PFS vs P in pts with previously-treated advanced HCC irrespective of age category. Clinical trial information: NCT01908426.

4091 Poster Session (Board #280), Sun, 8:00 AM-11:30 AM

Impact of cholangiocarcinoma (CC) molecular heterogeneity on outcome during first-line chemotherapy and access to targeted therapies in early clinical trials (CT). *First Author: Helena Verdaguer, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: CC has poor prognosis and limited therapeutic options beyond first-line therapy. It is molecularly heterogeneous with several gene alterations (alt) that can be matched to targeted treatments in CT. We investigated the impact of CC molecular profiling in the clinics. **Methods:** From 2011 to 2017, we identified 165 patients (pts) with advanced CC - 129 intrahepatic CC (ICC) and 36 extrahepatic CC (ECC) - whose tumors were analyzed in our center with NGS tests (124 had fusion panels). We retrospectively collected outcome information and access to CT. **Results:** Most pts were diagnosed at stage IV (67%) and received first-line gemcitabine plus platinum (80%). Most common alt found in ICC were mutations (mt) in *TP53* (19%), *IDH1* (14%), *CDKN2A* (9%), *IDH2* (7%), *ATM* (7%), *BAP1* (6%), *PIK3CA* (6%), *KRAS* (6%), *NRAS* (5%), *BRAF* (4%) and fusions in *FGFR2/3* genes (3%). In ECC, we found mt in *TP53* (28%), *CDKN2A* (11%), *PTEN* (11%), *PIK3CA* (6%), *BRCA2* (6%) and mt or amplifications (amp) in *ERBB2* (11%). With a median follow up of 56 months (m), median overall survival (OS) of the overall population was 23 m, with no differences between ICC and ECC (p = 0.83). There was statistically significant difference in OS between pts with *TP53* mt *vs TP53* wild type (wt) tumors (28 m *vs* 15 m, HR 1.8, p = 0.01). During first-line therapy, median progression free survival (PFS) was 6.6 m in *TP53* mt and 3.8 m in *TP53* wt patients (HR 2.3, p < 0.01). 40 pts (24%) were included in a CT, with 24 pts (15%) being matched by molecular alt. Most frequent matches were FGFR inhibitor (inh) (25% of pts with targetable fusion), IDH inh in 5 (21%), PI3K inh in 3 (13%), BRAF inh in 3 (13%). Among pts treated in matched CT, median PFS was 4 m; 2 pts (8%) achieved a partial response (1 MET amp;1 BRAF mut) and 11 (46%) had stable disease as best response. We found no associations between targetable gene alt and OS or PFS during first-line therapy. **Conclusions:** CC is a heterogeneous tumor with a broad spectrum of molecular alt that have prognostic and treatment implications. Matched therapies may confer clinical benefit. Molecular profiling of CC is of growing interest to improve the knowledge of this disease and its therapeutic opportunities.

4092 Poster Session (Board #281), Sun, 8:00 AM-11:30 AM

A bi-institutional phase II study of hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone (Dex) combined with systemic gemcitabine and oxaliplatin (GemOx) for unresectable intrahepatic cholangiocarcinoma (ICC). *First Author: Andrea Cercek, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite advances in systemic therapy for unresectable ICC, median survival remains less than 12 months (mo). HAI FUDR alone and combination systemic therapy both have activity in these patients. This trial investigated HAI FUDR/Dex plus GemOx. **Methods:** Thirty nine patients (pts) with unresectable ICC were enrolled at two institutions between 2013-17. Pts were treated with HAI FUDR and GemOx every 2 weeks. Progression-free survival (PFS) was calculated from date of HAI to progression of disease (POD) or death and compared to historical controls. Secondary outcomes included overall survival (OS), conversion to resection, response rates, and toxicity. PFS and OS were estimated using Kaplan-Meier methods. Twenty nine pts from MSK underwent targeted next generation tumor sequencing of > 400 genes (MSK-IMPACT). **Results:** Median age was 61 (range 38-80), 13 (33%) male. The median PFS was 11.5 mo, (90% CI:9.7mo), exceeding the historical controls of 6-8 mo. Eighteen pts (46%) had partial response (PR) and 20 (51%) had stable disease (SD), for a 97% disease control (PR+SD) rate. Three pts were converted to resectability and were censored at 12, 12 and 16 mo, respectively. Four pts (10%) had grade 4 toxicities requiring removal from the study, including portal hypertension, GDA aneurysm and GDA extravasation related to HAI catheter, and hyperbilirubinemia. The most common grade 3 toxicities were elevated liver enzymes (ALT 54%, AST 33% and bilirubin 18%), abdominal pain 13% and anemia 12%. At a median follow up of 17 mo, the 1 year OS was 86.4% [95%CI:70-94%] and the 2 year OS was 53% [95%CI: 32%-69%]. Most prevalent mutations were IDH1/2 (9/26, 34.6%), BAP1 (8/26, 30.7%), TP53 (4/26, 15.3%). IDH1/2 mutations were associated with OS benefit (p = 0.018). **Conclusions:** Combined HAI FUDR plus GemOx is effective therapy for unresectable ICC due to its high rate of tumor response and control, PFS benefit, and manageable toxicities. The regimen warrants further investigation in a randomized trial. Clinical trial information: NCT01862315.

4093 Poster Session (Board #282), Sun, 8:00 AM-11:30 AM

Understanding quality of life in hepatocellular carcinoma patients. *First Author: Stacie Hudgens, Clinical Outcomes Solutions, Tucson, AZ*

Background: Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer causing morbidity and adversely affects quality of life (QoL) from serious symptom burden. **Methods:** HRQoL collected in a multicenter, randomized, open-label, Phase 3 study compared first-line systemic treatment lenvatinib (LEN) to sorafenib (SOR) in unresectable HCC, were evaluated descriptively. Key QoL outcomes for patients progressing ≤3 months v > 3 months were modeled longitudinally and summarized using area under (AUC) the time curve analyses. The difference in AUC was calculated with contrasting domain parameter estimates of a mixed model with time, group, time*group, and a random intercept at baseline and Day 1 each cycle through Cycle 18. **Results:** 954 patients were randomized to LEN (N = 478) or SOR (N = 476). Trial outcomes: median OS LEN (13.6 mos) v SOR (12.3 mos), HR 0.92; 95% CI, 0.79–1.06; median PFS 7.4 v 3.7 mos, respectively (HR 0.66; 95% CI, 0.57–0.77; *P* < 0.0001). Baseline HRQoL outcomes (e.g. EORTC QLQ-C30, HCC18, and EQ-5D) were markedly worse across most domains for patients who progressed earlier on treatment for both LEN and SOR arms (EQ-5D health utility index = 0.82 and 0.84 (respectively; ≤ 3 months) v 0.88 and 0.86 (respectively; > 3 months). The difference in AUC for EORTC QLQ-C30 role functional status was 0.1644 (95% CI = -0.2281, 0.5569; p-value = 0.4113) and for physical function was 0.0974 (95% CI = -0.3963,0.5911; p-value = 0.6989) favoring LEN. The difference HCC specific symptoms (HCC18) markedly favored LEN on sex life (dif = -0.4244), fatigue (dif = -0.1830), and nutrition (dif = -0.1522) and favored SOR on abdominal swelling (dif = 0.2021). Differences in symptoms related to jaundice, body image, and fever was minimal between treatment arms (dif ≤ 0.05). **Conclusions:** More patients experienced disease progression earlier on therapy with SOR compared to LEN. In our analysis baseline QoL was more severely impacted HCC patients who progress earlier while on therapy, suggesting that patients treated with LEN have an added benefit in terms of QoL as progression occurred later compared to SOR treated patients. Functional and symptom differences in QOL measures, while not statistically significant, also favored patients treated with LEN. Clinical trial information: NCT01761266.

4094 Poster Session (Board #283), Sun, 8:00 AM-11:30 AM

Additional value of tumour growth rate (TGR) in patients (pts) diagnosed with well-differentiated neuroendocrine tumours (NETs) achieving RECIST-defined stable disease (SD): Subgroup analysis of the GREPONET study. *First Author: Angela Lamarca, Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Response evaluation with RECIST has limitations when applied to slow growing malignancies with low objective response rates, such as NETs, when most pts achieve SD as best response. TGR represents the percentage of change in tumour volume per month and is postulated to overcome such limitations. **Methods:** Pts from 7 centres with advanced, grade (G) 1/2 NETs from the pancreas (P) or small bowel (SB) initiating systemic treatment (ST) or watch and wait (WW) and who achieved SD as best response were eligible. Baseline and follow-up scans were retrospectively reviewed for TGR calculation (%/month) at 3 (+/-1) months (m) of study entry (TGR_{3m}). A previously identified TGR_{3m} cut-off of 0.8 %/m was applied to assess impact of TGR_{3m} on progression-free survival (PFS) (Kaplan-Meier/Cox Regression). **Results:** Out of 222 pts in the GREPONET study, 81 were eligible and included in this analysis: 54.3% SB, 45.7% P; 87.7% metastatic; 61.7% G2; 70.4% treatment-naïve). STs were; somatostatin analogues 34.6%, chemotherapy 22.2%, targeted therapies 12.4%, radionuclide therapy 4.9%; WW 25.9%. Median (med) PFS was 22.9m (95%CI 17.3-30.6); median follow-up 39.8m. TGR_{3m} was available for all 81 pts [med 0 (95%CI -28.7-71.5)]; TGR_{3m} cut-off of 0.8 %/m stratified SD pts in two groups with different outcomes: the pts with $TGR_{3m} < 0.8$ (55 pts; 67.9%; med TGR_{3m} -0.8 [95%CI -1.7-0]) had a significantly longer med PFS (27.4m (95%CI 19.7-39.1)) vs. pts with $TGR_{3m} \geq 0.8$ (26 pts; 32.1%; med TGR_{3m} 3.8 [95%CI 2.9-6.2]; med PFS 9.8m (95%CI 6.4-23.6)); p 0.003. TGR_{3m} and treatment were significant in univariate Cox regression and included in multivariable Cox regression: $TGR_{3m} \geq 0.8$ (HR 3.6 [95%CI 1.9-6.6]; $p < 0.001$) was independent factor related to shorter PFS. **Conclusions:** TGR_{3m} is able to subclassify patients otherwise defined as SD by RECIST in two groups with different outcomes. By applying TGR we identify pts at higher risk of early progression who may require closer radiological follow-up, even if initially defined as SD by RECIST.

4095 Poster Session (Board #284), Sun, 8:00 AM-11:30 AM

Assessing prognosis of neuroendocrine neoplasms: Results of a collaborative multinational effort including over 10.000 european patients—The ENETS registry. *First Author: Ivan Borbath, Department of Gastroenterology, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium*

Background: Global European high quality epidemiologic data on Neuroendocrine Neoplasms (NEN) are lacking. There is limited knowledge on the contribution of prognostic factors on patient (pt) management. **Methods:** The multinational ENETS registry (www.enets.org/the_registry.html) was launched in 2015. To date, data from 7 countries (Belgium, Czech republic, Germany, Greece, Poland, Spain, Switzerland) were analyzed, including age, gender, primary site, functional syndrome, WHO grade, stage according to TNM/ENETS, treatment modalities and overall survival (OS). **Results:** High quality data from 10.102 pts are presented. Median age at diagnosis is 59 y (10-102y), female represent 48%. Pancreas (2722 pts, 26%) and small intestine (2132 pts, 21%) NEN are the most frequent primaries. Functional syndrome is present in 26.9% of pts, 80% being carcinoid syndrome. Stage at diagnosis (n = 6297 pts) is IV in 46%, III in 16%, II in 11% and I in 27%. WHO grading (n = 7400) is G1 in 48%, G2 in 36% and G3 in 16%. Among metastatic pts (46% of total), liver is the most frequent site (77%), followed by lymph nodes (44%), bone, lung and peritoneum (10-15%). Surgery was performed in 71%, somatostatin analogues were given to 1/3 of pts, chemotherapy to 20%, molecular targeted therapies to 8% and PRRT to 9%. Median OS of all pts is 178 months. Five-year and 10-year OS are 74.5% and 60.9% respectively. OS is influenced by grade (G1: 279 months, G2: 167m, G3: 18m) and stage (I: Not reached, II: 225m, III: 160m, IV: 75m). Multivariable analyses show that grade and stage are independent predictors of OS: grade 2 vs grade 1 (HR 1.49, $p < 0.001$), grade 3 vs grade 1 (HR 7.56, $p < 0.001$), stage 3 vs stage 1 (1.59, $p = 0.001$) and stage 4 vs stage 1 (HR 3.99, $p < 0.001$). **Conclusions:** This analysis represents the largest multinational dataset of NEN patients to date, and highlights the crucial role of WHO grading (Ki67) for predicting patients' prognosis. In addition, it provides valuable information on patients' demographics, tumor characteristics and applied therapies.

4096 Poster Session (Board #285), Sun, 8:00 AM-11:30 AM

A phase I/II study of the combination of temozolomide (TM) and pazopanib (PZ) in advanced pancreatic neuroendocrine tumors (PNETs) (NCT01465659). *First Author: Manali A. Bhave, Northwestern University, Chicago, IL*

Background: PNETs are distinguished by increased vascularity and benefit from anti-angiogenic therapies. PZ is a tyrosine kinase inhibitor (TKI) of VEGFR-1-3, PDGFR-α, -β, and c-Kit with single agent activity in PNET (overall response rate (ORR) 22%, median PFS of 14 mo and median OS of 25mo). TM is an oral alkylating agent also with known single agent activity in well-differentiated NETs (PFS of 7 mo). The rationale for the combination of TM and VEGF TKI is based on preclinical synergism through alteration of the tumor microenvironment by VEGF TKI to enhance the activity of TM. **Methods:** This is an open-label phase I/II study to determine the maximum tolerated dose (MTD), safety profile, ORR and pharmacokinetics (PK) of TM and PZ in patients (pts) with advanced well-differentiated PNETs who received 1-4 prior therapies. In a 28-day cycle, TM was given days 1-7 and 15-21 with PZ 400 mg once daily continuously. Dose escalation cohorts of TM: (-2) 75 mg/m^2, (-1) 100 mg/m^2, and (1) 150 mg/m^2. PK analysis was performed for 6 pts at MTD. The phase II portion at MTD is ongoing. **Results:** 28 pts with advanced well-differentiated PNETs were enrolled in phase I between Feb 2013 and Jan 2016 (16 at cohort -2, 5 at cohort -1, and 7 at cohort 1). 2 pts were not evaluable for any endpoint. There were 5 dose-limiting toxicities (DLTs): hepatic dysfunction (2), thrombocytopenia (2) and neutropenia (1). The MTD was at dose level -2, TM 75 mg/m^2 and PZ 400 mg. The most common treatment-emergent adverse events were hepatic toxicity (16%), nausea (5%) and fatigue (5%). Best ORR was PR in 5 pts (25%) and SD in 9 pts (45%). At a median follow-up of 18.5 mo, the median PFS was 12.1 mo (95% CI, 5.7-25.1) and median OS was 36.2 mo (95% CI, 21.4-56.4). **Conclusions:** The combination of TM and PZ was tolerable at a dose level of -2 with hepatic toxicity and myelosuppression as the DLTs. The ORR was 25% with disease control rate of 70% in patients with previously treated advanced well-differentiated PNETs. The phase II component of the study is ongoing. Clinical trial information: NCT01465659.

4097 Poster Session (Board #286), Sun, 8:00 AM-11:30 AM

First in human phase 1/2a study of PEN-221 somatostatin analog (SSA)-DM1 conjugate for patients (PTS) with advanced neuroendocrine tumor (NET) or small cell lung cancer (SCLC): Phase 1 results. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Somatostatin receptor 2 (SSTR2) is highly expressed in NET and SCLC. PEN-221, a SSA-DM1 conjugate that targets SSTR2, results in complete tumor regressions in SSTR2+ SCLC xenograft models. This study assesses safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of PEN-221. **Methods:** Pts with progressive, advanced, SSTR2+ (by imaging) NET or SCLC were enrolled in escalating cohorts of 2-6 pts. The primary objective was to determine the maximum tolerated dose (MTD) of PEN-221 given every (q) 3 wks. An adaptive Bayesian logistic regression model was used to recommend doses. Intra-patient dose escalation was permitted. Preliminary efficacy was assessed using RECIST 1.1. **Results:** 23 pts (13 M/ 10 F) with NET (GI, pancreatic, lung, renal or pheochromocytoma; n = 9, 5, 5, 1, 2), or SCLC (n = 1) were treated in 7 cohorts (range 1-25 mg). As of 31 Jan 2018, the median/mean number of cycles is 3/5.8 (range 1-18), with 5 pts ongoing. PEN-221 was well tolerated with no dose limiting toxicities (DLTs) in the first 6 cohorts (1-18 mg; 20 pts). In cohort 7 (25 mg), 2 of 3 pts had DLTs that rapidly and fully resolved: Grade(G)3 ALT/AST rise (2 pts), of whom 1 had concurrent G3 total bilirubin rise and G3 mucositis. The MTD was established at 18 mg. The most frequent (≥20% pts) PEN-221 related adverse events were fatigue (43%), nausea (43%), diarrhea (39%), vomiting (26%), abdominal pain (22%), and decreased appetite (22%). PK was dose proportional, median $t_{1/2}$ ~1.7 h, with plasma exposures at MTD above preclinically efficacious levels. Among 15 NET pts who were evaluable for response, 11 had stable disease (SD) at 9 wks, of whom 8 were sustained for 18 – 45 wks, including 2 ongoing pts with SD for 44 and 45 wks. Target lesion shrinkage was observed in 3 pts (dose range 8-18 mg). One pt had a rapid and sustained decrease in chromogranin A and circulating tumor cells. One SCLC pt had SD for 12 wks. **Conclusions:** PEN-221 appears well tolerated with preliminary evidence of antitumor activity. PEN-221 (18 mg q 3 wks) will be evaluated in Phase 2a expansion cohorts enrolling midgut NET, pancreatic NET, and SCLC pts (EudraCT 2016-001468-12; NCT02936323). Clinical trial information: NCT02936323.

4098 Poster Session (Board #287), Sun, 8:00 AM-11:30 AM

Comprehensive genomic profiling of 724 gastroenteropancreatic neuroendocrine tumors (GEP-NETs). *First Author: Alberto Puccini, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: GEP-NETs are rare malignancies and their molecular characteristics are largely undefined. Here, we explored the underlying biology of GEP-NETs and the differences between gastrointestinal (GI) and pancreatic (PNET), high grade (HG) and low grade (LG) tumors. **Methods:** GEP-NETs were analyzed using NextGen sequencing (MiSeq on 47 genes, NextSeq on 592 genes), immunohistochemistry, and in-situ hybridization. Tumor mutation load (TML) was calculated based on somatic nonsynonymous missense mutations, and microsatellite instability (MSI) was evaluated by NGS of known MSI loci. **Results:** In total, 724 GEP-NETs were examined and categorized by location and grade: GI (N = 469), PNET (N = 255), HG (N = 135), and LG (N = 336). Demographics were as follow: female/male 51%/49%, median age 59 (19-90 yr). Among LG tumors, the most frequently mutated genes were *ATRX* (13%), *ARID1A* (10%) and *MEN1* (10%). Among HG, *TP53* (51%), *KRAS* (30%), *APC* (27%), *ARID1A* (23%) and *RB1* (11%). Immune-related biomarkers showed lower prevalence in LG tumors compared to HG: TML-high 1% vs 7% (P = .05), MSI-H 0% vs 4% (P = .04), PD-L1 overexpression 1% vs 6% (P = .03). Compared to LG, HG NETs showed a higher mean TML (9.5mut/MB v 5.1, P < .0001), higher mutation rate in *BRAF* (5.4% v 0%, P < .0001), *KRAS* (29.4% v 2.6%, P < .0001) and *PI3KCA* (7% v 0.3%, P < .0001). When compared to GI, PNET carried significantly higher frequency of *MEN1* (25.9% v 0.0%, P < .0001), *FOXO3* (8.6% v 0.8%, P = .005), *ATRX* (20.6% v 2.0%, P = .007), and *TSC2* (6.3% vs 0.0%, P = .007), but lower frequency of mutations in *APC* (1.0% v 13.8%, P < .0001). Comparison between LG GI vs LG PNET is reported in the table. **Conclusions:** Significant molecular differences were observed in GEP-NETs by tumor location and grade, indicating differences in carcinogenic pathways and biology, as well as response to therapy. HG tumors may benefit more from immunotherapy than LG tumors. Mutations in several targetable genes may provide novel therapeutic options and suggests the utility of genomic profiling in this tumor type.

Gene	Platform	LG GI	LG PNET	P-values
MEN1	NGS	0%	24%	< 0.001
ATRX	NGS	0%	33%	0.001
FOXO3	NGS	0%	12%	0.005
TSC2	NGS	0%	7.5%	0.03
CTNNB1	NGS	0%	2.2%	0.047
PR	IHC	3%	56%	< 0.001
TOP2A	IHC	4%	17%	< 0.001
TS	IHC	2%	13%	< 0.001

4099 Poster Session (Board #288), Sun, 8:00 AM-11:30 AM

First update on overall survival, progression-free survival, and health-related time-to-deterioration quality of life from the NETTER-1 study: 177Lu-Dotatate vs. high dose octreotide in progressive midgut neuroendocrine tumors. *First Author: Jonathan R. Strosberg, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: The final per-protocol statistical analysis (cut–off date 24 July 2015) of PFS, the primary endpoint of the NETTER-1 study, showed a significant difference ($p < 0.0001$) between the treatment arms. Supplemental updated analysis was requested by regulatory authorities for registration purposes. Quality of life (QoL) was analysed one year later, with a cut-off date of 30 June 2016 for time to clinically relevant deterioration (TTD) in health-related QoL (HRQoL). **Methods:** Overall survival (OS) and PFS were evaluated using Kaplan Meier methodology. HRQoL analysis was based on EORTC QLQC-30 and G.I.NET-21 questionnaires, completed at baseline and every 12 weeks thereafter. TTD was defined as the time from randomization to the first QoL deterioration ≥10 points for each patient in the corresponding domain scale. First OS regulatory update cut-off date was 30 June 2016. **Results:** At this first update, median OS was 27.4 months in Oct arm and still not reached in Lu arm. PFS at this date showed 30 events in the Lu arm and 78 in the Oct arm (HR: 0.21 CI: 0.14 0.33; $p < 0.0001$). HRQoL TTD was significantly longer in the Lu arm vs. the Oct arm for global health status (HR 0.406; p = 0.0006), physical functioning (HR 0.518; p = 0.0147), role functioning (HR 0.580; p = 0.0298), fatigue (HR 0.621; p = 0.0297), pain (HR 0.566; p = 0.0247), diarrhea (HR 0.473; p = 0.0107), disease related worries (HR 0.572; p = 0.0176) and body image (HR 0.425; p = 0.0058). **Conclusions:** This supplemental analysis from the NETTER-1 Phase III study confirms the clinically and statistically meaningful PFS benefit, and still suggests a survival benefit with 177Lu-dotatate. It also demonstrates that 177Lu-dotatate provides a significant quality of life benefit for patients compared to high-dose octreotide. Clinical trial information: NCT01578239.

4100 Poster Session (Board #289), Sun, 8:00 AM-11:30 AM

The role of Ki-67 in determining optimal chemotherapy in high grade neuroendocrine tumors. *First Author: Katharine Thomas, Ochsner Health System, New Orleans, LA*

Background: High grade (HG) neuroendocrine tumors (NETs) are rare neoplasms with limited data about optimal treatment. This retrospective analysis was performed to determine the most efficacious chemotherapy regimen in HGNETs. **Methods:** A single center, retrospective review of patients (pts) who received at least one chemotherapy regimen for HGNET between June 1, 2012 and June 1, 2017 was conducted. Data collection included demographics, pathologic characteristics, imaging results and treatment data. Progression free survival (PFS) was defined as date from initial chemotherapy until date of disease progression based on imaging or death. Median overall survival (mOS) was also analyzed. Chemotherapy regimens included combination capecitabine and temozolomide (CAPTEM), platinum-based therapy (cisplatin or carboplatin) or other (fluorouracil, or capecitabine based chemotherapy). Response to treatment was evaluated using RECIST 1.1. Subset analysis was performed based on Ki-67 (< 55% or ≥55%). **Results:** Fifty-five pts received chemotherapy. Median number of treatment for those with a Ki-67 of < 55% and ≥55% was 3 and 1, respectively. MOS was 18 months irrespective of chemotherapy regimen; mOS by Ki-67 was 40 months for Ki-67 < 55% versus 16 months for Ki-67 ≥ 55% (Logrank test p = 0.0016). Among all pts undergoing first line therapy, CAPTEM significantly improved PFS (p = 0.041). In a sub analysis, Ki-67 < 55 had a longer PFS with CAPTEM (12-mo), followed by other (7-mo) and platinum (4-mo). In pts with Ki-67 ≥ 55%, PFS was highest in platinum-based therapy (5-mo), followed by CAPTEM (2-mo) and other (1-mo). Kaplan-Meier 3- and 6-month PFS rates based on chemotherapy regimen for pts with Ki-67 < 55% and Ki-67 ≥55 are shown in the table. **Conclusions:** This study demonstrates optimal first line chemotherapy treatment is dependent on Ki-67. Pts with a Ki-67 < 55 and Ki-67 ≥55 have improved PFS with CAPTEM and platinum-based therapy, respectively. Ki-67 values should be considered when determining first line chemotherapy regimen among pts with HGNET.

			3-mo PFS rate by Ki-67 (%)		6-mo PFS rate by Ki-67 (%)	
1st Line Regimen	N	Median PFS (mo)	< 55%	≥55%	< 55%	≥55%
CAPTEM	15	12	77	50	77	50
Other	5	7	67	50	67	50
Platinum-based	35	4	51	58	25	36
Overall	55	5	65	57	54	38

4101 Poster Session (Board #290), Sun, 8:00 AM-11:30 AM

Peptide receptor radionuclide therapy (PRRT) transcriptomic signature in blood for prediction of ^{177}lu-octreotate efficacy. *First Author: Lisa Bodei, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: PRRT uses somatostatin receptor (SSR) expression on neuroendocrine tumors (NET) to deliver radiotherapy. Pretreatment patient stratification for response remains a key unmet need. NET transcript expression in blood integrated with tumor grade provides a PRRT predictive quotient (PPQ). This study validates the clinical utility for PRRT. **Methods:** Development and validation was undertaken in 3 independent ^{177}Lu-PRRT-cohorts. Specificity and prognostic value was tested in two somatostatin analog-treated and untreated patients. Developmental cohort: lung and gastroenteropancreatic [GEP] NETs (*n*= 72). The majority were GEP (71%), low grade (86% G1-G2). Prospective validation cohorts (*n*= 42-44) were well differentiated, low grade (86-95%) lung and GEP-NETs. SSA Cohort I *n*= 28 (100% low grade, 100% GEP-NET); SSA Cohort II *n*= 51 (98% low grade; 76% GEP-NET) and an untreated cohort *n*= 44 (64% low grade; 91% GEP-NET). NET blood gene transcripts (*n*= 8: growth factor signaling and metabolism) were measured pre-therapy and integrated with tumor Ki67 using a logistic regression model with a binary output: "predicted responder" (PPQ+); "predicted non-responder" (PPQ-). Response was evaluated using RECIST criteria [Responder (stable, partial/complete response) vs Non-Responder)]. All measurements and analyses were blinded. Statistics included Kaplan-Meier survival and test evaluation analyses. **Results:** Developmental cohort, 56% responded to PRRT. The PPQ predicted 100% of responders and 84% of non-responders (accuracy: 93%). In two validation cohorts (response: 64-79%), PPQ was 95% accurate (PPQ+ = 94-97%, PPQ- = 93-100%). Overall, median PFS was not reached in PPQ+ vs PPQ- (10-14 months; HR: 18-77, $p< 0.0001$). In comparator cohorts, the predictor (PPQ) was 47-50% accurate for SSA-treatment and 50% as a prognostic. No differences in PFS were respectively noted (PPQ+: 10-12 months vs. PPQ-: 9-15 months). **Conclusions:** The PPQ derived from circulating NET specific genes and tumor grade prior to the initiation of therapy is a highly specific predictor of the efficacy of PRRT with an accuracy of 95%.

4102 Poster Session (Board #291), Sun, 8:00 AM-11:30 AM

Clinical outcomes in patients with baseline renal dysfunction in the NETTER-1 study: 177Lu-Dotatate vs. high dose octreotide in progressive midgut neuroendocrine tumors. *First Author: Jonathan R. Strosberg, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Might potential nephrotoxicity be a risk for therapy with 177Lu-Dotatate? Among patients randomised in the NETTER-1 study, nephrotoxicity and treatment efficacy were evaluated in the two study arms (177Lu-Dotatate (177Lu) vs. high-dose octreotide (Oct)) according to renal function categories at baseline (no dysfunction eCrClC-G $\geq$ 60 ml/min vs. mild dysfunction eCrClC-G = 50 – 59.99 ml/min vs. moderate dysfunction eCrClC-G $<$ 50 ml/min). **Methods:** Changes in renal function were assessed in the two arms per the three baseline categories, and analysed via Fisher's exact test. The primary endpoint of the NETTER-1 study, progression-free survival (PFS), was evaluated after classifying the patients according to the baseline renal function categories (impaired vs. normal at baseline). **Results:** There were 93 patients with normal renal function, 11 with mild baseline renal dysfunction and 13 patients with moderate dysfunction in the 177Lu arm. Equivalent numbers were seen in the Oct arm (85 with normal function, 16 with mild and 9 with moderate dysfunction; p = 0.41825 for imbalance between the two study arms). The rates of deterioration of renal function over baseline in the two treatment arms for each of the three categories of baseline renal function, were similar (p = 0.70695; 1.0000; 1.000, respectively). In patients with no renal impairment at baseline, Kaplan-Meier analysis showed a greater PFS (p $<$ 0.0001 log-rank test); HR 0.180 [95% CI: 0.102 – 0.318] within the patients treated with 177Lu vs. those treated Oct. In those with renal impairment at baseline, Kaplan-Meier analysis showed a greater PFS (p $<$ 0.001 log-rank test); HR 0.251 [95% CI: 0.084 – 0.751] among the patients treated with 177Lu (N = 23) compared to those treated with Oct (N = 24). **Conclusions:** The NETTER-1 study did not show any evidence of nephrotoxicity associated with 177Lu treatment, even in patients with mild to moderate baseline impairment in renal function. Long-term analysis of renal function will be performed at time of overall survival analysis. Treatment with 177Lu resulted in a markedly longer PFS regardless of whether baseline renal function was normal or impaired.

4103 Poster Session (Board #292), Sun, 8:00 AM-11:30 AM

Optimal cut points for Ki-67 proliferative index in predicting survival in high grade neuroendocrine tumors. *First Author: Robert A. Ramirez, Louisiana State University Health Sciences Center, New Orleans, LA*

Background: High grade (HG) neuroendocrine tumors (NETs) are rare neoplasms with limited literature regarding their prognostic course. HG-NETs generally demonstrate aggressive behavior. We hypothesized that patients diagnosed with HG-NETs with a Ki-67 proliferative index of $\geq$55% will have a worse prognosis. **Methods:** Records of patients with HG-NETs seen at our clinic between June 1, 2012 and June 1, 2017 were retrospectively reviewed. Demographics, pathologic characteristics, primary site and treatment data were collected. Overall survival (OS) was measured from date of high-grade diagnosis to either the date of death or the study cutoff date (December 31, 2017). Subset analysis was performed based on Ki-67 at initial HG-NET diagnosis ($<$ 55% or $\geq$55%) as well as Ki-67 at initial NET diagnosis ($<$ 20%, $>$ 20-54%, or $\geq$55%). **Results:** Fifty-five patients were included in our study. Eleven patients were initially diagnosed with low/intermediate grade NETs (Ki-67 $<$ 20%) and subsequently transformed to HG-NETs (Ki-67 $>$ 20%) after progression. Median OS for the entire group was 18 months (m). The 6, 12 and 24m survival rate was 89%, 62%, and 40% respectively. A significant survival advantage was shown in patients with Ki-67 $<$ 55% as shown in the table (p $<$ 0.05) Survival did not vary significantly between primary tumor site. Low/intermediate (L/I) grade patients who transformed to HG-NETs had a median OS from HG diagnosis of 43m with 6, 12 and 24m survival rate of 100%, 82% and 64% respectively which was a significant compared to the entire cohort (p $<$ 0.05). **Conclusions:** Using a Ki-67 value of 55% is useful in conferring prognosis in patients with HG-NETs. Interestingly, patients who were initially diagnosed with L/I grade NETs and transformed to HG survived longer than those with an initial HG diagnosis. Treatment options for HG-NETs should take into account Ki-67 values.

Ki-67 Proliferative Index	N	Median OS (months)	6-month OS	12-month OS	24-month OS
Ki67 < 55%	27	35	96%	74%	53%
Ki-67≥55%	28	12	82%	50%	29%

4104 Poster Session (Board #293), Sun, 8:00 AM-11:30 AM

Pembrolizumab (P) monotherapy in patients with previously treated metastatic high grade neuroendocrine neoplasms (HG-NENs). *First Author: Namrata Vijayvergia, Department of Hematology/Oncology, Fox Chase Cancer Center, Philadelphia, PA*

Background: There is currently no standard therapy for metastatic HG-NENs after progression on platinum based therapy and available chemotherapy is of limited benefit. Given the promising activity of checkpoint inhibitors in small cell lung cancer, we initiated a phase II trial of P (PD-1 inhibitor) in pts with previously treated metastatic HG-NENs. **Methods:** A prospective, open-label, phase 2 trial, for which pts with metastatic, histologically confirmed HG-NENs (Ki67 $>$ 20%), excluding lung/thymus origin, were eligible after prior platinum based therapy. Other eligibility criteria included ECOG PS 0–1, adequate hematological, hepatic, and renal function. Pt selection was not based on PD-L1 expression but archival tissue was mandated for correlative testing of immunophenotype. P was administered at a dose of 200 mg every 3 weeks intravenously with and radiographic evaluation was conducted every 9 weeks. The primary endpoint was overall response rate. **Results:** Between 11/ 2016 and 1/ 2018, 21 pts (11 males/ 10 females) were enrolled from two institutions and received at least one dose of P, thus completing accrual. Grade 3 toxicities were observed in 6 pts (28%) with 4 (19%) at least possibly related to P (elevated liver enzymes, fatigue, hypercalcemia and hyperkalemia). Other common grade 1-2 toxicities observed include fatigue (32%), diarrhea (26%) and nausea/vomiting (37%). Efficacy analyses and correlative studies are underway and will be presented at the meeting. **Conclusions:** P as a single agent can be safely administered to pts with advanced HG-NENs with similar toxicity profile as described previously for this agent. Efficacy data and correlative analysis will be presented at the annual meeting. Clinical trial information: NCT02939651.

4105 Poster Session (Board #294), Sun, 8:00 AM-11:30 AM

Multicenter phase 2 study of nintedanib in patients (pts) with advanced progressing carcinoid tumors. *First Author: Renuka V. Iyer, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Serotonin is the cause of carcinoid symptoms and can signal the formation of fibroblasts via fibroblast growth receptors (FGFR). Nintedanib is an oral inhibitor of the FGFR pathway and several angiogenic signaling pathways thought to drive carcinoid tumor progression. We hypothesized that nintedanib may slow tumor progression in pts with progressing carcinoids in a phase 2 study. **Methods:** Thirty pts with unresectable/metastatic carcinoids on stable dose of somatostatin analogue for $\geq$3 months were included from two sites (NCT02399215). *Primary Endpoint*: progression free survival (PFS) rate at 16 wks. *Secondary Endpoints*: Objective response (complete + partial responses) using standard RECISTv1.1 criteria; overall survival (OS); change in QOL throughout treatment using EORTC QLQ–GI.NET21 questionnaire for carcinoid pts; and toxicity (graded using the NCI CTCAE version 4.0). **Results:** Baseline characteristics: M/F: 15/15), ECOG PS: 0/1/2: 11/17/2; Median age (years): 64.9 (45.1-77.2); site of origin: small bowel (13), colon (7), lung (4), gastric (1), unknown primary (5); PD on prior everolimus: 10/30 (30%). PFS rate at 16 wks was 86.7%; 95%CI: 72-95.3% (26 pts). The study was designed to compare to a historic PFS rate of 0.30 with everolimus. Kaplan Meier median PFS and OS estimates were 11 and 27.6 months, respectively, with 6 pts currently on active treatment. RECIST response: PR 1(4%), SD 20 (83%), PD 2(8%), NE 1(4%). Reasons for coming off therapy: progression 14 (58%), toxicity 5(21%), other (17%), death due to disease 1(4%). QOL was maintained or improved in at least 50% of subjects while on therapy. Treatment was held in 7 pts (23%) due to AEs. Highest grade AEs: gr2 in 14(47%) and gr3 in 8(27%) pts. The most common gr 2 were GI (9), heme (8) and gr 3 were hypertension (6) and decreased appetite (2). From individual Bayesian analysis using the nintedanib pop PK model developed, correlation between actual and predicted exposures, with 61% variability in the absorption rate between pts was seen. **Conclusions:** Nintedanib is active and well tolerated in pts with advanced carcinoids. PFS data are encouraging and expected to mature. Ongoing biomarker studies may allow optimal pt selection. Clinical trial information: NCT02399215.

4106 Poster Session (Board #295), Sun, 8:00 AM-11:30 AM

Clinicopathological, genomic and immunological features of hyperprogressive disease during PD-1 blockade in gastric cancer patients. *First Author: Yosuke Togashi, Division of Cancer Immunology, Exploratory Oncology Research and Clinical Trial Center, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Hyperprogressive disease (HPD) during PD-1 blockade reported in several cancer types is a big hurdle for applying cancer immunotherapy, whereas there is no report in gastric cancer (GC) and the detailed clinicopathological, genomic, and immunological features remain to be determined. **Methods:** To clarify clinicopathological, genomic, and immunological features of hyperprogressive disease during PD-1 blockade in patients with advanced GC, 36 patients with advanced GC who received nivolumab from October 2017 to December 2017 and underwent at least one imaging evaluation of their clinical responses were enrolled in this study. Tumor DNA/RNA samples and tumor-infiltrating lymphocyte (TIL) were also analyzed using next-generation sequencing and flow-cytometry assay, respectively. **Results:** Among 36 patients, four patients (11.1%) experienced hyperprogressive disease, and their prognosis was very poor with three of four patients died within very short period after the initial administration of nivolumab (range 20 to 65 days). Three and two among four patients were subjected to genome analyses and TIL analyses, respectively. One patient had an MDM2 gene amplification as was previously reported, whereas the other patients did not have any MDM2 gene family alterations. Immunological analyses in two patients revealed that effector regulatory T (eTreg) cells with proliferative capacity ($Ki67^{+}CD45RA^{-}FOXP3^{high}CD4^{+}$ T cells) were markedly increased in TILs from pre-treatment to hyperprogressive disease state, whereas those in non-hyperprogressive disease patients showed significant reduction. Especially, one patient without MDM2 gene amplification contained enormously high frequency of $Ki67^{+}$eTreg cell-infiltration in the tumor at HPD state. **Conclusions:** HPD during PD-1 blockade is observed in gastric cancer as well as other cancer types and the prognosis is very poor. High regulatory T cell-infiltration and MDM2 family gene alterations might contribute to HPD, which should be taken care during the treatment with anti-PD-1 antibodies.

4107 Poster Session (Board #296), Sun, 8:00 AM-11:30 AM

Gemcitabine plus nab-paclitaxel until progression or given sequentially with 5-fluorouracile plus irinotecan (FOLFIRI.3) for first-line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC): A randomized phase II study (PRODIGE 37-FIRGEMAX). *First Author: Julien Taieb, Sorbonne Paris Cité, Paris Descartes University, Department of Gastroenterology and Digestive Oncology, Georges Pompidou European Hospital, Paris, France*

Background: Chemotherapy is effective in mPDAC but new approaches are still needed to improve patients (pts) survival and quality of life. We have previously published successful results of a sequential treatment strategy of gemcitabine followed by an intensified FOLFIRI regimen[1] with good efficacy and tolerability results. In the present study, we tested the same sequence with the new gemcitabine + nab-paclitaxel (G+A) first-line standard therapy[2]. **Methods:** We randomized chemotherapy-naive pts with proven mPDAC, bilirubin levels ≤1.5 ULN and performance status (PS) 0-2 to receive in alternance G+A (MPACT regimen)[2] (2 months [mo]) and FOLFIRI.3 (FIRGEM regimen)[1] (2 mo; arm A), or G+A alone (arm B). The primary objective was to increase the 6-mo progression-free survival (PFS) rate from 40% (H0) to 60% (H1; binomial exact method; required 124 pts). Analyses were done in preplanned modified intent-to-treat (mITT, pts who received at least one dose of treatment) and per-protocol (PP, pts reaching the 2 mo treatment switch) populations. **Results:** Between Nov 2015 and Nov 2016, 127 pts were enrolled. Mean age was 64 years (range: 38-76), PS was 0/1/2 in 37/51/12%, no major imbalance for baseline characteristics was noted between arms. Main grade 3-4 toxicities per pt (%) were (arms A/B): diarrhea (13/2), nausea/vomiting (9/2), neutropenia (42/31), febrile neutropenia (2/0), skin toxicity (5/14), and peripheral neuropathy (13/20). No toxic deaths occurred. Best objective response rates (mITT) were A: 40% (95%CI, 28-54) and B: 25% (95%CI, 15-38). 6-mo PFS rates were A: 45% and B: 23% in mITT (n = 122; HR: 0.70; 95%CI, 0.48-1.03) and A: 60% and B: 30% in PP (n = 90; HR: 0.57; 95%CI, 0.36-0.90). Median OS (PP) was A: 15.8 and B: 12.4 mo (HR: 0.66. 95%CI, 0.37-1.16). **Conclusions:** The FIRGEMAX strategy with G+A followed by FOLFIRI.3 every 2 mo, appears to be feasible and effective, with manageable toxicities and decreased neurotoxicity, in patients with mPDAC able to reach > 2mo of treatment for their disease. *1-Trouilloud EJC 2014 2-Von Hoff NEJM 2013* Clinical trial information: NCT02827201.

4108 Poster Session (Board #297), Sun, 8:00 AM-11:30 AM

Targeting advanced pancreatic cancer with activated t cells armed with anti-CD3 x anti-EGFR bispecific antibody. *First Author: Lawrence G. Lum, Emily Couric Cancer Center, Charlottesville, VA*

Background: Conventional chemotherapy (CT) for advanced pancreatic cancer (PC) is associated with dismal response rates and poor survival. Arming anti-CD3 activated T cells (ATC) with anti-CD3 x anti-EGFR bispecific antibody (EGFRBi) makes every ATC into a non-MHC-restricted EGFR-specific cytotoxic T lymphocyte. Engagement of CD3 on T cells and EGFR on PC cell lines leads to cytokine secretion, proliferation, cytotoxicity by ATC, and inhibition of tumor growth. **Methods:** We report on 9 LAPC and MPC patients (pts) (5 phase I and 4 phase I/II pts). In our phase I study at Karmanos Cancer Institute (KCI) on NCT0140874, EGFRBi-armed T cells (EGFR BATs) were used to target EGFR in 5 pts with unresectable or metastatic PC in a phase I dose escalation involving 3 weekly infusions of 10, 20, and 40 x 10^9 BATs per infusion followed by a booster infusion 3 months later for up to 80 x 10^9 BATs if they were stable or better. In a phase II study performed at KCI on NCT02620865 and continued at the University of Virginia (UVA) on NCT03269526, 4 pts received two infusions per week of 10^{10} EGFRBi BATs for 4 weeks for a total of 8 x 10^{10}. **Results:** Following the BATs infusions in the phase I study at KCI, one pt was stable for 6.5 months and 2 pts who progressed after the infusions developed complete responses (CRs) to subsequent CT. Remarkably, pt IT20104 who was stable for 1 year on capecitabine had a "flare" or "pseudoprogression" after 3 BATs infusions, but subsequently achieved a CR to capecitabine and has been off therapy for 1 year (40.8 months after enrollment). The median overall survival (OS) in 5 pts was 31.0 months [13.6, 14.5, 31.0, 40.8 (CR) and 42.5 months after enrollment] with the median time to progression (TTP) of 7.0 months. In summary, 5 of 5 pts in the phase I survived > 1 year. In the phase II study, two pts have stable disease at 2.3 and 21.5 months, respectively. The median OS is 31.0 months for all 9 patients. **Conclusions:** While these patients are selected, these results are promising. Targeting PC with EGFR BATs may have improved OS in a small series of pts. The series provides evidence for anti-tumor activity of EGFR BATs, and, in addition, the BATs infusions may enhance tumor responses to subsequent CT. Clinical trial information: NCT01420874.

4109 Poster Session (Board #298), Sun, 8:00 AM-11:30 AM

Sequential treatment with Nab-paclitaxel plus Gemcitabine and Folfirinox in metastatic pancreatic adenocarcinoma: GABRINOX phase II results. *First Author: Eric Assenat, Institut du Cancer de Montpellier (ICM), Univ Montpellier, Montpellier, France*

Background: Folfirinox (FFX) and Nab-paclitaxel/Gemcitabine (AG) showed significant efficacy improvement compared to Gemcitabine alone in metastatic pancreatic cancer (mPC). Alternating AG and FFX may overcome resistance and delay tumor progression. We designed a multicenter phase I-II trial to evaluate a sequential treatment with AG followed by FFX in 1st-line. Phase I established the recommended doses and confirmed the feasibility in a 12-patient expansion cohort (Assenat et al, ESMO 2016). Phase II assessed the efficacy of the recommended doses. **Methods:** During phase II, AG and FFX were administered sequentially, each AG cycle followed by 2 FFX cycles. All chemotherapeutic agents were administered according to standard practice. The primary endpoint was the objective response rate (ORR). **Results:** 58 patients were included in 3 centers, between 2014 and 2016. Patients were 50% male, median age 60 years (34-72), ECOG PS 0 (37.9%) or 1 (62.1%). A median of 4 (1-9) cycles were administered, during 34.2 weeks (2.1-79.4). Neurotoxicity rate was low (gr3: 5.2%). Main grade 3/4 toxicities were thrombosis (17.2%/0%), thombopenia (31%/1.7%), neutropenia (34.5%/22.4%), febrile neutropenia (1.7%/1.7%), nausea (17.2%/0%), diarrhea (25.9%/1.7%), weight loss (1.7%/0%) and asthenia (31%/0%). No toxic death was reported. Efficacy analysis included 57 patients. Response was complete in 3.5% patients; partial in 59.7%; disease was stable in 21% patients, progressive in 15.8%. The primary objective was met with an ORR of 63.2% (95% CI: 49.3-75.5). After a median follow-up of 18.6 months (95% CI: 14.5-25.6), the median progression-free and overall survival were 9.6 months (95% CI: 6.0-12.3) and 17.8 (95% CI: 11.7-21.3) months. **Conclusions:** This phase II study confirmed the phase I data with an acceptable toxicity and a high response rate for this alternating AG and FFX treatment. Survival results are promising and justify considering further randomized trials in these setting. Clinical trial information: NCT01964287.

Time (months)	PFS rate (%)	95% CI	OS rate (%)	95% CI
9	51.6	[37.8-63.8]	70.3	[56.6-80.4]
12	41.2	[27.3-54.7]	61.5	[47.6-72.7]
15 (PFS) / 18 (OS)	29.2	[16.2-43.4]	47.9	[33.3-61.0]

Survival analyses: n = 58

4110 Poster Session (Board #299), Sun, 8:00 AM-11:30 AM

Phase 1b/2 trial of cancer stemness inhibitor napabucasin (NAPA) + nab-paclitaxel (nPTX) and gemcitabine (Gem) in metastatic pancreatic adenocarcinoma (mPDAC). *First Author: Tanios S. Bekaii-Saab, Mayo Clinic, Phoenix, AZ*

Background: NAPA is an oral investigational agent, hypothesized to inhibit cancer stemness pathways, including STAT3 pathway implicated in cancer stem-cell viability. We report updated data in a study of mPDAC patients (pts) (NCT02231723) treated with NAPA + nPTX + Gem, including a subgroup of pts eligible for enrollment in the ongoing phase 3 study (NCT02993731, CanStem111P). **Methods:** A phase 1b/2 multicenter study in mPDAC pts was done to assess the recommended phase 2 dose, PK profile, and signals of anticancer activity of NAPA + nPTX + Gem. Pts received NAPA 240 mg BID + weekly nPTX 125 mg/m^2 + Gem 1000 mg/m^2 for 3 of every 4 weeks until disease progression or other discontinuation criteria. **Results:** Of 59 study pts, 47 (79.7%) were treatment-naïve, and 12 (20.3%) had prior adjuvant treatment. There were no notable PK interactions or dose-limiting toxicities. The most common adverse events included grade 1 diarrhea, neuropathy, pyrexia, and grades 1/2 nausea and fatigue. Among all 59 pts, disease control rate (DCR) was observed in 46 (78.0%) with 2 complete responses (CR) (3.4%) and 26 partial responses (PR) (44.1%) with maturing median progression-free survival (mPFS) and overall survival (mOS) of 7.06 and 9.59 mo, respectively. Among the 50 evaluable pts by RECIST, DCR was 92.0%, with 2 CR (4.0%) and 26 PR (52.0%). Of 9 nonevaluable pts, treatment stopped due to disease progression (3), death (1), noncompliance (2), pt withdrawal (2), and insurance coverage loss (1). In 29 pts eligible for CanStem111P trial, mPFS and mOS is 7.10 and 12.62 mo, respectively. Clinical trial information: NCT02231723. ORR, objective response rate; N/A, not yet reached [1]Evaluable: received ≥1 dose of study drug and had ≥1 on-study RECIST evaluation **Conclusions:** NAPA was well tolerated when combined with nPTX + Gem, with encouraging signs of activity in mPDAC, which are now being further investigated in an ongoing phase 3 study.

	DCR %		ORR %			
Subset	Evaluable[1]	All	Evaluable	All	1 yr OS rate (95% CI)	2 yr OS rate (95% CI)
All	92.0	78.0	56.0	47.5	46 (33,58)	13 (5,25)
Pts eligible for CanStem111P	88.5	79.3	53.8	48.3	54 (34,70)	N/A

4111 Poster Session (Board #300), Sun, 8:00 AM-11:30 AM

A phase 1/2, open-label dose-escalation study of liposomal irinotecan (nal-IRI) plus 5- fluorouracil/leucovorin (5-FU/LV) and oxaliplatin (OX) in patients with previously untreated metastatic pancreatic cancer (mPAC). *First Author: Andrew Peter Dean, St. John of God Hospital, Subiaco, Australia*

Background: nal-IRI+5-FU/LV is effective for patients with mPAC after disease progression following gemcitabine-based therapy. The current study (NCT02551991) is a phase 1/2, open-label trial to assess the safety, tolerability, and dose-limiting toxicities (DLT) of nal-IRI+5-FU/LV+OX (NAPOX) for the first-line treatment of patients with mPAC and to determine Phase 3 dosing. **Methods:** NAPOX is being evaluated in patients ≥18 yrs with previously untreated mPAC, with an ECOG performance status ≤1 and adequate organ function. Three of 4 dose-escalation cohorts of NAPOX, dosed on day 1 and 15, have been initiated. Safety and tolerability are the primary endpoints of this study, with assessment of exploratory efficacy signals. **Results:** As of 10 Nov 2017, 24 patients (Cohort A: n = 7; Cohort B: n = 7; Cohort C: n = 10) have received ≥1 dose of NAPOX (median age: 66.0 yrs, range: 44–78 yrs). Five patients reported ≥1 DLT (Cohort A: n = 2/7; Cohort B: n = 1/7; Cohort C: n = 2/10). The most frequent treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) disorders (Cohort A: 71%; Cohort B: 71%; Cohort C: 60%). Grade 3 or 4 TEAEs were GI disorders (Cohort A; 43%; Cohort B: 14%; Cohort C: 50%) and neutropenia (Cohort A: 43%; Cohort B: 29%; Cohort C: 40%). The best overall response was partial response (PR) in 6/24 patients (Cohort B: n = 3/7; Cohort C: n = 3/10). In Cohort B (the lowest and most tolerable cohort), n = 5/7 patients reached disease control (PR or stable disease > 16 weeks), with n = 4/7 patients were treated for ≥24 weeks. **Conclusions:** Initial analysis suggests a well-tolerated dose and promising antitumor clinical activity of NAPOX. Dose escalation and expansion is ongoing. Clinical trial information: NCT02551991.

	Dose			Current Patients		Grade 3/4 TEAEs			
Cohort	nal-IRI (mg/m^2)	5-FU/LV (mg/m^2)	Oxaliplatin (mg/m^2)	Dosed (n)	Ongoing (n)	Neutropenia (n)	Diarrhea (n)	Vomiting (n)	Nausea (n)
A	80	2,400 / 400	60	7	0	3	3	1	0
B	60	2,400 / 400	60	7	2	2	1	0	0
C	60	2,400 / 400	85	10	3	4	3	3	2
D*	65	2,400 / 400	70	-	-	-	-	-	-

* Cohort not yet initiated

4112 Poster Session (Board #301), Sun, 8:00 AM-11:30 AM

A phase II study of pre- and post-operative gemcitabine and erlotinib plus pancreaticoduodenectomy (PD) for patients with resectable pancreatic ductal adenocarcinoma (PDAC): ACOSOG Z5041 trial (Alliance). *First Author: Alice Chia-chi Wei, University of Toronto, Toronto, ON, Canada*

Background: For resectable PDAC (without vascular involvement) post-operative adjuvant therapy remains the standard, though there is considerable interest in a neoadjuvant approach. This study evaluates overall survival (OS) with perioperative gemcitabine + erlotinib (G+E) combined with PD for resectable PDAC. **Methods:** ACOSOG Z5041 was a prospective, multicenter, single-arm phase II trial of pre- and postoperative G+E for resectable PDAC. Key eligibility requirements were localized biopsy-confirmed PDAC in the pancreatic head, resectable without evidence of tumor involvement of major mesenteric vessels. Patients (pts) received standard G+E (100 mg days 1-43) prior to and following surgery. The primary endpoint was 2-year overall survival (OS); secondary endpoints included toxicity profile, response rate, resection rate and time to progression. The study was closed early due to slow accrual; no formal hypothesis testing was performed. **Results:** 116 meeting eligibility requirements were enrolled; 114 who initiated treatment were evaluable. By central radiologic review, 97 pts met protocol resectability criteria, 17 pts were beyond. Median age was 66 years (39-88); 55 females (48%). Grade 3+ toxicity was reported in 68 (60%) and 90 (79%) pts during the neoadjuvant phase and overall. 22 (19%) pts did not proceed to surgery. 92 (81%) pts had surgery; 83 (73%) were resected with PD, 9 (8%) were unresectable. R0 and R1 margins were 67 (81%) and 15 (18%) of resected pts, respectively. 54 received post-operative G+E (65% resected, 47% evaluable). 2-year OS for evaluable pts was 40% (95%CI 31-49%) with median OS 21.3 (95%CI 17-26) months. 2-year OS for resected pts was 52% (95%CI 37-59%) with median OS 25.4 (95%CI 22-30) months. **Conclusions:** For resectable PDAC, neoadjuvant therapy provides 2-year OS similar to pts able to receive standard adjuvant therapy. Importantly, futile PD was avoided in 27% pts. Further evaluation of neoadjuvant therapy in resectable PDAC is warranted as more active chemotherapy regimens emerge. Support: U10CA180821, U10CA180882; Clinical trial information: NCT00733746.

4114 Poster Session (Board #303), Sun, 8:00 AM-11:30 AM

Comprehensive molecular profiling of paired patient samples of primary and metastatic (met) pancreatic ductal adenocarcinoma (PDAC). *First Author: Neel Trivedi, Medstar Georgetown University Hospital, Washington, DC*

Background: Pancreatic cancer is the third leading cause of cancer-related death in the U.S. The vast majority of pancreatic cancer is PDAC (90%). Most patients with PDAC die from complications from met disease, thus it is vital to better understand the molecular changes that promote met spread. Prior studies have shown few molecular changes between primary and met PDAC in unpaired analyses, but limited data exist on large-scale comparisons between paired samples from the same patient. **Methods:** We analyzed next-generation sequencing (NGS) and immunohistochemistry (IHC) data from 123 patients with multiple PDAC tumors profiled by Caris Life Sciences and compared paired primary and met samples from the same patient. After patients with unrelated second primary cancers were excluded, 113 pairs were used for analysis. McNemar's test was used to compare primary and met tumor pairs. **Results:** The most common sites of mets were liver (33%), lung (19%), and peritoneum (18%). The average time between samples was 21.3 months (range 1-92). *KRAS* status changed in 13.2% of pairs (5.7% gained, 7.5% lost, n = 53, P = 0.710), *TP53* status changed in 16.1% (16.1% gained, 0% lost, n = 31, P = 0.025), and *SMAD4* status changed in 14.8% (7.4% gained, 7.4% lost, n = 27, P = 1.000). Mets gained expression of TOPO1 (37.5%, n = 80, P = 0.003), TOP2A (42.6%, n = 47, P = 0.003), PTEN (27.3%, n = 66, P = 0.050), and PD-L1 (11.1%, n = 36, P = 0.180). Tumor mutational burden (TMB) increased in mets in 11 of 12 pairs with TMB data (mean 6.67 v. 4.42 mutations per megabase, P = 0.0015 by Wilcoxon signed-rank test). **Conclusions:** *KRAS* mutational status between primary and met PDAC pairs was usually concordant but changed more often than previously reported. TOPO1, TOP2A, and PTEN expression were significantly discordant. The rate of discordance and increase in TMB support profiling of PDAC mets. Continued research into which mutations play key roles in PDAC mets could yield new targets for future therapies.

4115 Poster Session (Board #304), Sun, 8:00 AM-11:30 AM

Geographic and ethnic heterogeneity in the *BRCA1/2* pre-screening population for the randomized phase III POLO study of olaparib maintenance in metastatic pancreatic cancer (mPC). *First Author: Talia Golan, Institute of Oncology, Sheba Medical Center, Ramat Gan, Israel*

Background: Germ-line mutations in *BRCA1/2* (g*BRCA*m) can cause defective repair of double-strand DNA breaks and are a risk factor for mPC. The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib exploits homologous recombination repair deficiency in *BRCA*m tumors to produce synthetic lethality. Its efficacy is being evaluated in the POLO trial (NCT02184195). It is unknown how geography and ethnicity impact uptake of *gBRCAm* pre-screening in mPC. **Methods:** POLO is an international, ongoing, placebo-controlled trial to determine efficacy of olaparib (tablet formulation) maintenance monotherapy in *gBRCAm* pts with mPC. Mandatory pre-screening involves *gBRCA* testing by Integrated BRACAnalysis (Myriad Genetic Laboratories/MGL). The current analysis includes pts with *gBRCA*m previously identified by MGL or via pre-screening. Demographic/clinical history data were collected at enrollment. **Results:** 2206 pts from 12 countries were tested between 10/14 and 12/17. Pre-screening identified 130/2179 (6.0%) with a new *gBRCAm*; 27 additional pts had a previously known *gBRCAm* that were confirmed by Myriad testing; total 159/2206 (7.2%). Pre-screened pts were 57.2% male; 21% had early-onset mPC (Age in yrs: < 33: 0.6%; 33-49: 20.3%; 50-64: 49.4%; 65-88: 29.7%). *gBRCAm* pts were younger (57.9 vs. 61.1 yrs).The countries with the highest rates of new gBRCAm by pre-screening were: USA 37/288 (12.8%), Israel 26/230 (11.3%), France 24/293 (8.1%), Germany 17/262 (6.4%), Italy 15/250 (6%), Spain 14/344 (4%), and Korea 10/196 (5.1%). Outside US and Israel (populations enriched in Ashkenazi Jews), *gBRCAm* was newly identified in 96/1668 (5.75%). All pts with a known *gBRCAm* were White; all *gBRCAm* in African American/Asian/Hispanic pts (n = 19) were first identified by pre-screening. **Conclusions:** 6-7% unselected mPC have *gBRCAm*, with substantial geographic variability. Pts with *gBRCAm* were diagnosed at younger ages. Non-White pts were universally unaware of familial *gBRCAm* before pre-screening, highlighting potential disparities in uptake of genetic testing in minority populations and emphasizing the need to improve access to testing. Clinical trial information: NCT02184195.

4116 Poster Session (Board #305), Sun, 8:00 AM-11:30 AM

Potentially curative combination of TGF-b1 inhibitor losartan and FOLFIRINOX (FFX) for locally advanced pancreatic cancer (LAPC): R0 resection rates and preliminary survival data from a prospective phase II study. *First Author: Janet E. Murphy, Massachusetts General Hospital, Boston, MA*

Background: FFX is under study in LAPC for its potential for curative resection, but the downstaging rate remains low. Preclinical data suggest that inhibition of the renin-angiotensin system with losartan reduces TGF-b1 activity, enhancing intratumoral penetration of chemotherapy by remodeling desmoplasia and improving perfusion. This study investigated the R0 resection rate of FFX/losartan in LAPC. **Methods:** LAPC pts (per NCCN criteria), ECOG PS 0-1 were enrolled in a single institution NCI-sponsored phase II study (NCT01821729). Pts received 8 cycles FFX/losartan. If the tumor was radiographically resectable after chemotherapy, pts received short-course chemoradiation (CRT) in 5 fractions (protons 25 GyE, capecitabine 825 mg/m2 bid). If the tumor still abutted vasculature, pts received CRT to 50.4 Gy with a vascular boost to 58.8 Gy. Primary endpoint was R0 resection rate. Secondary endpoints were mPFS, mOS and circulating biomarkers of losartan activity. **Results:** 50 pts enrolled from 8/2013 to 7/2017. One pt withdrew consent, and 49 pts were evaluable for this analysis. Median age was 63y (42-78), tumor size was 41mm (18-68). Tumor was in the pancreatic head in 31 (63%) of pts. 39 pts received 8 cycles of FFX/losartan, while 10 had fewer than 8 cycles due to progression (4), losartan intolerance (3), and toxicity (3). Grade 3 or greater toxicity occurred in 25 (51%) pts, including diarrhea , thrombocytopenia, nausea, and neutropenia/febrile neutropenia. No single grade 3+ toxicity occurred in more than 14% of pts. 46 pts recieved CRT: 7 pts (14%) had short-course, while 39 pts (80%) had long-course CRT. 39 pts underwent attempted surgery, with 34 pts resected. R0 resection was achieved in 30 pts (61% of evaluable pts, 88% of resected pts), with R1 resection in 4 pts. Overall mPFS was 17.5 months and mOS 31.4 months. Among resected pts, mPFS was 21.3 months and mOS was 33.0 months. Biomarker analysis showed superior OS in pts with lower plasma levels of HGF at baseline. **Conclusions:** FFX/losartan achieved a remarkably high (61%) R0 resection rate in LAPC pts. A multi-center randomized Phase II trial is planned. Clinical trial information: NCT01821729.

4117 Poster Session (Board #306), Sun, 8:00 AM-11:30 AM

Nab-paclitaxel plus S-1 followed by S-1 maintenance therapy as a first-line strategy for advanced pancreatic adenocarcinoma. *First Author: Yan Shi, Chinese PLA General Hospital, Beijing, China*

Background: Growing evidence support maintenance therapy (MT) offer clinical benefit in pancreatic, colorectal and lung cancers. In our phase II trial, nab-paclitaxel plus S-1 (NPS) showed encouraging objective response rate (ORR) as first-line treatment in advanced pancreatic adenocarcinoma (APAC), in which S-1 was an option as MT after NPS. Our observational study aims to evaluate the effectiveness and tolerability of strategically using S-1 as MT after NPS in APAC. **Methods:** Between Jan 2014 and Oct 2017, 122 patients with APAC treated with NPS were included in this observational study. In patients without progression after at least 4-cycle of NPS (nab-paclitaxel, 240mg/m^2 every 3-week; S-1, 80-120 mg/d per body surface area on day 1-14 of each 21-day cycle) or treatment discontinued due to any reasons, S-1 monotherapy was allowed to be given as MT at physician's discretion according to patients' desire and ECOG performance status. Patients were followed up every 2 months until death. ORR, progression-free survival (PFS), overall survival (OS) and safety were measured. **Results:** In 8 locally advanced and 114 metastatic APACs, ORR, median PFS and OS were 49.2%, 7.5 (95%CI 6.0 to 9.0m) and 10.7 months (95%CI 8.6 to 12.8m), respectively. Total 84 patients had no progression after a median of 4 cycles of NPS (2 to 8 cycles), in which 49 had a median of 4-cycle S-1 MT (1 to 32 cycles). Median PFS and OS in patients with S-1 MT were 10.4 months (95% CI 7.9 to 12.9m) and 16.7 months (95%CI 14.5 to 18.9m) compared to 5.1 months (95%CI 4.7 to 5.5m) and 8.1 months (95%CI 6.4 to 9.8m) without S-1 MT ($P < 0.001$). In patients with stable disease (n = 31), mPFS and mOS in S-1 MT group were 10.4 (95%CI 6.9 to 13.9m) and 16.4 months (95%CI 13.8 to 19m) compared to 5.2 (95%CI 4.3 to 6.1m) and 8.1 (95%CI 6.7 to 9.5m) without S-1 MT ($P < 0.05$). Survival rates were 79.1% and 65.7% at 1 year, 61.9% and 33.4% at 2 years in patients with or without S-1 MT, respectively. S-1 MT group had a higher incidence of grade 3 or 4 leukopenia/neutropenia (20.4%) compared to 12.8% in the group without MT. **Conclusions:** Maintenance with S-1 after NPS was effective and well tolerated in APAC, which offered a new first-line strategy for APAC with a promising OS and PFS.

4118 Poster Session (Board #307), Sun, 8:00 AM-11:30 AM

Prospective trial of preoperative FOLFIRINOX in patients with resectable pancreatic ductal adenocarcinoma (PDAC): Report of early endpoints. *First Author: Safi Shahda, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Chemotherapy and surgical resection improve survival in patients with PDAC. Neoadjuvant therapy (NAT) may allow better selection for resection and provides early treatment of micrometastases. We aimed to assess pathologic response, percent of patients who undergo resection, toxicity, perioperative mortality and survival after NAT in patients with resectable PDAC **Methods:** Patients with radiographically resectable PDAC were enrolled on this single-arm clinical trial. Patients received FOLFIRINOX (5FU bolus 400 mg/m^2, leucovorin 400 mg/m^2, 5FU infusion 2400 mg/m^2, oxaliplatin 85 mg/m^2, and irinotecan 180 mg/m^2) on days 1 and 15 of every 28-day cycle. NAT with 2 cycles was followed by restaging imaging prior to surgical exploration and resection. Pathologic response was graded as G1: < 10%, G2: 10-90% and G3 > 90% viable tumor. This study was IRB approved **Results:** Between 6/2014-10/2017, 51 patients consented and 48 enrolled. Demographics: 30 male and 18 female; median age was 65 years (36-76) and race: 43 W, 3 AA, and 2 other. At the data cutoff (12/31/17), 3 patients have not yet had surgical evaluation. Of 45 patients, 36 have completed all planned preoperative chemotherapy. Thirty-five patients have undergone resection with the following features; R0 margin status: 88%, AJCC7 stage IB: 3%, IIA: 22% and IIB: 74%. Pathologic responses were G1: 6%, G2: 31% and G3: 63% without pathologic CR. Four patients (9%) progressed while on NAT, 3 (7%) were found to have metastatic disease during surgery, and none with local progression prohibiting surgical resection. Two patients died on study; one with complications related to NAT. 30-day postoperative mortality was not observed. **Conclusions:** NAT is feasible in patients with resectable PDAC and may select out patients with aggressive biology who would not benefit from resection. Pathologic responses were observed without pCR. Survival data are maturing. Clinical trial information: NCT02178709.

4119 Poster Session (Board #308), Sun, 8:00 AM-11:30 AM

Overall survival of PEGylated pegilodecakin with 5-FU/LV and oxaliplatin (FOLFOX) in metastatic pancreatic adenocarcinoma (PDAC). *First Author: J. Randolph Hecht, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA*

Background: The therapeutic options for 2nd line therapy PDAC remain unsatisfying with 5-FU/LV plus oxaliplatin or nal-irinotecan resulting in a mOS of 5-6 mo. PDAC has been largely refractory to immune-oncology approaches and CD8+ T cells are rare in most PDAC. AM0010 stimulates survival, expansion and cytotoxicity of intratumoral CD8+ T cells. Immune activation, durable stable disease and a 1yr survival of 22.5% was seen in salvage PDAC patients (pts) receiving AM0010 alone. AM0010 has synergistic anti-tumor activity with 5-FU/LV or oxaliplatin in preclinical models. Here we report on the safety, efficacy and overall survival of AM0010 + FOLFOX as 2nd and later line treatment in PDAC pts. **Methods:** PDAC pts progressing on a median of 2 prior therapies (range 1-5) were treated with AM0010 (5ug/kg SQ, qd) + FOLFOX (n = 21). The safety population (n = 25) included also 4 pts with prior oxaliplatin / 5-FU. Tumor responses were assessed with irRC. The survival population included all patients without prior platinum containing regimen. Biomarkers included the sequence analysis of blood derived T cells for T cell clonality. **Results:** AM0010 + FOLFOX, was generally well tolerated. G3/4 TrAEs included thrombocytopenia (56%), anemia (44%), neutropenia (36%) and fatigue (12%). Most cytopenias had a short duration and reaching retreatment criteria within 2-5 days after dose interruption. Dosing AM0010 for 5 days followed by a 2 days dose holiday has avoided G3/4 cytopenias. Grade1/2 but no higher grade neuropathy was observed in 16% of patients. Of 19 evaluable pts, 2 had an irCR, 1 had irPR with 100% reduction in tumor burden, ORR is 15.8%, DCR is 78.9%. With median follow-up of 23.4 months (range 18.9 - 28.9), mPFS was 2.6 mo, mOS was 10.2 mo and 1-year and 2-year survival was 43% and 28.8%, respectively. The expansion of previously non-detected T cell clones correlated with OS $>$ 8 months. **Conclusions:** AM0010 in combination with FOLFOX is well tolerated in patients with metastatic PDAC, and has a reduced incidence of FOLFOX related neuropathy. Immune activation and overall survival are encouraging in this advanced PDAC population. This regimen is currently being studied in a phase 3 trial. Clinical trial information: NCT02009449.

4120 Poster Session (Board #309), Sun, 8:00 AM-11:30 AM

Prognosis of resectable pancreatic cancer based on systemic therapy sequence and regimen: An NCDB analysis. *First Author: Aileen Deng, Thomas Jefferson University Hospital, Philadelphia, PA*

Background: While surgical resection can cure pancreatic cancer (PC), the majority of patients who undergo resection recur. As newer multi-agent chemotherapy regimens have evolved for metastatic PC, there has been increased interest in its use in the neoadjuvant (NAT) setting. However, U.S. clinical practice patterns vary widely. We evaluated the effect of systemic therapy sequence and regimen on prognosis in resected PC. **Methods:** Adult patients with resected, clinical stage I or II PC were identified in the NCDB from 2010-2015. Patients who received NAT followed by resection were matched by a minimum distance approach with those who underwent upfront resection (UR) with or without adjuvant therapy (AT) based upon demographics and disease-specific variables. OS was compared with Kaplan-Meier curves in matched cohorts. The effects of single-agent (SA) versus multi-agent (MA) chemotherapy (CT) on OS was evaluated using multivariate Cox proportional hazards regression model. **Results:** We identified 23,576 patients with clinical stage I or II resected PC. 3,446 patients who received NAT were matched with 3,446 patients who underwent UR. Those who received NAT had improved OS compared to those who underwent UR with or without AT (median survival time [MST] 27.9 versus 23.3 months, respectively; log-rank $p < 0.0001$). Among different treatment sequences, patients who received both NAT and AT had the longest OS compared to those who received either NAT or AT alone (MST 31.3 versus 26.2 versus 26.5 months, respectively; log-rank $p < 0.0001$). In patients treated with NAT alone, those who received MA CT had an improved OS compared to those who received SA CT (adjusted HR 0.72, 95% CI 0.64-0.81). In patients who received MA chemotherapy, MA NAT was associated with an 18% reduction in risk of death compared to those treated with MA AT (adjusted HR 0.82, 95% CI 0.73-0.93). **Conclusions:** In resectable PC, patients who received both NAT and AT had improved survival compared to those who receive NAT or AT alone. This supports future evaluation of maintenance therapy in the adjuvant setting. MA NAT was associated with improved survival compared to SA NAT. This supports current clinical practice and ongoing clinical trials.

4121 Poster Session (Board #310), Sun, 8:00 AM-11:30 AM

A phase II trial of neoadjuvant gemcitabine/nab-paclitaxel and SBRT for potentially resectable pancreas cancer: An evaluation of acute toxicity. *First Author: Manisha Palta, Duke University Medical Center, Durham, NC*

Background: The optimal management of potentially resectable pancreas cancer is unknown. The high rates of local and distant failures following surgical resection highlights the need for improvement in both local and systemic therapies. The combination of newer systemic therapies with ablative radiotherapy could be better tolerated and associated with improved treatment outcomes. **Methods:** Patients with newly diagnosed, previously untreated, non-metastatic pancreatic cancer who were candidates for resection were prospectively enrolled in this single arm study. Patients received a neoadjuvant regimen of 2 cycles of gemcitabine (1000mg/m^2)/ nab-paclitaxel (125mg/m^2) and SBRT (25Gy in 5 fractions). After neoadjuvant treatment patients were restaged and considered for resection. The primary study endpoint was acute toxicity as assessed by CTCAE V 4.0. The primary study hypothesis was that this neoadjuvant regimen would result in Grade 3+ non-hematologic acute toxicity of $<$ 50% (as per RTOG 97-04). **Results:** Twenty-five patients were accrued to this study. 28% had resectable and 72% had borderline resectable disease (per NCCN criteria). 96% of patients received both cycles of systemic therapy and all 25 patients went on to SBRT and completed the planned radiotherapy course. The rate of acute non-hematologic Grade 3+ toxicity with the neoadjuvant regimen was 20% (5/25). The rate of overall Grade 3+ toxicity with neoadjuvant gemcitabine/ nab-paclitaxel was 52% and Grade 3+ non-hematologic toxicity was 17%; exact 80% CI of (8%, 32%). No Grade 3+ acute toxicity was seen with neoadjuvant SBRT and 28% experienced Grade 2 toxicity. 17/25 (68%) patients went on to surgical resection and 93% achieved an R0 resection. Actuarial local control is 77% and medial overall survival is 24 months. **Conclusions:** A neoadjuvant approach of gemcitabine and nab-paclitaxel followed by SBRT in patients with potentially resectable pancreatic cancer was well tolerated. Given robust patient accrual, the initial enrollment was expanded to 40 patients and accrual is ongoing. Prospective evaluation of this treatment regimen in a randomized fashion is warranted. Clinical trial information: NCT02318095.

4122 Poster Session (Board #311), Sun, 8:00 AM-11:30 AM

Quantitative multiplex immune fluorescence to reveal the impact of chemoradiation therapy on modulation of the immune micro-environment of pancreatic ductal adenocarcinoma. *First Author: Thomas Enzler, New York Presbyterian - Columbia, New York, NY*

Background: Patients with advanced pancreatic ductal adenocarcinoma (PDA) continue to have median survival under one year and to date immunotherapy has largely been unsuccessful. Radiation or chemoradiation can cause the release of tumor antigens and pro-inflammatory cytokines leading to stimulation of anti-tumor immunity. We sought to quantify this effect by comparing immune cell infiltrations of PDAs treated with chemoradiation or not treated prior to surgical resection. **Methods:** Slides obtained from surgical specimens were stained using opal fluorophores for CD3, CD8, CD4, FOXP3, CD68, Ki-67, and DAPI for nuclear staining. This method allowed simultaneous evaluation of different markers using quantitative multiplex immunofluorescence (qmIF). Images were taken with automated imaging system VECTRA and analyzed for cell densities in tumor and stromal compartments. We included 20 patients who underwent chemoradiation and 12 patients without neoadjuvant treatment. **Results:** When comparing treated vs. non-treated tumors, total CD3+ densities were significantly higher in stromal tissue of treated tumors (P = 0.0002). There was also a significant increase in CD3+CD8+ T cell densities (P = 0.0006) and CD3+CD4+FOXP3- T cell densities (P = 0.0037) in the stromal tissue of treated tumors. Conversely, CD4+FOXP3+ T cells were significantly increased in the tumor microenvironment (TME) of non-treated tumors when compared to treated tumors (P = 0.0003). No clear differences in infiltrating CD68+ macrophages were observed between the groups. **Conclusions:** To our knowledge this is the first time that immune cell infiltrates of PDA either treated with neoadjuvant chemoradiation or not treated were compared using qmIF. The higher counts of T helper cells and cytotoxic T cells found in treated tumors can be explained by the increased immunogenicity caused by chemoradiation-therapy. The higher densities of CD4+FOXP3+ cells in non-treated tumors likely reflect the immunosuppressive TME. We will try to identify biomarkers predictive of outcome and, hopefully, our findings will provide rationale for the development of new treatment strategies.

4123 Poster Session (Board #312), Sun, 8:00 AM-11:30 AM

Safety, efficacy and pharmacodynamics (PD) of MEDI9447 (oleclumab) alone or in combination with durvalumab in advanced colorectal cancer (CRC) or pancreatic cancer (panc). *First Author: Michael J. Overman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Oleclumab is a human mAb that binds to CD73 and inhibits production of immunosuppressive adenosine. This is a first-in-human study to investigate the safety, efficacy, and pharmacodynamics of oleclumab alone or in combination with durvalumab in patients (pts) with advanced panc or MSS-CRC. **Methods:** A 3+3 dose-escalation design was followed in which pts received one of 4 escalating doses of oleclumab IV with or without durvalumab 10 mg/kg IV Q2W until disease progression, followed by study expansion with high dose of oleclumab plus durvalumab 10 mg/kg Q2W. AEs and tumor response (RECIST v1.1) were assessed. Free soluble CD73 and cell surface CD73 on lymphocytes were measured by ELISA and flow cytometry, respectively. Tumoral CD73 was centrally assessed by an *in situ* enzyme assay and IHC. **Results:** The initial dose-escalation and PD exploration enrolled 42 monotherapy and 24 combination pts with no reported DLTs. The minimum target serum concentration was exceeded at the top 2 doses. Sustained decrease in free soluble CD73 and CD73 on peripheral T cells was demonstrated across all doses and pts. Decreased CD73 enzymatic activity was observed in all evaluable frozen tumor biopsy samples (n = 4) 20 days after treatment with the top 2 doses of oleclumab. Treatment with oleclumab alone decreased tumoral CD73 expression (5/9) while increasing CD8+ TILs in all 5 samples. Subsequently, durva + oleclumab highest dose was selected for expansion in 2-5L CRC (21 pts) and 2-3L panc (20 pts). The most commonly reported TRAEs in combo expansion were diarrhea (8.7%), pyrexia (8.7%), fatigue (6.5%), and increases in ALT (6.5%), AST (6.5%), and ALP (6.5%). PR was observed for 1/21 CRC (5L) and 2/20 panc (2 and 3L) pts; SD was observed in 2/21 CRC and 3/20 panc pts. Duration of treatment for subjects with disease control was 84-322 days (CRC) and 28-232 days (panc). Treatment is ongoing for 1 CRC (322 days) and 2 panc pts (140 and 182 days). **Conclusions:** Treatment with oleclumab and durvalumab had a manageable safety profile and PD consistent with mechanism of action. Combination therapy has encouraging clinical activity in panc and potentially in CRC pts. Clinical trial information: 02503774.

4124 Poster Session (Board #313), Sun, 8:00 AM-11:30 AM

Final results from a phase II study of 5-fluorouracil, oxaliplatin, and dasatinib (FOLFOX-D) in previously untreated metastatic pancreatic adenocarcinoma. *First Author: Thomas J. George, University of Florida, Health Cancer Center, Gainesville, FL*

Background: Systemic chemotherapy for pancreatic adenocarcinoma (PCa) improves survival but most targeted agents have consistently failed to demonstrate clinical benefits. Src is overexpressed in PCa and promotes an aggressive cancer phenotype. Dasatinib (D) is an oral multi-tyrosine kinase inhibitor (TKI) affecting tumor proliferation through inhibition of Src, Bcr-Abl, CKit and other pathways. Inhibition of Src is associated with biologic modifications favorably modifying the PCa phenotype and has synergy with restoring inherent chemosensitivity. Src inhibition can also increase oxaliplatin activity and modulate Tcell responses. The addition of D to the well-established backbone of FOLFOX represents a multifaceted line of scientific investigation. **Methods:** This phase II trial is to determine activity and toxicity of FOLFOX + D in previously untreated metastatic PCa. Pts must have at least 1 RECIST measurable target lesion, ECOG PS 0-2, normal QTc and adequate organ function. Treatment is standard q14d cycles of mFOLFOX6 with continuous D (150mg PO daily). Tumor assessments occur q8w. Endpoints are PFS (primary), objective and biochemical response rates, clinical benefit rate, freedom from metastases, overall survival (OS), toxicity, and quality of life. Exploratory tissue, CTC and serum analyses to identify predictors of response are planned. Sample size is based on a 50% improved median PFS from 4 (historical) to 6 mo. **Results:** 42 of 44 enrolled pts are evaluable. Baseline demographics are in Table 1. Median PFS was 4.0 mo (95% CI 2.3-8.5; range 0.1-43.3) and OS was 10.6 mo (95% CI 6.9-12.7; range 0.1-47.9). RR was 24% with clinical benefit rate (CR + PR + SD) of 60%. 10 pts (24%) were on active therapy more than a year with a few long term exceptional responders. Toxicity has been previously reported. Molecular profiling of Src expression and circulating biomarkers is ongoing. **Conclusion:** Addition of D to FOLFOX failed to significantly improve PFS in an unselected cohort of PCa pts. Toxicity was manageable. Analysis of Src expression in exceptional responders is ongoing. Clinical trial information: NCT01652976.

Baseline patient demographics

Variable	Median value (%)
Age	65 (range 29-81)
Race	Caucasian n = 37 (88)
Gender	Male n = 28 (67)
Prior adjuvant therapy	7 (17); gemcitabine-based
History of diabetes	11 (26)
Current or Former smoker	20 (48)
Serum CA19-9	3011 (range 1- > 10000) U/mL
ECOG PS	0 (n = 22); 1 (n = 17); 2 (n = 3)

4125 Poster Session (Board #314), Sun, 8:00 AM-11:30 AM

Adjuvant treatment for resected sub-centimeter T1 pancreatic cancer. *First Author: Walid Labib Shaib, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: The standard of care for pancreatic cancer (PC) patients with resected stage I to III is adjuvant chemotherapy. The role of adjuvant treatment for sub-centimeter T1 stage is unknown. This study evaluated treatment patterns and survival outcomes in T1 stage PC using National Cancer Database (NCDB). **Methods:** Retrospective review of the NCDB was conducted for T1 (tumor confined to the pancreas and 2 cm across or smaller), lymph node negative, surgically resected PC and no prior therapy. Patient demographics, tumor histology, treatment modalities, and survival trends were examined between 2004 and 2013. Adjuvant treatments were analyzed. Kaplan-Meier analysis and the log-rank tests were performed to determine the unadjusted association between overall survival (OS), size and treatment. **Results:** A total of 964 patients met criteria for inclusion. The median age was 66 (32-90). Majority were Caucasian (N = 807, 83.7%); 53.5% were female (N = 515), and moderately differentiated (N = 447, 46.4%). Tumors of 1-2cm constituted 71.2% (N = 686); 28.8% < 1cm (N = 178). Majority had negative surgical margins (N = 887, 93.3%). Patients who received surgery alone were 48.3% (N = 466); 27.5% received adjuvant chemotherapy (N = 265), and 22.6% had adjuvant chemotherapy and radiation (N = 218). Patients with < 1cm tumors who received adjuvant therapy had a median OS that was not reached v. 85.3 mo who received surgery alone (P = 0.41). In patients with 1-2 cm tumors, the median OS for patients who received adjuvant treatment was 70.7 mo v. 30.8 mo for patients who received surgery alone (P < 0.0001). The 12-mo, 24-mo, and 60-mo survival was 93.2%, 75.6% and 53.6% respectively, v. 72.5%, 61.0%, and 31.0%, respectively, for patients who received surgery alone. These results of adjuvant therapy for tumors < 1 cm v. 1-2 cm are paralleled for patients who received adjuvant chemotherapy (P = 0.08), and any adjuvant radiation (P = 0.15). **Conclusions:** This is the first report of adjuvant treatment analysis for resected PC patients with sub-centimeter stage I disease. Adjuvant treatment does not appear to improve survival in sub-centimeter T1, stage I PC.

4126 Poster Session (Board #315), Sun, 8:00 AM-11:30 AM

Precision medicine for pancreatic cancer patients:preliminary results from the know your tumor program. *First Author: Emanuel Petricoin, George Mason University, Manassas, VA*

Background: To democratize the implementation of precision medicine (PM) in the care of pancreatic cancer patients, the Know Your Tumor (KYT) program was initiated US-wide using a turn-key PM operating system that produces a treatment decision support tool/report. **Methods:** Tumor samples were obtained for 640 patients from 287 high-volume academic and local community practices covering 44 states. Our system provides a standardized workflow within an IRB-approved registry protocol from patient intake through multi-omic molecular profiling, integration of treatment history followed by computational analysis to produce a treatment decision support tool of patient-tailored therapeutic options. Longitudinal outcome is collected on every patient along with treatment decisions, and patient experience. **Results:** Tumor samples were adequate for next-generation sequencing in 96% and immunohistochemistry in 91% of patients. *KRAS* mutations were identified in 92% of pancreatic ductal adenocarcinomas. A tumor board reviewed the results for every patient and found actionable genomic alterations in 50% of patients (with 27% highly actionable) and actionable proteomic alterations (excluding chemopredictive markers) in 5%. Actionable alterations commonly found were in DNA repair genes (*BRCA1/2* or *ATM* mutations, 8.4%) and cell cycle genes (*CCND1/2/3* or *CDK4/6* alterations, 8.1%). A subset of samples was assessed for actionable phosphoprotein markers. To date, 126 (19.7%) patients have utilized a molecularly matched therapy. Patients with highly actionable biomarkers who received matched therapy (n = 17) had a median progression-free survival (PFS) of 4.1 months, significantly longer than patients without highly actionable biomarkers (n = 72; PFS = 2.8 months; adjusted *P*-value = 0.03). **Conclusions:** A comprehensive PM system can be implemented in community and academic settings, with highly actionable findings observed in ~25% of pancreatic cancers. Patients whose tumors have highly actionable molecular alterations and who receive matched therapy demonstrated significantly increased PFS. Our findings support expansion and further prospective evaluation of precision oncology in pancreatic cancer.

4127 Poster Session (Board #316), Sun, 8:00 AM-11:30 AM

Chemotherapy and radiotherapy application for pancreatic cancer in Europe and USA: An international population-based study. *First Author: Lei Huang, German Cancer Research Center (DKFZ), Heidelberg, Germany*

Background: The role of chemotherapy in the treatment of pancreatic cancer (PaC) has been well-established, while radiation plays ambiguous roles. This large-scale international population-based study aimed to investigate the trends and variations in the application of chemotherapy and radiotherapy for PaC in Europe and the US and to explore the application determinants. **Methods:** Population-based data from multiple European national cancer registries and the US Surveillance, Epidemiology, and End Results (SEER)-18 database during 2003-2014 were analyzed. Temporal trends and geographical variations in the application of chemotherapy and radiotherapy were quantified using age standardization. Associations between treatment and demographic and clinical characteristics were assessed using multivariable logistic regression. **Results:** A total of 141,533 PaC patients were analyzed. From 2003-2005 to 2012-2014, chemotherapy application rates increased in most countries and more strongly among resected cancers, while radiation rates were generally low with a slight decline or no obvious trend. In 2012-2014, 13.1% (Estonia) to 64.4% (Belgium) of patients with resected PaC and 18.1% (Slovenia) to 60.0% (Belgium) of those with unresected cancer underwent chemotherapy. Radiation was administered in 2.6% (the Netherlands) to 26.7% (the US) of resected and 0.7% (the US) to 6.2% (Belgium) of unresected tumors. Strong temporal and geographical variations were observed. Patterns and strengths of the associations between treatment administration and demographic and clinical factors including age, tumor TNM stage, and location differed substantially between resected and unresected diseases and varied greatly across countries. **Conclusions:** Administration of chemotherapy but not radiotherapy for PaC increased during the last decade in Europe and the US. The evidence from randomized trials majorly supporting chemotherapy does not seem to have been implemented into the wider clinical practice in many countries. The uptake strongly varied between countries, highlighting the need for standardization in PaC treatment to improve patient care.

4128 Poster Session (Board #317), Sun, 8:00 AM-11:30 AM

DNA repair deficiency, genomic instability and immune profiling in a phase 1 study of locally advanced pancreatic cancer patients treated with veliparib, gemcitabine and radiotherapy. *First Author: Richard Tuli, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: A phase I trial of veliparib (V), gemcitabine (G) and radiotherapy (RT) was conducted to determine the maximum tolerated dose (MTD) and clinical activity in patients with and without DNA damage repair (DDR) defects. **Methods:** LA patients were treated with weekly G (1000 mg/m2), daily RT (36 Gy/15 fractions) and daily V 20 mg BID for 3 weeks escalated per Bayesian method followed by standard chemotherapy. DAVID was used to interpret differential gene expression. Cox regression model was used to identify DDR pathways associated with survival. Next generation sequencing (NGS) identified genetic mutations involved in DDR, tumor mutation burden (TMB) and microsatellite instability (MSI) status. Blood samples were interrogated for PAR protein and cytokines using an ELISA and electrochemiluminescent array, respectively. The log-rank test was used to evaluate differences in PFS and OS. **Results:** 34 patients were enrolled from 2013 to 2016. MTD of veliparib was 40 mg BID with gemcitabine 400 mg/m2 and RT (36 Gy/15). 12 patients experienced DLT (83.3% lymphopenia, 8.3% neutropenia). Median PFS and OS were 10 and 15 months, respectively. Gene expression analysis identified DDR defects in 50% of patients. Median PFS and OS were significantly higher for these biomarker positive patients (17 vs. 8 mos, $p < .01$; 22 vs. 12 mos, $p < .001$, respectively). NGS identified 10 DDR mutations which were not prognostic of outcome. median TMB was 1.8 mut/Mb. A single MSI high patient was identified who was also TMB high (> 20 mut/MB) and harbored DDR deficiency by NGS. Lower PAR levels were associated with borderline statistically significant improvements in both PFS and OS ($p < .06$). Higher levels of IL2 and IL12 and lower levels of FLT1 were associated with improved PFS and OS ($p < .05$). **Conclusions:** The combination of V, G and RT was well tolerated. DDR alterations were identified in a large proportion of patients and were associated with improved PFS and OS. Whereas most patients were MSS and had low TMB, those with higher levels of pro-inflammatory cytokines were likely to harbor DDR alterations which were associated with improved outcomes. Clinical trial information: NCT03245541.

4129 Poster Session (Board #318), Sun, 8:00 AM-11:30 AM

High prevalence of hereditary cancer syndromes and outcomes in adults with early-onset pancreatic cancer. *First Author: Maria Fernanda Montiel, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Most patients with Pancreatic Ductal Adenocarcinoma (PDAC) are diagnosed over the age of 65. Individuals diagnosed under the age of 60 are considered to be early-onset and potentially at high risk for a genetic predisposition. We aimed to determine the prevalence of germline mutations among early-onset PDAC, as well as their influence in prognosis. **Methods:** A High Risk Cohort (HRC) and a General Cohort (GC) were included in this study. The HRC patients were patients with PDAC who met referral criteria for genetic counseling and were seen at The University of Texas MD Anderson Cancer Center (MDACC) from 2005-2016. The GC patients had metastatic PDAC and were seen at MDACC between 2010-2016. Either gene-specific (targeted) or panel DNA germline sequencing for the 13 most common genes associated with pancreatic cancer (*ATM*, *APC*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PALB2*, *STK11*, *EPCAM, PMS2)* was performed. Survival outcomes were analyzed with respect to germline mutational status and age by using Kaplan-Meier curves. **Results:** A total of 409 patients underwent genetic testing (277 from High Risk and 132 from General Cohort). As expected, the HRC had higher prevalence of germline mutations compared to the general cohort: 17.3% vs 6.81%. The most common mutations in both cohorts were in BRCA1/2 and MMR genes. Patients younger than 60 years old had significantly higher prevalence of germline mutations in both the HRC (OR: 1.93 +/-1.03-3.70, P: 0.039) and GC (4.78 +/-1.10-32.95, P: 0.036). With respect to clinical outcomes, the GC patients with germline mutations had significant higher median survival as compared to patients without mutations, 18.2 months vs 9.2 months respectively (HR: 0.44, 95% CI of HR: 0.25-0.76, *P*= 0.030). In the HRC, only patients older than 60 years old with mutations had better overall survival compared to the group without mutations (HR: 0.40, 95% CI of HR: 0.20-0.80, *P*= 0.038). **Conclusions:** Germline mutations are highly prevalent in patients with PDAC of early-onset and can be predictive of better outcomes. Considering emerging screening strategies for relatives carrying susceptibility genes as well as impact on therapy choices, genetic counseling and testing should be encouraged in young onset PDAC.

4130 Poster Session (Board #319), Sun, 8:00 AM-11:30 AM

Outcome driven persona-typing for precision oncology: Beyond a genomics centered view of individualized therapy. *First Author: Emanuel Petricoin, George Mason University, Manassas, VA*

Background: Precision oncology is currently being defined mainly by a genomics-oriented view to tumor biology. However, a multi-omic view to tumor biology and more accurate outcome prediction is emerging. Combining this with treatment history, clinical-epidemiological data, and outcomes data may provide patient-specific descriptors that in N-dimensional space constitute population based "personas" that share common outcome destinies and identify response predictors to any given therapy. **Methods:** We utilized our database from 919 pancreatic adenocarcinoma patients within our ongoing registry study as a feasibility study. Commercial exome (315 genes by NGS) and proteomic data (24 proteins by IHC) as well as previous and current treatment history, epidemiological data and outcomes data were collected on every patient. Overall Survival (OS) was calculated and 10 individual outcome "personas" were created that spanned short-term survival (< 6 months) to long term survival (32-110 months). Statistical analysis of individualized gene, protein, specific treatment type, disease stage, location, age, gender, ethnicity, was used to determine key principal components that significantly ($p < 0.05$) described each outcome persona to create a unique persona-type identifier. **Results:** Proteomic information was significantly associated with outcomes more frequently then genomic information ($p = 0.02$). Longest term outcome personas (OS > 32 months) were characterized by increased PD1 and decreased TS protein levels along with increased frequency of BRCA2 genomic alterations and treatment with off-label targeted therapy. Shorter term personas (OS < 6 months) were described by high TS protein levels along with genetic alterations in MYCL1, MYST3, VEGFA, ZNF703 and KEL. **Conclusions:** Persona-typing can be used to define and map key characteristics that associate with outcome and specific treatment. In the future, individual patients can be mapped to predefined personas that could more accurately describe outcome destiny and optimized/personalized therapy options.

TPS4131 Poster Session (Board #320a), Sun, 8:00 AM-11:30 AM

An investigator initiated multicenter phase I/II study of paclitaxel, ramucirumab with nivolumab as the second-line treatment in patients with metastatic gastric cancer. *First Author: Tomohiro Nishina, Shikoku Cancer Center, Matsuyama, Japan*

Background: Paclitaxel (PTX) and ramucirumab (RAM) is a standard regimen as the second-line treatment for metastatic gastric cancer (mGC). In the phase III ATTRACTION-2 trial, nivolumab (NIVO) significantly improved overall survival (OS) over placebo for metastatic gastric cancer (mGC) patients (pts) refractory to standard therapies. In preclinical models, anti-angiogenesis agents with immune-checkpoint inhibitors demonstrated enhanced activity against cancer cells compared with either drug alone. **Methods:** We are conducting a phase I/II study to determine the recommended phase II dose (RP2D) and evaluate the efficacy, safety and biomarkers of the combination regimen of PTX, RAM with NIVO in pts with mGC as the second-line treatment. Key eligibility criteria are: mGC pts who were refractory or intolerant to fluoropyrimidine and platinum in the first-line treatment, and had no prior immunotherapy; an age of 20 years or older; ECOG performance status of 0-1; and controllable hypertension. Phase I is designed to determine RP2D in the dose de-escalation design of NIVO (q4w, 3 mg/kg on days 1 and 15 for level 1 and 1 mg/kg for level −1) with fixed doses of PTX and RAM (q4w, 80 mg/m^2 on days 1,8 and 15 and 8 mg/kg on days 1 and 15, respectively). Primary endpoint is progression-free survival (PFS) rate at 6 months in pts treated with RP2D. Using a single stage binomial design, this study requires 43 pts, with a PFS rate at 6 months of 50% deemed promising and 35% unacceptable (one-sided alpha = 0.1; beta = 0.25). 35 patients have been enrolled since Feb 2017. Clinical trial information: UMIN000025947.

TPS4132 Poster Session (Board #320b), Sun, 8:00 AM-11:30 AM

FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab for patients with advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction as second-line therapy: The RAMIRIS study. *First Author: Sylvie Lorenzen, Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum rechts der Isar, Technische Universitat Munchen, Munich, Germany*

Background: The majority of patients with gastroesophageal cancer present with inoperable or metastatic disease. After failure of first-line chemotherapy, ramucirumab is a proven option as monotherapy and in combination with paclitaxel as second line treatment in advanced gastric cancer. Irinotecan has shown significant improvement of overall survival compared to best supportive care (BSC) in the second line setting and is an accepted safe and efficient standard chemotherapeutic treatment for patients with refractory gastroesophageal cancer. More and more patients get treated with taxanes in the perioperative or 1st line metastatic setting. For those patients the benefit of a combination of ramucirumab and paclitaxel is unclear, and many physicians would choose an irinotecan based regimen as second line treatment. This provides a rationale for the evaluation of FOLFIRI + ramucirumab. **Methods:** This is a prospective, multicenter, randomized, investigator initiated phase II trial. Patients with advanced gastric or esophagogastric junction cancer will be randomized 2:1 to FOLFIRI (irinotecan 180 mg/m^2; 5-FU 400 mg/m^2; leucovorin 400 mg/m^2; 5-FU 2400 mg/m^2 on day 1 and 15 of a 28-day cycle) plus ramucirumab 8mg/kg every two weeks (Arm A) or paclitaxel 80 mg/m^2 (days 1, 8, 15 of a 28-day cycle) plus ramucirumab 8mg/kg every two weeks (Arm B). Primary endpoint of the trial is OS rate after 6 months, based on the ITT population. The experimental therapy (FOLFIRI + Ramucirumab; n = 67) is considered to be a highly promising candidate for further development (e.g. in a phase III trial), if the true OS rate amounts to 65% or more, as this corresponds to the efficacy of the standard ramucirumab-paclitaxel regimen according to the RAINBOW study in the western population. Secondary endpoints are progression-free survival, response rate, safety and tolerability. Currently (Jan 2017) 40 of planned 111 patients are randomized. Clinical trial information: NCT03081143.

TPS4133 Poster Session (Board #321a), Sun, 8:00 AM-11:30 AM

A randomized phase 2, multicenter, open-label study of trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing gastric cancer. *First Author: Kensei Yamaguchi, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: There is no HER2-targeted therapy for patients with HER2-positive gastric cancer who progressed on trastuzumab-based therapy. DS-8201a is a novel HER2-targeted antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a cleavable peptide-based linker (deruxtecan), and with a high drug-to-antibody ratio of 7 to 8. In the ongoing phase 1 DS8201-A-J101 trial, DS-8201a showed a manageable safety profile and promising antitumor activity in salvage-line subjects with gastric cancer who previously received trastuzumab (confirmed objective response rate [ORR] of 45.5% at Oct 16, 2017 data cutoff) (Iwasa et al, ASCO-GI 2018). **Methods:** The randomized, phase 2, multicenter, open-label, DESTINY-Gastric01 study will assess the efficacy and safety of DS-8201a in HER2-expressing gastric cancer subjects. The primary cohort, HER2-positive (IHC 3+ or IHC 2+/ISH+) subjects who progressed after ≥2 prior regimens and previously received trastuzumab, will be randomized (2:1) to DS-8201a (6.4 mg/kg dose; once every 3 weeks) or physician's choice (irinotecan or paclitaxel). Two nonrandomized exploratory cohorts will assess the efficacy and safety of DS-8201a in subjects with HER2-low gastric cancer (IHC 2+/ISH- and IHC 1+, respectively) who are treatment-naïve to HER2-targeted therapies. The primary endpoint is ORR assessed by an independent central review; secondary endpoints include overall survival (OS), progression-free survival, duration of response, disease control rate, pharmacokinetics, and safety (as shown in ClinicalTrials.gov). The primary analyses for ORR and interim OS analysis will occur after all subjects complete tumor assessments on week 18 and when approximately 108 OS events are observed, whichever comes later. The primary cohort will enroll 180 subjects; providing 92.9% power to detect a difference between the ORR of 40% for DS-8201a vs 15% for physician's choice. Each exploratory cohort will enroll a maximum of 20 subjects. Enrollment began in October 2017. As of Feb 13, 2018, 12 of 180 subjects have been enrolled. Clinical trial information: NCT03329690.

TPS4134 Poster Session (Board #321b), Sun, 8:00 AM-11:30 AM

MORPHEUS: A phase Ib/II trial platform evaluating the safety and efficacy of multiple cancer immunotherapy (CIT) combinations in patients (pts) with gastric or pancreatic cancer. *First Author: Do-Youn Oh, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of (South), Korea*

Background: Multiple cancers have been treated successfully with CIT; nonetheless, only subsets of pts experience durable response with CIT monotherapy. CIT combinations may therefore be needed to simultaneously address multiple mechanisms of cancer immune evasion. The MORPHEUS platform consists of multiple, global, open-label, randomized Phase Ib/II trials designed to investigate CIT combinations in pts with different tumor types. Using a randomized trial design, multiple CIT combination arms will be compared with a single control arm. Furthermore, the design of the trials will aid in the development of CIT combinations by identifying early signals and offers the flexibility to open new treatment arms with novel CIT combinations and to close arms that show minimal clinical activity or unacceptable toxicity. Various CIT combinations that simultaneously enhance immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination will be evaluated. Here, we describe MORPHEUS Phase Ib/II trials in pts with gastric or gastroesophageal junction cancer (GC) or metastatic pancreatic ductal adenocarcinoma (mPDAC), both representing major unmet medical needs. **Methods:** MORPHEUS-GC (NCT03281369) will enroll 2 cohorts, including pts with advanced unresectable or metastatic GC who are chemotherapy naive or have progressed on platinum- or fluoropyrimidine-based chemotherapy. MORPHEUS-PDAC (NCT03193190) will enroll pts with mPDAC who have progressed on 1 line of prior chemotherapy. Additional eligibility criteria include measurable disease per RECIST v1.1 and accessibility of the tumor for biopsy. Pts in both trials will be randomized to one of the CIT combination arms or a control arm (up to 8 arms across 2 cohorts in GC; 4 arms in PDAC). In the setting of unequivocal disease progression/toxicity, pts may be eligible to switch to a different CIT combination arm. Safety measures and investigator-assessed ORR per RECIST v1.1 are primary endpoints. PFS, OS, DCR and DOR are among the secondary endpoints. Exploratory biomarkers will also be examined. Clinical trial information: NCT03281369 and NCT03193190.

TPS4135 Poster Session (Board #322a), Sun, 8:00 AM-11:30 AM

FIGHT: A phase 3 randomized, double-blind, placebo controlled study evaluating (bemarituzumab) FPA144 and modified FOLFOX6 (mFOLFOX6) in patients with previously untreated advanced gastric and gastroesophageal cancer with a dose finding phase 1 lead-in. *First Author: Daniel V.T. Catenacci, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: FGFR2b overexpression and *FGFR2* gene amplification occurs in approximately 10% of patients with gastric cancer (GC) and is associated with a poor prognosis and the presence of metastases. Bemarituzumab, a first-in-class afucosylated, humanized IgG1 monoclonal antibody, selectively binds to FGFR2b, inhibiting ligand binding and blocking receptor activation and downstream signaling. Bemarituzumab is glycoengineered to enhance antibody-dependent cell-mediated cytotoxicity (ADCC). A phase 1 study of bemarituzumab monotherapy in solid tumors (Catenacci D, Rha S, Bang YJ, et.al. ASCO 2017) identified no dose-limiting toxicities. The reported response rate was 19% (4/21) with median duration of response of 15.4 weeks in patients with late-line GC and high FGFR2b overexpression. Based on the safety and activity profile of bemarituzumab monotherapy in GC, we designed a phase 3 trial with safety run-in of bemarituzumab in combination with mFOLFOX6. **Methods:** The FIGHT study (FPA144-004; NCT03343301) is a global, randomized, double-blind, placebo-controlled phase 3 trial evaluating bemarituzumab and mFOLFOX6 in first-line patients with advanced GC. Patients with unresectable locally advanced, or metastatic GC are eligible if tumors have *FGFR2* amplification by circulating tumor DNA (ctDNA) or FGFR2b overexpression by immunohistochemistry (IHC). Eligible patients are randomized 1:1 to bemarituzumab + mFOLFOX6 versus placebo + mFOLFOX6. Bemarituzumab or placebo dosing will continue every 2 weeks until radiographic or clinical disease progression, or intolerable toxicity. The primary endpoint is overall survival (OS) and key secondary endpoints include investigator-assessed progression-free survival (PFS) and objective response rate (ORR). The primary analyses will be event-based. The FIGHT Phase 3 trial is preceded by a Phase 1 safety evaluation in gastro-intestinal tumors without selection for FGFR2b. This portion of the trial initiated in December 2017 and is currently in progress with accrual to phase 3 expected in mid-2018. Clinical trial information: NCT03343301.

TPS4136 Poster Session (Board #322b), Sun, 8:00 AM-11:30 AM

KEYNOTE-585: Phase 3 study of chemotherapy (chemo) + pembrolizumab (pembro) vs chemo + placebo as neoadjuvant/adjuvant treatment for patients (pts) with gastric or gastroesophageal junction (G/GEJ) cancer. *First Author: Yung-Jue Bang, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of (South), Korea*

Background: The FDA approved pembro for treating pts with recurrent locally advanced or metastatic G/GEJ adenocarcinoma whose disease has progressed on or after ≥2 prior therapies and whose tumors express PD-L1 (combined positive score ≥1). Combining chemo with pembro in the neoadjuvant/adjuvant setting may be beneficial for pts with locally advanced, resectable G/GEJ cancer. KEYNOTE-585 is a phase 3, randomized, double-blind study of chemo + pembro versus chemo + placebo as neoadjuvant/adjuvant treatment for locally advanced resectable G/GEJ cancer. **Methods:** Key eligibility criteria are age ≥18 years; previously untreated G/GEJ adenocarcinoma (Siewert type 2 or 3 tumor; Siewert type 1 tumor eligibility limited to those for whom planned treatment is perioperative chemo and resection), with no evidence of metastatic disease; planned surgery after preoperative chemo; ECOG performance status 0-1; adequate organ function; no active autoimmune disease. Pts will be randomly assigned 1:1 to receive chemo + pembro (arm 1) or chemo + placebo (arm 2). Pts will receive neoadjuvant (preoperative) chemo + pembro every 3 weeks (Q3W) for 3 cycles or chemo + placebo Q3W for 3 cycles followed by surgery, then adjuvant chemo + pembro Q3W for 3 cycles or chemo + placebo Q3W for 3 cycles, then monotherapy with pembro or placebo Q3W for 11 cycles; treatment will occur for up to 17 cycles. Chemo is cisplatin 80 mg/m^2 IV + either capecitabine 1000 mg/m^2 orally twice daily or 5-fluorouracil (5-FU) 800 mg/m^2 IV (investigator s choice). Pembro 200 mg was administered by IV. Adjuvant monotherapy is pembro (arm 1) or placebo (arm 2). In a separate safety cohort, 5-FU 2600 mg/m^2 IV + docetaxel 50 mg/m^2 IV + oxaliplatin 85 mg/m^2 IV + leucovorin 200 mg/m^2 IV (FLOT) is being evaluated as a potential chemo option. Primary end points are overall survival, event-free survival per central review, and pathologic complete response (no invasive disease and histologically negative nodes) rate. Adverse events are graded per NCI CTCAE v4.0 and will be monitored for 30 or 90 days after treatment. Pts will be followed for survival. Planned enrollment is 800 pts. Clinical trial information: NCT03221426.

TPS4137 Poster Session (Board #323a), Sun, 8:00 AM-11:30 AM

NCI 10066: A phase 1 / 2 study of olaparib in combination with ramucirumab in metastatic gastric and gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Michael Cecchini, Yale University, New Haven, CT*

Background: Gastric cancer remains a significant health problem in the US and globally with more than 951,600 annual cases worldwide. Moreover, the incidence of GEJ-centered adenocarcinoma is increasing dramatically in Western countries. First line chemotherapy has a < 12month median survival. In 2nd line, ramucirumab, a monoclonal antibody against VEGFR2 is approved as single agent or with paclitaxel. Hypoxia mimetic agents such as ramucirumab down-regulate homologous recombination and sensitize tumors to Poly ADP ribose polymerase inhibition (PARPi). Gastric cancer is also known to have a homologous recombination deficiency (HRD) subtype. We therefore proposed combining the PARPi olaparib with ramucirumab in metastatic gastric and GEJ adenocarcinoma. **Methods:** The study is sponsored by the Clinical Therapy Evaluation Program and is active throughout the Extended Therapeutics Clinical Trials Network. A phase 1 3+3 dose escalation is followed by an open-label single arm phase 2. The primary objective of phase 1 is to establish the safe dose of olaparib with ramucirumab. The phase 2 primary objective is to measure efficacy by the objective response rate (ORR). Eligible patient received ≥ 1 line of prior chemotherapy, no prior angiogenesis inhibitors or PARPi, have measurable disease, usual laboratory parameters, and ECOG PS 0-1. Phase 1 will enroll 9-18 patients depending on DLT. In phase 2, the BROCA-HR gene panel is an integrated biomarker. This panel includes 87 DNA repair genes, 17 of which would be expected to confer HRD when mutated. In gastric cancer these HRD genes are mutated in up to 35% of tumors reported in COSMIC and TCGA. However, given the uncertainty of the biomarker distribution in our study, 40 patients will be enrolled in phase 2 and the ORR will be stratified by biomarker distribution. The H_0 is ORR of < 5% based on the historical control for ramucirumab. The H_1 is 25% ORR for the BROCA-HR positive cohort and 20% for the negative cohort. A pre-treatment biopsy for BROCA-HR testing is required. Other studies include detecting mutational signatures, PAR substrate analysis, and PDX generation. Phase 1 is currently enrolling. Clinical trial information: NCT03008278.

TPS4138 Poster Session (Board #323b), Sun, 8:00 AM-11:30 AM

An intergroup phase III trial of ramucirumab plus irinotecan in third or more line beyond progression after ramucirumab for advanced gastric cancer (RINDBeRG trial). *First Author: Daisuke Sakai, Osaka Gastrointestinal cancer chemotherapy Study Group (OGSG), Osaka, Japan*

Background: Ramucirumab, an anti-VEGFR2 fully human monoclonal IgG1 antibody showed survival benefits in two randomized trials of 2nd line chemotherapy for advanced gastric cancer (AGC), and ramucirumab plus paclitaxel is recognized as 2nd line standard treatment. It has been suggested that sustained VEGF blockade might contribute to long-term disease control in various cancers. **Methods:** This randomized phase III study comparing irinotecan ± ramucirumab recruits patients with AGC from 110 institutions participating in 9 clinical trial groups in Japan. Primary endpoint is overall survival (OS), with the assumed hazard ratio of 0.77 (power of 80% and significance level of one-sided 0.05). Secondary endpoints include progression-free survival, time to treatment failure, response rate, disease control rate, and safety. Major eligibility criteria are: 1) histologically proven gastric or esophagogastric adenocarcinoma, 2) unresectable or recurrent disease, 3) two or more lines of chemotherapy with platinum, fluoropyrimidines, taxanes, and ramucirumab (no prior use of irinotecan), 4) disease progression during prior chemotherapy containing ramucirumab, 5) age ≥ 20years, 6) performance status (PS) 0-1, 7) evaluable disease as defined in the RECIST v1.1, 8) adequate hematologic, renal, hepatic and metabolic function (including urinary protein = 0 or 1+), 9) expected survival ≥ 90 days, 10) written informed consent. Patients are randomly allocated (1:1) to ramucirumab plus irinotecan or irinotecan alone. Irinotecan is administered at a dose of 150 mg/m2, every two weeks, in both arms, and ramucirumab at a dose of 8 mg/kg is added biweekly. Status: Opened to accrual February 2017, at 31 Jan 2018, 87/400 patients have been enrolled. Clinical trial information: UMIN000023065.

TPS4139 Poster Session (Board #324a), Sun, 8:00 AM-11:30 AM

Iconic: Peri-operative immuno-chemotherapy in operable oesophageal and gastric cancer. *First Author: Sonia Mansukhani, The Institute of Cancer Research, London, United Kingdom*

Background: Peri-operative chemotherapy with 5FU, oxaliplatin and docetaxel (FLOT) is a new standard of care in resectable gastro-oesophageal adenocarcinoma (GOA), however with 3y survival rates of only 57% there is a need to further improve outcomes by developing innovative therapeutic combinations. PD1/PDL1 checkpoint inhibitors have shown activity in GOA and we are conducting a single-arm phase II trial to investigate the safety and efficacy of the anti-PDL1 antibody avelumab in combination with FLOT (FLOT-A) as peri-operative therapy in resectable GOA. The combination aims to generate synergy by enhancing progression through the cancer-immunity cycle via the pro-immunogenic effect of FLOT chemotherapy and simultaneous avelumab-induced release of the immune inhibitory effect of the PD1/PDL1 checkpoint. **Methods:** The 2-stage trial design will evaluate the safety and efficacy of avelumab (starting dose: 10mg/kg IV 2 weekly, pre-planned dose reduction to 7mg/kg IV 2 weekly if dose limiting toxicities occur) with standard dose FLOT chemotherapy (5FU 2600mg/m2/24hr, leucovorin 200mg/m2, oxaliplatin 85mg/m2 and docetaxel 50mg/m2) for pts with operable GOA treated on a peri-operative pathway. Stage 1 will establish the safe and maximum tolerated dose of FLOT-A using a 3+3 dose finding design. Stage 2 will assess the efficacy of FLOT-A based on pathological complete response (pCR) rate and peri-op safety. The primary endpoint is pCR. Using an A'hern single stage design to rule out a lower limit of 10% pCR rate and demonstrate an increase to 25% requires the inclusion of 40 pts, to achieve 80% power and a 1-sided 0.05 significance level. An interim analysis will assess safety and Mandard tumour regression grading (TRG) after 15 pts become evaluable. If $\geq$5 pts achieve TRG 1-3 the trial will expand to 40 pts. Secondary endpoints are ORR, PFS and OS. Exploratory objectives will investigate dynamic changes of immune infiltrates in baseline and on-treatment biopsies and correlate neoepitope load, blood lymphocyte activation and faecal microbiome with tumour response. Recruitment commenced in July 2017 and 40 pts will be recruited in 2 years. Clinical trial information: NCT03399071.

TPS4140 Poster Session (Board #324b), Sun, 8:00 AM-11:30 AM

Induction nivolumab or nivolumab/ipilimumab prior to concurrent chemoradiation plus nivolumab in patients with operable stage II/III esophageal/gastroesophageal junction cancer. *First Author: Ronan Joseph Kelly, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Neoadjuvant chemoradiation (cRT) prior to surgical resection in stage II/III esophageal/gastroesophageal junction (EC/GEJ) cancer results in a complete pathologic response rate of approximately 20-25%, in adenocarcinoma subtypes. The appearance of favorable microenvironment features (enhanced tumor lymphocytes, perivascular lymphocytes and tertiary lymphoid structures) after induction therapy in resected EC suggest tumors may respond favorably to immune based therapy and in particular to PD-1 based checkpoint blockade when combined with cRT prior to surgical resection. In addition, preclinical models suggest that esophageal radiation significantly increases PD-L1 expression. The Phase III Attraction 2 study has demonstrated activity of nivolumab in a subset of heavily pretreated patients with gastroesophageal cancer. This trial proposes to evaluate the safety/efficacy of induction nivolumab or nivolumab plus ipilimumab prior to concurrent chemoradiation plus nivolumab in operable stage II/III EC. **Methods:** This is an open-label, single-arm, multicenter clinical study that will enroll 32 patients. Eligible subjects consist of adults with histologically confirmed, resectable stage II/III EC/GEJ located below the carina. Subjects must be newly diagnosed and cannot have received prior treatment. A pre-treatment biopsy is required prior to two cycles of induction nivolumab (arm A) or one cycle of induction nivolumab/ipilimumab (arm B). A repeat research biopsy is performed after the induction phase and prior to initiation of carboplatin/paclitaxel/RT plus nivolumab. Nivolumab 240mg is administered every 2 weeks for 5 cycles in total (two as induction and three with concurrent cRT). An Ivor-Lewis esophagectomy is performed approximately 6-10 weeks post completion of cRT. The primary endpoint is safety. Secondary endpoints include an assessment of the pathological complete response rate, recurrence free survival, overall survival and immunologic correlates. The study was initiated in July 2017 and is ongoing at Johns Hopkins and at the Allegheny Health Network. Clinical trial information: NCT03044613.

TPS4141 Poster Session (Board #325a), Sun, 8:00 AM-11:30 AM

IMbrave150: A randomized phase III study of 1L atezolizumab plus bevacizumab vs sorafenib in locally advanced or metastatic hepatocellular carcinoma. *First Author: Richard S. Finn, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Hepatocellular carcinoma (HCC) is a lethal disease with the highest mortality-to-incidence ratio of any solid tumor. The current standard of care for 1L treatment of patients (pts) with locally advanced or metastatic HCC is sorafenib (sor), a multikinase inhibitor. Single-agent treatment involving inhibition of PD-L1/PD-1 immune checkpoint or VEGF has shown modest activity in HCC. Evidence from a Phase I study (Stein ASCO 2018, submitted) in HCC supports a strong scientific rationale for combining atezolizumab (atezo; anti–PD-L1) with bevacizumab (bev; anti-VEGF) to achieve greater clinical benefit. In addition to its anti-angiogenic activity, bev may have immunomodulatory effects in the tumor microenvironment (increased DC maturation, enhanced T-cell infiltration, reduced MDSCs and Tregs in tumors) that can potentially increase the efficacy of atezo in inhibiting PD-L1/PD-1 signaling and restoring anti-tumor T-cell activity. **Methods:** IMbrave150 (YO40245) is a Phase III, open-label, multicenter, randomized study to evaluate atezo + bev vs sor in pts with locally advanced or metastatic and/or unresectable HCC. Eligible pts will be naive to prior systemic therapy for HCC, have $\geq$ 1 measurable untreated lesion (per RECIST v1.1), Child-Pugh class A liver function and ECOG PS 0/1. Pts with bleeding or high risk for bleeding with untreated varices will be excluded. Randomization will be stratified by region (Asia [excluding Japan] vs rest of world), macrovascular invasion and/or extrahepatic spread (presence vs absence), baseline α-fetoprotein level ($<$ 400 vs $\geq$ 400 ng/mL) and ECOG PS (0 vs 1). Pts will be randomized 2:1 to receive atezo (1200 mg) plus bev (15 mg/kg) IV Q3W or sor (400 mg) PO BID until loss of clinical benefit or unacceptable toxicity. No crossover will be allowed. Co-primary and secondary efficacy endpoints are listed in Table. $\approx$ 480 pts are planned to be enrolled globally. Clinical trial information: NCT03434379.

Efficacy endpoints.

Co-primary
ORR (investigator [INV]-assessed per RECIST v1.1), OS
Secondary
PFS, DOR, TTP (INV-assessed per RECIST v1.1)
ORR, PFS, DOR, TTP (independent review facility (IRF)-assessed per RECIST v1.1)
ORR, PFS, DOR, TTP (IRF-assessed per HCC mRECIST)

TPS4142 Poster Session (Board #325b), Sun, 8:00 AM-11:30 AM

A multi-center randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first line therapy for patients with advanced unresectable biliary tract cancer. *First Author: Vaibhav Sahai, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI*

Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis with a median overall survival (OS) less than 12 months. This randomized, multi-institutional, phase 2, two-arm study is designed to investigate the role of combinational immunotherapy, using nivolumab with chemotherapy (gemcitabine/cisplatin) or as dual immunotherapy (nivolumab and ipilimumab) in pts with advanced BTC. **Methods:** Key eligibility criteria include histologically confirmed advanced, unresectable biliary adenocarcinoma (intrahepatic or extrahepatic and gallbladder) without prior systemic treatment, measurable disease per RECISTv1.1, ECOG PS 0-1, and absence of autoimmune disease and/or chronic steroid use. Primary objective is to evaluate the progression-free survival (PFS) rate at 6 months. Secondary objectives include evaluation of overall response rate (ORR) per immune related (ir)RECIST, median PFS and OS and safety in this patient population. Exploratory objectives include identification of biomarkers of response and mechanisms of resistance through serial (before, on and post therapy) biopsies and blood collection, including sequential whole exome/transcriptomic analysis and immune cell subset analysis (tissue and blood). Arm A therapy provides gemcitabine 1000 mg/m^2, cisplatin 25 mg/m^2 on days 1, 8 with nivolumab 360 mg on day 1 every 3 weeks for 6 months. In the absence of disease progression, pts may continue single agent nivolumab for up to 2 years. Arm B therapy includes nivolumab 240 mg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks for up to 2 years in absence of disease progression. Accrual goal is 32 evaluable pts per arm. Using a null hypothesis value of 59% median PFS at 6 months, and an 80% alternative hypothesis, this ongoing study has $>$ 80% power, with a one-sided alpha of 0.05 to identify treatment efficacy in one or both study arms. Clinical trial information: NCT03101566.

TPS4143 Poster Session (Board #326a), Sun, 8:00 AM-11:30 AM

TREETOPP: A phase 2/3 study of varlitinib plus capecitabine versus placebo plus capecitabine as second-line treatment in patients with advanced or metastatic biliary tract cancers (BTCs). *First Author: Milind M. Javle, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BTCs are rare and have a poor prognosis. These cancers are often diagnosed at advanced stage with limited treatment options and poor overall survival (OS). Overexpression of epidermal growth factor receptor (EGFR), HER2, HER3, and HER4 vary from 23-57%, 4-13%, 12-23% and 59-60% of BTCs, respectively. Varlitinib is a small molecular tyrosine kinase inhibitor of EGFR, HER2 and HER4 with potent antitumor effect in preclinical BTC models. Varlitinib also demonstrated tumor shrinkage responses and durable disease stabilization in BTC patients in Phase IB study. **Methods:** A randomized, double-blind, placebo-controlled phase 2 (Part 1)/ 3 (Part 2) study to compare the efficacy of varlitinib (300 mg BID, every day) versus placebo, when combined with capecitabine (1000 mg/m^2, BID for 14 days). The primary endpoints of Part 1 are objective response rate (ORR) and progression-free survival (PFS) and for Part 2 is OS. Eligible patients include those with confirmed advanced or metastatic 2nd line BTC, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer and carcinoma of ampulla of Vater. Patients must have failed gemcitabine-contained 1st line systemic treatment. The target sample size is 482 patients, and enrollment has started on May 24, 2017. Safety data will be listed and summarized. Co-primary endpoints of Part 1 will be analyzed using data from an Independent Central Review of radiological data. A Hochberg procedure will be used to control the familywise type I error rate for Part 1 at the 10% level (one-sided). For Part 2, the primary endpoint, OS, will be tested at the two-sided 5% significance level. Clinical trial information: NCT03093870.

TPS4144 Poster Session (Board #326b), Sun, 8:00 AM-11:30 AM

A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. *First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Thus far, sorafenib remains the standard of care for first line systemic therapy in patients with advanced HCC but patient prognosis and quality of life (QOL) continues to be poor. HCC may be responsive to immunotherapy due to higher expression of immunosuppressive cells and upregulation of CTLA-4 and PD-1 immune checkpoints (Gao et al 2009, Hato et al 2014, Pardee & Butterfield 2012). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are also associated with upregulation of regulatory T cells and PD-L1/PD-1 expression (Miroux et al 2010, Pardee & Butterfield 2012). Blockade of PD-L1/PD-1 or CTLA4 immune checkpoints demonstrated clinical benefit in HCC as monotherapy. In preclinical studies, combination of anti-PD-L1 and anti-CTLA-4 antibodies enhanced antitumour activity compared to monotherapy, indicating that the two pathways are non-redundant (Stewart, et al). Early clinical data from a phase I/II trial combining anti-PD-L1 and CTLA-4 (NCT02519348) demonstrated safety and a durable objective response rate (ORR) of 18%, prompting study expansion. **Methods:** HIMALAYA (NCT03298451) is the first randomized, open-label, multicenter, phase 3 study to assess the efficacy and safety of D+T combination therapy versus sorafenib in the first-line treatment of patients with unresectable, histologically-confirmed HCC. Patients will be randomized to arms evaluating D monotherapy, D+T combination therapy, or sorafenib monotherapy. Patients will be stratified according to macrovascular invasion (yes versus no), etiology of liver disease (HBV versus HCV versus others), and performance status (ECOG 0 vs 1). The primary endpoint for this study is overall survival (OS). Secondary endpoints include ORR, duration of response, disease control rate, progression-free survival, and time to progression according to RECIST v1.1 using investigator assessments. Safety and health-related QoL will also be assessed. Clinical trial information: NCT03298451.

TPS4145 Poster Session (Board #327a), Sun, 8:00 AM-11:30 AM

Liposomal irinotecan (nal-IRI) plus 5-fluorouracil (5-FU) and leucovorin (LV) or gemcitabine plus cisplatin in advanced cholangiocarcinoma: The AIO-NIFE-trial, an open label, randomized, multicenter phase II trial. *First Author: Thomas Jens Ettrich, Ulm University, Ulm, Germany*

Background: Biliary tract cancer (CCC) is associated with a poor prognosis due to mostly advanced stages at diagnosis. Overall survival does not exceed 6 months and the 5-year overall survival rate is less than 5% for patients with advanced or metastatic disease. Advanced CCC shows response to chemotherapy resulting in an improved disease control, improved survival and quality of life (QoL). In the ABC-02 phase III trial, gemcitabine combined with cisplatin compared with gemcitabine alone prolonged PFS (8.0 vs. 5.0 mo) and OS (11.7 vs. 8.1 mo) and is considered as standard of care. So far this regimen has not been compared with other active combination regimen. Irinotecan in combination with 5-FU showed promising results in 1st- and 2nd-line therapy in many GI cancers. In pancreatic adenocarcinomas, the combination of liposomal irinotecan (nal-IRI) plus 5-FU/LV improves survival in a post gemcitabine-based treatment setting. Our research hypothesis is that this regimen compares well with respect to clinical endpoints with the standard of care gemcitabine plus cisplatin in patients with advanced CCC. **Methods:** NIFE is a randomized study for patients (to be enrolled n = 92) with locally advanced or metastatic, non-resectable, intra- or extrahepatic cholangiocarcinoma): Arm A (experimental): Nal-IRI 80 mg/m2, leucovorin 400 mg/m2, 5-FU 2400 mg/m2, on day 1, cycle q2w), Arm B (standard): Cisplatin 25 mg/m2 and Gemcitabine 1000 mg/m2 on day 1 and 8, cycle q3w. NIFE is an open label, non-comparative, multicenter, two-sided phase II study with an unconnected analysis of the results in both arms against a fixed PFS rate ($<$ 40% at 6months). The randomization (1:1) is eminent to achieve two comparable patient groups. Primary objective is PFS at 6 months. Key secondary objectives are 3-year OS, PFS, ORR, DCR and QoL/ TUDD. There will be a retrospective surgical and radiological review. Tissue and blood sample collection will be mandatory for biomarker analyses (microdissection and exome sequencing of tumor tissue, ctDNA exome sequencing, transcriptome, miRNA-arrays). Start was in Q I/2018 in 25 centers in Germany. Clinical trial information: NCT03044587.

TPS4146 Poster Session (Board #327b), Sun, 8:00 AM-11:30 AM

A multicenter pilot study of nivolumab (NIVO) with drug eluting bead transarterial chemoembolization (deb-TACE) in patients (pts) with liver limited hepatocellular carcinoma (HCC). *First Author: James J. Harding, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Emerging preclinical and clinical data indicate that regional therapies impact the immune microenvironment, induce a peripheral immune response, and may augment the effects of immune checkpoint blockade. Given the activity of NIVO in the metastatic setting, we propose to test the safety of NIVO at earlier stages of HCC (BCLC-B) as an adjuvant therapy to TACE. **Methods:** This is a multicenter phase 1 study of the combination of NIVO and deb-TACE in unresectable HCC pts (BCLC Stage B) who are not candidates for curative treatment and have Child Pugh A hepatic function (NCT03143270). The primary objectives are to assess the safety, tolerability, and to define the optimal dosing schedule of the combination. A modified 3 + 3 design will sequentially treat pts with differing schedules of NIVO relative to deb-TACE. For all cohorts, deb-TACE (loaded with 75mg of doxorubicin) is administered on Day 0. NIVO is dosed at 240mg IV every 14 days for 1 year. In Cohort 1, NIVO is administered beginning on day +14 after deb-TACE. In Cohort 2, interrupted NIVO dosing begins at Day -28 but is held on the Day 0 at the time of deb-TACE, then restarted on Day +14. In cohort 3, continuous NIVO dosing begins on Day -28 without interruption during deb-TACE. If limiting toxicities occur in $\leq$33% of each cohort; cohort 3 will be defined as the recommended schedule for this combination. This cohort will then be expanded to a total of 16 pts. Cross-sectional imaging is completed at baseline, 1 month post-embolization, and every 3 months until disease progression, intolerable toxicities, or consent withdrawal. Secondary endpoints include overall response rate by modified Response Evaluation Criteria in Solid Tumors (RECIST) and RECIST v1.1, time to progression, progression-free and overall survival. Correlative objectives include sequential whole blood sampling and biopsies (pretreatment, on-treatment, at progression) to define mechanisms of anti-PD-1 resistance and to explore the effect of different schedules of treatment on the immune environment. Up to 28 pts will enroll at 4 sites over a 2 year period. Cohorts 1 and 2 have completed enrollment as of February 2018. Clinical trial information: NCT03143270.

TPS4147 Poster Session (Board #328a), Sun, 8:00 AM-11:30 AM

Pembrolizumab-based therapy in previously treated high grade extrapulmonary neuroendocrine carcinomas. *First Author: Claire Hooker, University of California, San Francisco, San Francisco, CA*

Background: The efficacy of immune checkpoint inhibitors (CPI) has not been established in extrapulmonary high grade neuroendocrine carcinomas (EP-HGNECs), a disease for which additional treatment options are needed. Pembrolizumab (PEM) has demonstrated safety and preliminary efficacy in small cell lung cancer. This phase 2 study aims to evaluate the efficacy and safety of PEM-based therapy in biomarker unselected EP-HGNECs. **Methods Design:** Open label, adaptive Simon's 2-stage study of PEM alone (Part A) and PEM plus chemotherapy (weekly irinotecan (IRI) or paclitaxel (P); dealers' choice) (Part B). If more than 2 responses out of 14 pts by week 18 (stage 1 part A), then 21 additional patients (pts) will enroll in stage 2 (Part A), which corresponds to H_0 10% vs. H_1 26% at type I error of 0.05 with power 80%. If there is insufficient activity, the study will proceed to Part B, with a safety lead-in of 6-12 pts for IRI/PEM (up to two dose levels, 1 and -1), then 16 additional patients will be accrued for a total of 22 patients treated with PEM plus chemotherapy based on one-side binomial test of H_0 10% vs. H_1 31% at type I error of 0.05 with power 80%. Total N needed to attain 80% power will be either 35 (Part A) or 36-42 (Part A then B) with overall type I error of 0.1. Key eligibility: EP-HGNEC of all sites (excluding Merkel cell carcinoma) with progression during or after first line systemic therapy, no prior CPI, bilirubin and creatinine $\leq$1.5x ULN, ECOG PS 0-1, agreeable to baseline tumor biopsy. Treatment: PEM 200 mg IV Q21days for up to 35 treatments. Primary endpoint (EP): Overall radiographic response rate by RECIST1.1. Secondary EP: Safety, duration of response, overall survival, progression-free survival. Exploratory EP: irRECIST v RECIST1.1, baseline PBMC and tumor immune cell profiles, T cell receptor (TCR) repertoires change from baseline to post treatment time points, tumor mutation profile, Ki67 index, PD-L1 expression. Current enrollment: 5 of planned 14 patients in stage I of Part A (6/2017-present). Clinical trial information: NCT03136055.

TPS4148 Poster Session (Board #328b), Sun, 8:00 AM-11:30 AM

A phase I/II study of fosbretabulin in combination with everolimus in neuroendocrine tumors that have progressed after at least one prior regimen for metastatic disease. *First Author: Aman Chauhan, University of Kentucky, Lexington, KY*

Background: Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are rare tumors. Recent SEER database analysis shows consistent surge in the incidence of GEPNETs. Due to indolent nature of GEPNETs the prevalence of disease far exceeds the incidence. Treatment options for metastatic progressive neuroendocrine tumors are expanding. Fosbretabulin is a synthetic, water-soluble, phosphorylated prodrug of the natural product Combretastatin A4 (CA4P), which was originally isolated from the bark of the South African bush willow, Combretum caffrum. Fosbretabulin is the lead compound in a class of agents termed vascular disrupting agents (VDAs) and has shown activity as single agent in ovarian cancers and GEPNETs. Rationale: The vasoconstrictive effect of fosbretabulin is potent, though short-lived (4-8 hours), with no cumulative adverse effect. Everolimus inhibits angiogenesis, slows tumor growth and has a prolonged half-life (30 hours). Combining these two agents with distinctly different mechanisms of action may improve tumor control without additional toxicities, and has the potential of reducing drug resistance. **Methods:** This is an investigator initiated, single center, open label, phase I/II study involving gastroenteropancreatic neuroendocrine tumors, consisting of a dose escalation Part A followed by an expansion cohort Part B. Primary Objective is to establish the maximum tolerated dose of the combination of everolimus and fosbretabulin in neuroendocrine tumors that have progressed after at least one prior regimen for metastatic disease. Secondary Objectives include evaluation of safety profile of the combination and to observe and record anti-tumor activity. Patients will be treated with daily oral everolimus. Fosbretabulin will be administered IV either q3 weekly or q weekly based on partial order continuous reassessment model (PO CRM). Clinical trial information: NCT03014297.

TPS4150 Poster Session (Board #329b), Sun, 8:00 AM-11:30 AM

A phase I/II study of ribociclib plus everolimus in patients (pts) with metastatic pancreatic adenocarcinoma (mPAC) refractory to chemotherapy. *First Author: Benjamin Adam Weinberg, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: mPAC has a poor prognosis, with a 5-year survival rate of 2.3%. CDK4/6 is often deregulated in mPAC due to loss of *CDKN2A* via homozygous deletion or epigenetic silencing, resulting in the loss of the p16INK4a protein that naturally inhibits CDK4/6. CDK4/6 inactivates the retinoblastoma protein (RB), allowing E2F family transcription factors to promote cell cycle progression. Inhibitors of CDK4/6 have been ineffective as single agents in part due to Ras-mediated activation of alternate signaling pathways including the PI3K-mTOR pathway. We have shown that co-inhibition of the CDK4/6 and mTOR pathways suppresses growth in mPAC patient-derived xenografts. We are investigating the activity of the combination of ribociclib (a CDK4/6 inhibitor) and everolimus (an mTOR inhibitor) in pts with mPAC. **Methods:** This is a phase I/II, single-arm, open-label study. Eligible pts are $\geq$ 18 years old, have histologically confirmed mPAC with progression on at least 1 prior 5-FU- and 1 gemcitabine-based regimen, an ECOG performance status of 0-1, normal bone marrow and hepato-renal function, and no concurrent anticancer therapy. Exclusion criteria are use of prior CDK or mTOR inhibitors or known CNS metastases. Pts in the phase I portion will be enrolled in a 3+3 design to find the recommended phase II dose (RP2D) of ribociclib with dose escalation and de-escalation levels. Pts in the phase II portion will receive ribociclib at the RP2D daily for 21 days out of a 28 cycle with everolimus 2.5 mg daily continuously. The phase II portion will use a Simon's Minimax 2-stage design. Disease will be assessed by imaging every 8 weeks. Treatment will continue if it is tolerated and there is no disease progression. The primary endpoint of the phase II portion is progression free survival (PFS) at 8 weeks. Secondary endpoints are median PFS, median overall survival, best overall response rate by RECIST 1.1, and safety. Correlative studies include assessment of the pharmacodynamic effects on the RB pathway using pre- and on-treatment tumor biopsies, tumor sequencing, and analysis of circulating tumor DNA. Enrollment began in Q2 2017 with a goal accrual of 44 pts. Clinical trial information: NCT02985125.

TPS4151 Poster Session (Board #330a), Sun, 8:00 AM-11:30 AM

Entinostat in combination with nivolumab for patients with advanced cholangiocarcinoma and pancreatic adenocarcinoma. *First Author: Marina Baretti, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: The use of antibody therapy targeting immune checkpoints has become a major focus of cancer immunotherapy, with the most compelling activity seen in the minority of patients with immunogenic tumors, where T cell infiltration naturally occurs while most pancreatic cancer (PDAC) and cholangiocarcinoma (CC) are not highly immunogenic, due to an immunosuppressive microenvironment and lack of tumor antigen expression and recognition. Our laboratory has explored entinostat, a histone deacetylase inhibitor (HDACi) to alter the function of suppressive myeloid derived suppressor cells (MDSC) in favor of recruiting T cells in murine PDAC models, showing that entinostat improves survival when given with anti-PD1 therapy. Our efforts are focused on producing new treatment options for CC and PDAC patients using epigenetic and immunotherapy combinations. **Methods:** An open-label, two-arm study enrolling patients with histologically confirmed unresectable or metastatic CC or PDAC, who have progressed after at least one line of prior therapy. Eligibility criteria include having measurable disease, performance status $\leq$1, and good end organ function. Exclusion criteria include history of autoimmune disease. Patients have a pre-treatment biopsy followed by 14 days of entinostat at a dose of 5 mg oral once a week followed by a second biopsy. Patients then begin nivolumab 240 mg every two weeks combined with entinostat until disease progression. The study is planned with 27 evaluable subjects per histology based on a Simon's two-stage design that allows early termination for lack of efficacy. The primary objective of the trial is to determine whether the combination of entinostat plus nivolumab yields a clinically compelling antitumor activity measured as objective response rate (ORR, assessed by RECIST 1.1). Secondary objectives will include progression free survival (PFS), overall survival (OS), safety and immunological correlates to evaluate the effect of HDAC inhibition on the TME by interrogating clinical specimens. The clinical study has been activated in November 2017 (NCT03250273) and 10 of planned 54 patients have been enrolled. Clinical trial information: NCT03250273.

TPS4152 Poster Session (Board #330b), Sun, 8:00 AM-11:30 AM

Phase 1b study of gemcitabine, nab-paclitaxel, and ficlatuzumab in patients with advanced pancreatic cancer. *First Author: Kimberly Perez, Dana-Farber Cancer Institute, Boston, RI*

Background: Nearly 80% of patients diagnosed with pancreatic ductal adenocarcinoma(PDAC) present with advanced, unresectable disease at the time of diagnosis, and as a result only about 4% will live 5 years after diagnosis. Paired-related homeodomain transcription factor 1 (Prrx1) isoforms – Prrx1a and 1b - are involved in pancreatic development, pancreatitis, and carcinogenesis. Prrx1a stimulates metastatic outgrowth and mesenchymal-epithelial transition(MET). Prrx1b promotes invasion and epithelial-mesenchymal transition (EMT). HGF is a novel transcriptional target of Prrx1b. Ficlatuzumab is a potent and selective recombinant humanized hepatocyte growth factor (HGF) inhibitory immunoglobulin G subclass 1 monoclonal antibody. It neutralizes HGF/c-Met binding and HGF-induced c-Met phosphorylation thereby inhibiting the c-Met pathway which has been associated with progression from primary to metastatic disease. In preclinical pancreatic adenocarcinoma models, inhibition of Prrx1b-HGF signaling using ficlatuzumab in combination with gemcitabine reduced primary tumor volume and eliminated metastatic disease. **Methods:** Patients with untreated metastatic PDAC will be enrolled in a phase Ib dose escalation study with 3+3 design and three dose cohorts of ficlatuzumab administered with gemcitabine (1000 mg/m^2) and nab-paclitaxel (125 mg/m^2) given 3 weeks on and 1 week off, followed by 18 patient expansion phase at maximally tolerated dose (MTD) for safety evaluation. The primary objective is to identify the MTD of ficlatuzumab when administered in combination with gemcitabine and nab-paclitaxel in patients with previously-untreated advanced pancreatic cancer. Secondary objectives include evaluation of safety, response rate and progression-free survival. Exploratory objectives will be performed to evaluate serum and tumor biomarkers of disease response. This analysis will include evaluation of a BDX004 prognostic proteomic signature detected in patients' pre-treatment blood sample. A pre-treatment biopsy will also be interrogated for HGF and markers of the cMet pathway; by immunohistochemistry, exome and transcriptome sequencing, and organoid development. Clinical trial information: NCT03316599.

TPS4153 Poster Session (Board #331a), Sun, 8:00 AM-11:30 AM

SWOG S1505: A randomized phase II study of perioperative mFOLFIRINOX vs. gemcitabine/nab-paclitaxel as therapy for resectable pancreatic adenocarcinoma. *First Author: Davendra Sohal, Cleveland Clinic, Cleveland, OH*

Background: Clinical outcomes after curative therapy for resectable pancreatic ductal adenocarcinoma (PDA) remain suboptimal. Series show that 70-85% of patients die of systemic recurrence. Improved overall survival (OS) in the metastatic setting with the use of multi-agent chemotherapy regimens (FOLFIRINOX, gemcitabine/nab-paclitaxel) holds the promise of progress in the curative setting as well. However, aggressive systemic therapy is usually not feasible after major pancreatic surgery. Therefore, early control of systemic disease by increased preoperative chemotherapy may improve outcomes. Furthermore, the perioperative platform facilitates early identification of patients with chemotherapy-resistant tumors and allows prospective biomarker studies in the future. **Methods:** This is a randomized phase II study intended to choose the most promising perioperative regimen to test in a larger trial. Eligibility requirements include adult patients with an ECOG PS of 0 or 1, a confirmed histopathologic diagnosis of PDA, and resectable disease as confirmed by central radiology review: no involvement of the celiac, common hepatic, or superior mesenteric arteries (and, if present, variants); no involvement, or $< 180°$ interface between tumor and vessel wall, of the portal or superior mesenteric veins; patent portal vein/splenic vein confluence; no metastases. Treatment includes 12 weeks [either 6 doses of mFOLFIRINOX (5-fluorouracil, irinotecan, oxaliplatin – without bolus 5-FU and leucovorin), or 9 doses of gemcitabine/nab-paclitaxel, on standard schedules] of preoperative chemotherapy, followed by surgical resection and 12 weeks of identical postoperative chemotherapy. Primary outcome is 2-year OS, using a "pick the winner" design with minimum two-year OS of 40% assuming a 58% alternative hypothesis, 88% power, and a 1-sided α of 0.05, providing 90% probability of selecting the better regimen with a total sample size of 150 patients. Correlative studies are planned. The study opened through the National Clinical Trials Network (NCT02562716), and is supported by NIH/NCI/NCTN grants CA180888, CA180819, CA180821, CA180833. Clinical trial information: NCT02562716.

TPS4154 Poster Session (Board #331b), Sun, 8:00 AM-11:30 AM

A SU2C catalyst randomized phase II trial of pembrolizumab with or without paricalcitol in patients with stage IV pancreatic cancer who have been placed in best possible response. *First Author: Vincent M. Chung, City of Hope, Duarte, CA*

Background: Pancreatic cancer remains a deadly disease and despite advances in chemotherapy treatment, survival for most patients is still less than one year. Refractory pancreatic cancer has not been responsive to checkpoint inhibitors and only in the small population of MSI high pancreatic cancers have we seen activity. The microenvironment plays an important role in limiting the immune response and researchers from the Salk Institute demonstrated that vitamin D receptor agonists sensitize both primary and metastatic pancreatic cancer lesions to checkpoint blockade. Our trial evaluates the role of maintenance immunotherapy and paricalcitol after best response to cytotoxic chemotherapy. **Methods:** This SU2C Catalyst trial will be conducted at Honor Health Research Institute, City of Hope National Medical Center and University of California San Diego Moores Cancer Center. Patients with metastatic pancreatic cancer receiving standard first line chemotherapy are eligible to be randomized after achieving best response defined as stable disease or partial response for 2 months with no further shrinkage of $\geq$ 20% on scan and no further decrease of $\geq$ 10% in the tumor markers while on chemotherapy. Patients with a serum vitamin D level $\geq$ 50 ng/mL are excluded. The primary endpoint of this study is to estimate the percentage of patients progressing at 6 months while on maintenance therapy. Secondary objectives evaluate the toxicity of the combination, overall survival and tumor mutational landscape. Twenty-four patients are planned to be randomized 1:1 to either pembrolizumab 200 mg every 3 weeks plus paricalcitol 25 mcg 3 times per week or pembrolizumab plus placebo. Archival tumor tissue is required and optional biopsies are allowed to further explore biomarkers of response to therapy. ClinicalTrials.gov Identifier: NCT03331562 Support: Stand Up To Cancer (SU2C) Catalyst Merck Grant Clinical trial information: NCT03331562.

TPS4155 Poster Session (Board #332a), Sun, 8:00 AM-11:30 AM

A phase I/II study of trifluridine/tipiracil (TAS-102) in combination with nanoliposomal irinotecan (NAL-IRI) in advanced GI cancers. *First Author: Olatunji B. Alese, Winship Cancer Institute, Atlanta, GA*

Background: Trifluridine/tipiracil (FTD/TPI, also known as TAS-102) is a combination of a nucleoside analogue and a thymidine phosphorylase inhibitor. TAS-102 has shown activity in 5FU-resistant colorectal cancer (CRC). Nano liposomal-Irinotecan (Nal-IRI) achieve higher intra-tumor concentrations than irinotecan (142-fold) and its major metabolite, SN-38 (9-fold), resulting in superior anti-tumor activity compared to free irinotecan in multiple tumor xenografts. Clinical trials have established activity of Nal-IRI combined with 5FU in pancreatic cancer. The combination of Nal-IRI with the more potent nucleoside analogue TAS-102 may result in a more effective systemic therapy regimen in CRC and pancreatic cancer. The aim of this study is to define the recommended phase II dose (RP2D) of the combination and evaluate the activity in pancreatic cancer and CRC. **Methods:** Eligible patients for the phase I trial include stage IV or locally advanced unresectable gastrointestinal adenocarcinomas, who have failed at least one prior therapy; age $\geq$18 years, ECOG PS 0-1 and measurable disease per RECIST 1.1. The trial design is standard 3+3. TAS-102 is administered orally in four dose levels of 25, 25, 30, 35mg/m^2 BID on days 1-5, with Nal-IRI at corresponding dose levels of 50, 70, 70, 70mg/m^2 IV on day 1 , in 14-day cycles. After recommended phase II doses are established, an expansion phase will enroll 20 patients with pancreatic adenocarcinoma (Arm A) and 20 patients with colorectal adenocarcinoma (Arm B). These patients must have either locally advanced unresectable or metastatic disease, and have failed at least one prior therapy that must not have included irinotecan. The primary endpoint of the phase II portion is overall response rate. Simon's two-stage design will be used for each arm of the phase II component. In the first stage, 10 patients will be accrued. If there are fewer than 1 responder, the cohort will be stopped. Otherwise, 10 additional patients will be accrued for a total of 20. Enrollment to the escalation phase I part of the study started in February 2018. Clinical trial information: NCT03368963.

TPS4156 Poster Session (Board #332b), Sun, 8:00 AM-11:30 AM

SM-88 in advanced cancers of the pancreas (SMACP). *First Author: Marcus Smith Noel, University of Rochester James P. Wilmot Cancer Institute, Strong Memorial Hospital, Rochester, NY*

Background: Treatment options for recurrent/refractory advanced pancreatic cancer (PC) include largely ineffective toxic therapies or palliation. SM-88 is a combination of dysfunctional tyrosine derivative (TD), mTOR inhibitor, CYP3a4 inducer and oxidative stress catalyst, previously reported to have activity in a variety of cancers and settings, with no drug-related grade 3 or 4 toxicity (J Clin Oncol 36, 2018 (suppl 6S; abstr 175. JCO 35, 2017 (supp e14060) Reduction of circulating tumor cells (CTCs), RECIST responses and prolonged duration of clinical benefit have also been reported with SM-88 in multiple tumor types including PC. (J Clin Oncol 31, 2013 (suppl; abstr e22095). We now describe an ongoing trial of SM-88 in metastatic PC. **Methods:** This is a prospective, multicenter ($>$ 30 sites), North American Phase II trial evaluating SM-88 as a single agent in recurrent PC. Eligible patients must have histologically confirmed metastatic PC, ECOG PS $<$ 3, measurable disease, and have received at least one line of prior therapy. MSI-H tumors must have had targeted therapy. 36 subjects are planned for the 1st stage, randomized 1:1 between the currently utilized clinically active regimen and a 2X dose, with the expansion dose selected based on clinical benefit and toxicity. Using Fleming's two-stage minimax design, based on overall response rate at 16 weeks, with H(0): ORR $<$ 8% vs H(1): ORR $>$ 16% ,99 evaluable will be required, yielding $>$ 95% power to detect an OS of 90% at 6 months compared to historical OS of 55%. Primary endpoints are ORR and OS. Secondary endpoints include PFS ratio, disease control rate duration of response, and time to subsequent treatment. Correlative studies include circulating tumor cells (CTCs) with genomics, tumor markers, EORTC QLQ-C30 and EORTC QLQ-PAN26, pharmacokinetics, pro-insulin, leptin and neutrophil:lymphocyte ratio, A known toxicity of SM-88 is skin hyperpigmentation and this will be investigated as a possible biomarker along with other exploratory endpoints. Clinical trial information: NCT pending

TPS4157 Poster Session (Board #333a), Sun, 8:00 AM-11:30 AM

A phase II trial of cabozantinib and erlotinib for patients with EGFR and c-MET co-expressing metastatic pancreatic adenocarcinoma. *First Author: Olumide B. Gbolahan, Indiana University School of Medicine, Indianapolis, IN*

Background: c-MET over-expression is associated with poor prognosis in pancreatic ductal adenocarcinoma (PDAC)(Kim JH, et al. Oncotarget. 2017; 8(42):73098-104). It activates mitogenic signaling, and this may contribute to the limited clinical activity of erlotinib in metastatic PDAC, given the cross talk between EGFR and c-MET(Dulak AM, et al. Oncogene. 2011; 30(33):3625-35). Preclinical data suggests that the addition of cabozantinib (a c-MET antagonist) to erlotinib improves anti-tumor activity. The combination in our lab resulted in significant tumor shrinkage, and improvement in survival in a *KPC* PDAC mouse model compared to treatment with gemcitabine alone. We designed this study to determine the activity of cabozantinib (Cabo) and erlotinib (Eelo) in a population of metastatic PDAC patients whose tumors co-overexpress EGFR and c-MET. **Methods:** This is an open-label, single arm, Phase II trial of the combination of cabozantinib and erlotinib in metastatic PDAC. Male and female patients $>$ 18years with biopsy proven PDAC and radiologically measurable metastatic disease following progression after first line therapy are eligible. Patients must have tumor tissue available from a surgical resection or archived core biopsy. Only those whose tumors express at least 2+ EGFR and c-MET based on IHC will be allowed on study. ECOG PS2 and above, prior use of Cabo or Erlo, and symptomatic brain metastasis or brain metastasis requiring steroids will exclude patients from this study. Cabo will be administered at 40mg daily dose and Erlo at 100mg daily dose every 28 days without break. The study will be conducted at the Indiana University Simon Cancer Center. The primary objective is to demonstrate at least a 15% radiographic response rate for the combination in the selected population. Secondary objectives include assessment of safety and estimation of PFS, ORR and OS. Based on a Simon two stage design, we will enroll 37 patients in total. If there are no radiologic responses in the 11 patients tested in the first stage, the trial will be closed. The trial opened in November 2017, we have screened 4 patients and enrolled 1. ClinicalTrials.gov Identifier: NCT03213626

TPS4158 Poster Session (Board #333b), Sun, 8:00 AM-11:30 AM

PRIMUS-001: An adaptive phase II study of FOLFOX-A (FOLFOX and *nab*-paclitaxel) versus AG (*nab*-paclitaxel and gemcitabine) in patients with metastatic pancreatic cancer, with integrated biomarker evaluation (ISRCTN75002153) – Part of Precision-Panc. *First Author: Janet Shirley Graham, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom*

Background: Platinum-containing regimens (e.g. FOLFIRINOX) have shown survival benefit for pancreatic cancer (PC), with some "exceptional responders"; biomarkers (BM) of response are not well defined. Tumors with mutations in *BRCA1/2* and other Fanconi Anemia genes, are preferentially sensitive to DNA-damaging agents (e.g. platinum) through synthetic lethality mechanisms, as they are defective in DNA damage response (DDR). We have shown that DDR deficiency may be present in 20% of PC. PRIMUS-001 aims to exploit defective DDR as a therapeutic vulnerability, with integrated study of BM of DNA-damaging agent response. **Methods:** PRIMUS-001 will enroll patients who are profiled molecularly using Precision-Panc NGS Diagnostic (BM via bespoke clinical grade assay). It is a multicentre, randomized (1:1), open-label, phase II trial comparing FOLFOX-A (*nab*-paclitaxel 150mg/m^2 IV, oxaliplatin 85mg/m^2, folinic acid 350mg flat dose, fluorouracil infusion 2400mg/m^2 continuous IV infusion) vs AG (*nab*-paclitaxel 125mg/m^2, gemcitabine 1000 mg/m^2). Treatment is until progression or unacceptable toxicity. PFS is the primary endpoint alongside assessment of the predictive value of BM (enhanced benefit of FOLFOX-A in BM+ve). The study has 2 interim futility analyses at which recruitment may: stop, continue in all-comers or BM +ve only. The final analysis occurs at 416 PFS events (460 patients recruited). The study determines if a phase III should occur in all-comers (+/- BM testing), be restricted to BM +ve patients or should not occur. The study has 87% power (5% 1-sided level of statistical significance) to detect a an increase in median PFS from 5.5 to 7.3 mnths in all-comers. In BM +ve patients there is 89% power (10% 1-sided) to detect an increase in median PFS from 5.5 to 10 mnths. The main inclusion and exclusion criteria are similar to major efficacy trials. Patients must come from the Precision-Panc Master Protocol with tumor tissue suitable for molecular analysis. Current Enrolment: To date 4 patients have been randomized: 3 to receive FOLFOX-A and 1 to receive AG treatment Clinical trial information: 75002153.

4500 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Pembrolizumab monotherapy as first-line therapy in advanced clear cell renal cell carcinoma (accRCC): Results from cohort A of KEYNOTE-427. *First Author: David F. McDermott, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Programmed death-1 (PD-1) inhibitor–based combination therapy shows clinical benefit in first-line accRCC. However, data are limited on clinical impact of first-line PD-1 inhibitor monotherapy. KEYNOTE-427 (NCT02853344) is a single-arm, open-label, 2-cohort, phase 2 study that evaluates efficacy and safety of the PD-1 inhibitor pembrolizumab (pembro) as first-line monotherapy in accRCC and anccRCC. Results from the accRCC cohort (cohort A) are presented. **Methods:** Patients (pts) with histologically confirmed accRCC who received no prior systemic therapy were eligible. Additional key eligibility criteria included measurable disease (RECIST v1.1, independent central review [ICR]) and Karnofsky performance status ≥70%. Pembro 200 mg was administered intravenously Q3W for 2 y or until confirmed progressive disease, unacceptable toxicity, or pt decision to withdraw. Primary end point: objective response rate (ORR) per RECIST v1.1, ICR. Additional end points included duration of response, safety, and biomarkers associated with response. **Results:** At data cutoff (Oct 6, 2017), median (range) follow-up was 7.2 (0.9-11.7) mo. 110 pts were enrolled; 107 included in the efficacy analysis (opportunity for ≥1 postbaseline assessment). Median age (range) was 64 (29-87); 78% were male. 37.3%, 47.3%, and 15.5% of pts had IMDC risk categories of favorable, intermediate, and poor, respectively. Confirmed ORR by ICR was 33.6% (n = 36; 95% CI, 24.8-43.4) with 1 complete response (0.9%) and 35 (32.7%) partial responses. ORR for pts with favorable, intermediate/poor risk IMDC was 27.5% and 37.3%, respectively. Median duration of response was not reached (range, 1.4+ to 8.2+). 73.6% of pts experienced a treatment-related adverse event (AE); most common (≥10%) were fatigue (23.6%), pruritus (21.8%), diarrhea (16.4%), rash (13.6%), and arthralgia (11.8%). 18.2% experienced a grade 3-5 treatment-related AE; 1 patient had grade 5 pneumonitis. **Conclusions:** Pembro monotherapy demonstrated promising efficacy and acceptable tolerability in pts with accRCC. Potential tissue-based biomarkers associated with response will be presented. Clinical trial information: NCT02853344.

ABSTRACT WITHDRAWN

4502 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of sorafenib (So) in patients (pts) with metastatic renal cell carcinoma (mRCC) after a radical resection of the metastases: RESORT trial. *First Author: Giuseppe Procopio, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Radical metastasectomy (Mtx) followed by observation (Obs) is a commonly used strategy in selected mRCC pts. RESORT was the largest prospective study that assessed the role of angiogenesis inhibition in mRCC pts after radical Mtx. **Methods:** The main eligibility criteria were a previous nephrectomy, predominant clear cell histology, a radical excision of no more than 3 metastases. All pts were randomized (1:1) within 12 weeks (wks) from surgery to receive SO or Obs for a maximum of 52 wks with stratification according to time from nephrectomy to metastases (more vs less than 12 months-mos), site of disease (lung vs others) and number of lesions (single vs multiple). SO was administered at the standard dose 400 mg twice daily. Radiologic restaging was performed every 12 wks. The primary endpoint was recurrence-free survival (RFS), defined as the time from randomization to disease relapse or death. A blood sample for exploratory analysis was collected at defined timepoints. **Results:** From November 2012 to November 2017, 76 pts were enrolled (32 in SO and 36 in Obs arm); 6 pts were screening failure and 2 pts never started treatment. An interim analysis was performed in the Intention To Treat population (median follow-up 21 mos) included 68 pts with well balanced baseline characteristics between the two arms. Median RFS was 29 mos (95%CI 10-NA) in SO arm versus 35 mos (95% 17-NA) in the Obs arm: 12 and 24 mos RFS was 62% (95% CI 46-84) and 52% (95% CI 35-76) in SO while 74% (95% CI 59-91) and 59% (95% CI 42-82) in Obs arm respectively. No differences in RFS were observed considering the stratification factors. Grade 3 adverse events with SO were 22% vs 3% in the Obs arm. Only 2 pts received the full SO dose, the remaining 30 pts had at least one interruption or dose reduction. Considering the % of administered vs planned dose as a continuous variable in a Cox model, a slight decrease of the recurrence risk was observed when increasing SO dose, however the number of events observed was too small to obtain reliable estimates. **Conclusions:** Sorafenib was safe but did not affect RFS in pts with mRCC after complete Mtx. Clinical trial information: NCT01444807.

4503 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

First results from the primary analysis population of the phase 2 study of erdafitinib (ERDA; JNJ-42756493) in patients (pts) with metastatic or unresectable urothelial carcinoma (mUC) and *FGFR* alterations (FGFRalt). *First Author: Arlene O. Siefker-Radtke, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ERDA is an FGFR inhibitor with activity in pts with mUC and FGFRalt. FGFRalt occur in 10-20% of mUC and are enriched in immunologically "cold" luminal 1 UC. Two independent published reports showed a 5% investigator-reported response rate to prior immune checkpoint inhibitors (ICI) among pts with select FGFRalt, suggesting a need for new treatment options in this population. Here we report efficacy and safety of ERDA in the global open-label phase 2 study BLC2001 (NCT02365597). **Methods:** Pts had measurable mUC with prespecified FGFRalt, ECOG 0-2, and progression during/following ≥ 1 line of prior chemo or ≤ 12 mos of [neo]adjuvant chemo, or were cisplatin ineligible, chemo naïve. Prior ICI treatment was allowed. The optimal schedule of ERDA determined in the initial part of the study was 8 mg/d continuous ERDA in 28-d cycles with uptitration to 9 mg/d if protocol-defined target serum phosphate level was not reached and if no significant treatment-related adverse events (TRAEs) occurred. Primary end point was ORR, with a null hypothesis of ORR ≤ 25%. **Results:** 96 pts were treated with median 5 cycles of optimized ERDA dose regimen; 10% were chemo naïve, 47% had received ≥ 2 prior lines of therapy, 80% had visceral metastases. There was a 42% confirmed (c) ORR (RECIST 1.1) (3% CR, 39% PR) and 80% disease control rate (CR + PR + SD). There was a 70% cORR among pts with prior ICI (n = 21). AEs were manageable; 10% discontinued due to TRAEs; there were no treatment-related deaths (Table). **Conclusions:** Treatment with ERDA yielded a robust response rate and was tolerable in pts with chemorefractory mUC and FGFRalt, a population with poor prognosis and high unmet need based on low response rate to prior ICI. Final primary analysis results, including OS, PFS, and response duration, will be presented. Phase 3 is ongoing. Clinical trial information: NCT02365597.

	ERDA (n = 96)	
AEs, n (%)		
Serious TRAEs	7 (7)	
	All	**Grade 3***
Most common TRAEs, any grade		
Hyperphosphatemia	66 (69)	2 (2)
Stomatitis	45 (47)	8 (8)
Diarrhea	40 (42)	3 (3)
FGFR inhibitor class effect AEs (summed terms)		
Skin and nail AEs	63 (66)	13 (14)
Eye AEs	55 (57)	5 (5)
Retinopathy	2 (2)	1 (1)

*Highest grade of listed TRAEs.

4504 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Updated results from the enfortumab vedotin phase 1 (EV-101) study in patients with metastatic urothelial cancer (mUC). *First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients (pts) with mUC are in need of novel therapies. Enfortumab vedotin (EV) is an antibody–drug conjugate that delivers a microtubule-disrupting agent to tumors expressing Nectin-4, a protein overexpressed in most urothelial cancers. Preliminary results of the EV-101 study (NCT02091999) suggest EV is active and tolerable at the RP2D of 1.25mg/kg; updated results from pts with mUC treated at RP2D are reported. **Methods:** Patients with mUC treated with ≥1 prior chemotherapy or who were ineligible for cisplatin received a 30-min infusion of EV on Day 1, 8, and 15 of each 28-day cycle. The primary objective was tolerability; antitumor activity (per RECIST v1.1), assessed by investigators every 8 wk, was a secondary objective. **Results:** As of 11 Jan 2018, 155 pts with mUC have been enrolled; 112 received EV at RP2D (median age 67 yr [range 24–86]). Bladder was the primary tumor site in 84 pts (75%) and 32 (29%) had liver metastases (LM). Ninety-one pts (81%) received prior platinum chemotherapy; 67 (60%) received ≥2 prior therapies in the metastatic setting, including 84 (75%) who had a checkpoint inhibitor (CPI). Consistent with previous reports, EV was generally well tolerated. Grade ≤2 fatigue (50%) was the most commonly reported treatment-related AE (TRAE). The most common Grade ≥3 AEs, regardless of attribution, were anemia (7%), hyponatremia (6%), urinary tract infection (6%), and hyperglycemia (5%). Four pts experienced a fatal TRAE (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, multiorgan failure). Confirmed CR and PRs were observed in 3 and 34 pts, respectively; ORR = 33% (95% CI 24.7–42.9). Eight unconfirmed PRs were pending assessment. Additionally, ORRs in study subpopulations were 32% (prior CPI, n = 84), 37% (CPI naïve, n = 27), and 26% (LM/prior CPI, n = 23). Overall median DOR was 24.3 wk (95% CI 16.3–47.3) and PFS was 23.1 wk (95% CI 20.1–24.1). Median OS was 12.5 mo (95% CI 8.1–14.8) with 76 pts (68%) censored and OS at 6 mo was 75.1%. However, time-to-event endpoints continue to evolve. **Conclusions:** Enfortumab vedotin has encouraging ORR and PFS in heavily pretreated pts with mUC, including pts with LM and prior CPI treatment. Survival data awaits maturity. Clinical trial information: NCT02091999.

4505 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Cctg BL12: Randomized phase II trial comparing nab-paclitaxel (Nab-P) to paclitaxel (P) in patients (pts) with advanced urothelial cancer progressing on or after a platinum containing regimen (NCT02033993). *First Author: Srikala S. Sridhar, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Nab-P has shown promising activity as second line treatment of advanced urothelial cancer post platinum (Ko YJ, Lancet Oncol 2013) and may be more active and less toxic compared to P. **Methods:** Canadian Cancer Trials Group led a multicentre randomized phase II trial comparing Nab-P 260mg/m2 IV q21 days to P 175mg/m2 IV q21 days in pts with advanced urothelial cancer progressing after one line of platinum-based therapy. The primary endpoint was progression free survival (PFS); secondary endpoints included overall survival (OS), response rate (RR), adverse events (AEs) using CTC AE V4.03 and QOL (EORTC-C15-PAL, FACT-Taxane). A sample size of 199 pts was selected to detect target PFS HR of 0.67 using a 1-sided 5% level test with 81% power. Stratification factors included ECOG, liver mets, LN only mets, Hb level and ≤6mo from last platinum regimen. **Results:** 199 pts from Canada and Australia were enrolled from 2014-2017 with median age 67y, including 72% males, 30% liver mets, 84% ECOG 0/1 and 55% ≤6mo from last platinum therapy. Relative dose intensity ≥90% was 78% for Nab-P vs 67% for P. With median follow up 16.4mo, median PFS for Nab-P was 3.4mo vs 3.0mo for P (HR 0.92, 90%CI 0.68-1.23, p = 0.31); median OS for Nab-P was 7.5mo vs 8.8mo for P (HR 0.95, 90%CI 0.70-1.30, p = 0.40). RR were similar, Nab-P 21% vs P 23% (p = 0.97). Rate of Grade(Gr)3+ all causality AEs was 67% for Nab-P vs 46% for P (p = 0.009); peripheral sensory neuropathy was 74% (Gr3+ 7%) for Nab-P vs 66% (Gr3+ 3%) for P (p = 0.27 (all grades), 0.33(Grd3+)). There were no significant differences in mean scores in any domain of QOL between Nab-P and P. **Conclusions:** Nab-P has similar efficacy and QOL compared to P as second line therapy in advanced urothelial cancer. Gr3+ all causality AEs were higher in the Nab-P arm. Clinical trial information: NCT02033993.

4506 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS). *First Author: Thomas Powles, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

Background: Atezolizumab is a PD-L1 inhibitor which is licenced in metastatic urothelial cancer. This study investigates the efficacy and safety of neoadjuvant atezolizumab given prior to cystectomy in operable muscle invasive transitional cell carcinoma bladder cancer. **Methods:** This single arm phase 2 study investigated 2 cycles of atezolizumab (1200mg Q3) prior to cystectomy in muscle invasive transitional cell cancer (T2-4N0M0). Pathological complete response (pCR) occurring in ≥20% of patients was the primary endpoint. Biomarker analysis on sequential tissue was a co-primary endpoint. Cross sectional imaging was performed at baseline and prior to cystectomy which occurred 4 - 8 weeks after starting atezolizumab. Radiological response was assessed. Adverse events (AEs) and surgical complications were assessed using CTCAE v4.03 and the Clavien-Dindo classification. The IDMC reviewed the first 69 patients (of 85) and supported this interim presentation. **Results:** The median age of the 69 patients was 73 years (range 54-88). At baseline pT2, T3, T4 disease occurred in 77%, 16% and 7% of patients respectively. 14 (20%) patients had only 1 cycle (8 due to AEs). 7 patients did not have cystectomy (1 disease progression, 2 treatment related AE). There was 1 potential treatment related death during treatment/perioperative period (cardiovascular disease). Treatment related grade 3/4 toxicity occurred in 12% of patients. Grade 3 or 4 surgical complications occurred in 31% of pt. The pCR rate was 18/62 (29%) [95%CI: 18% to 42%] (pT0 23%, Tis 6%, T1 10% T2 21% T3 24% T4 16% stage at surgery). 39% of patients were down staged to non-muscle invasive disease. 3/18 (17%) of the pCR patients had pT3/4 disease at baseline. 30 patients had sequential imaging and radiologically measurable disease at baseline. 23% [95%CI, 10% to 42%] and 13% [95%CI, 4% to 31%] of these patients radiologically responded and progressed respectively. Biomarker results including T cell infiltration and PD-L1 status before and after therapy will be presented. **Conclusions:** Neoadjuvant atezolizumab is safe and associated with a meaningful pathological CR rate at this interim stage. Further exploration is justified. Clinical trial information: NCT02662309.

4507 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Preoperative pembrolizumab (pembro) before radical cystectomy (RC) for muscle-invasive urothelial bladder carcinoma (MIUC): Interim clinical and biomarker findings from the phase 2 PURE-01 study. *First Author: Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy*

Background: MIUC is an aggressive disease and cisplatin-based neoadjuvant chemotherapy is administered in a minority of pts. Pembro is an EMA and FDA-approved therapy for metastatic UC after platinum failure or for cisplatin-ineligible pts. **Methods:** PURE-01 (NCT02736266) is an open-label, single-arm, phase 2 study. Pts have predominant UC histology and cT≤3bN0 stage. Pts are enrolled regardless of cisplatin eligibility. Disease assessment is made via CT, PET/CT, and multiparametric bladder MRI (mpMRI). Pts receive 3 cycles of pembro 200mg q3w before RC. Pathologic complete response (pT0) in ITT population is the primary endpoint. The H_1 is pT0 ≥25% and H_0 pT0≤15%. 71 pts will be enrolled, with 43 pts at first stage according to MinMax design. ≥7pT0 are required at first stage. Biomarker analyses include: IHC PD-L1 combined positive score (CPS, Dako 22C3) and genomic sequencing with hybrid-capture based comprehensive genomic profiling. Tumor mutational burden (TMB) is determined on 1.1 Mbp of sequenced DNA and reported as mutations (mut) per megabase (Mb) and microsatellite instability is determined on 114 loci. **Results:** From 02/17-02/18, the first stage of 43 pts was completed (36M, 7F). 27 had cT3, 16 cT2; 59% had TMB > 10 mut/mb; 9% TMB > 20 mut/mb. All tumors were microsatellite stable. All pts had evident disease at mpMRI before pembro. One pt (2.3%) had G3 irAE (ALT increase) and suspended pembro; 6 (13.9%) had reversible G2 irAE. At the time of this analysis, 25 pts are evaluable for the primary endpoint. There were 8/25 pT0 (32%, 95%CI: 16.7-47.6) and 3 pTa/is (total pT < 2 rate: 44%). In TURB samples, mean CPS score for pT0 pts was 44.8% vs 17.4% non-pT0 pts ($p < 0.001$), mean TMB was 11.2 mut/mb vs 11.2 mut/mb, respectively. On 9 evaluable pts, substantial differences were found in pre- vs post-pembro genomic alterations (GA). Mean pre-pembro GA/tumor was 8.7; mean post-pembro GA/tumor was 7 (mean 47.5% overlapping GA). **Conclusions:** Pembro is safe and has already exceeded the pT0 responses required at first stage. PD-L1 CPS may be predictive of pT0 response, and full translational findings at first stage will be presented. Clinical trial information: NCT02736266.

4508 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Multicenter randomized phase 2 trial of paclitaxel, ifosfamide, and cisplatin (TIP) versus bleomycin, etoposide, and cisplatin (BEP) for first-line treatment of patients (pts) with intermediate- or poor-risk germ cell tumors (GCT). *First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A prior single arm phase 2 trial of TIP in intermediate- and poor-risk GCT found superior rates of response, progression-free survival (PFS), and overall survival (OS) compared to historical controls with BEP (JCO 34:21, 2016) leading to this randomized phase 2 study of TIP vs. BEP conducted across 7 centers. **Methods:** From 7/2013 to 7/2017, pts age ≥18 with untreated, IGCCCG intermediate- (LDH modified to ≥3x upper limit of normal) or poor-risk GCT were randomized to 4 cycles of TIP (paclitaxel 120mg/m^2 days 1-2; ifosfamide 1200mg/m^2 days 1-5; and cisplatin 20mg/m^2 days 1-5) or standard BEP. Prophylactic G-CSF was given to both arms whereas levofloxacin was optional but encouraged for TIP pts. The primary endpoint was the 6-month favorable response rate (CR + PR-negative markers). With alpha of 0.1, a sample size of 88 pts had 80% power to detect a one-sided increase in 6-month favorable response rate from 65% with BEP to 85% with TIP. PFS, OS, and biologic correlates including next generation sequencing (NGS) were secondary endpoints. **Results:** Of 91 eligible pts (n = 45 TIP, n = 46 BEP), 81 had nonseminoma,10 had seminoma; 37 had intermediate-risk and 54 poor-risk. Primary site was testis in 69, mediastinum in 19, and retroperitoneum in 3. 86 pts (TIP: n = 42; BEP; n = 44) were evaluable for 6-month favorable response with no difference between the two arms overall (76% for TIP vs. 73% for BEP) or among intermediate- (100% vs. 88%) or poor-risk (57% vs. 63%) pts. With median follow-up of 1.71 years, estimated 1-year PFS was 72% for both arms (Table). Toxicity and biologic correlate data including NGS will be presented at the meeting. **Conclusions:** First-line TIP did not improve but had a similar 6-month favorable response rate as BEP among pts with intermediate- or poor-risk GCT. TIP could represent an alternative to BEP for pts with a contraindication to bleomycin. Clinical trial information: NCT01873326.

Characteristics and outcomes for evaluable Pts.

	TIP (n = 42)	BEP (n = 44)
IGCCCG Risk, n		
Intermediate	19	17
Poor	23	27
Response, %		
CR	45	45
PR-negative markers	31	27
Favorable Response	76	73
IR	24	27
1-year PFS, % (95% CI)	72 (56, 83)	72 (56, 82)

4509 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Pegilodecakin with nivolumab (nivo) or pembrolizumab (pembro) in patients (pts) with metastatic renal cell carcinoma (RCC). *First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pegilodecakin (PEGylated hIL-10, AM0010) alone produced 25% partial responses (PR) in heavily pre-treated (median prior therapies 3) RCC pts. IL-10 receptors and PD1 are expressed on activated and exhausted CD8+ T cells. IL-10 stimulates the cytotoxicity and proliferation of CD8+ T cells. This provides a rationale for combining pegilodecakin with anti-PD-1. **Methods:** Between 2/20/2015 and 11/18/16, 38 pts with metastatic RCC (87% clear cell) were enrolled in a phase Ib trial and received pegilodecakin at 10 (n = 6) or 20 ug/kg (n = 32, QD SC) and nivo (n = 29; 3mg/kg, q2wk IV) or pembro (n = 9; 2mg/kg, q3wk IV). Pts had intermediate- or poor-risk disease by IMDC criteria (94%) and a median of 1 prior therapy (range: 1-3), including at least one VEGFR-TKI. **Results:** Pegilodecakin + nivo or pembro was well tolerated. TrAEs were reversible and transient. G3/4 TrAE in pts who received pegilodecakin (20 ug/kg) + nivo or pembro included anemia (10), thrombocytopenia (7), and hypertriglyceridemia (6). Two pts had a reversible cytokine release syndrome with splenomegaly and increased immune mediated red blood cell phagocytosis (HLH) most likely due to T-cell activation, as both pts had PRs. Pts on 10ug/kg pegilodecakin + nivo or pembro did not have G3/4 anemia or thrombocytopenia. As of 1/29/2018, response evaluation by irRC yielded 14 PRs of 34 evaluable pts (41%) including 3 complete response [CRs] (9%); 15 additional pts had stable disease (44%), 8 of whom had a tumor reduction of more than 30%. By RECIST, ORR and disease control rate (DCR) were 53% and 81%. Median progression-free survival (PFS) was 16.7 mos with pegilodecakin + pembro, and was not reached for pegilodecakin + nivo at a median follow up of 13.8 mos (range: 0.5-19.8). The 1y- overall survival for pegilodecakin + anti-PD-1 is 89%. Pegilodecakin strongly expanded previously undetectable T cell clones in the blood, which correlated with tumor response. Nanostring expression profiling separated pts with CR/PR from progressive disease. **Conclusions:** Pegilodecakin with nivo or pembro is well-tolerated in mRCC pts; the recommended phase 2 dose is 10ug/kg. The efficacy and the observed CD8+ T cell activation are very encouraging. Clinical trial information: NCT02009449.

4510 Poster Discussion Session; Displayed in Poster Session (Board #336), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase 1/2 study evaluating the efficacy and safety of the oral CXCR4 inhibitor X4P-001 in combination with axitinib in patients with advanced renal cell carcinoma. *First Author: Ulka N. Vaishampayan, Karmanos Cancer Center, Detroit, MI*

Background: X4P-001 is an oral, selective, allosteric inhibitor of the chemokine receptor CXCR4, which is a promising novel target in renal cell carcinoma (RCC). X4P-001 in combination with the tyrosine kinase inhibitor axitinib demonstrated greater than additive anti-tumor activity in xenograft models mediated by decreased myeloid-derived suppressor cell trafficking and reduced proangiogenic signaling. **Methods:** This is a Phase (Ph) 1/2 trial in patients (pts) with advanced clear cell RCC who have failed at least one prior therapy. The safety, tolerability, and recommended Ph 2 dose (RP2D) of X4P-001 in combination with axitinib was established in Ph 1. Here we report results for preliminary efficacy in both the Ph1 dose escalation cohorts and the Ph 2 expansion cohort of pts treated at the RP2D. **Results:** The Ph 1 portion of the study is completed and established the combination therapy to be safe and tolerable at the RP2D of 400 mg QD X4P-001 + 5 mg BID axitinib. As of 01 January 2018, data are available for 10 pts in Ph 1 and 41 pts in Ph 2 treated at the daily 400 mg dose (either 200 mg BID or 400 mg QD) of X4P-001 + 5 mg BID axitinib. The median age was 64 years (range 41-87). Patients had received a median of 2 prior lines of systemic therapy (1 line: 29%; ≥ 2 lines: 71%). Seven pts (13.7%) were discontinued from the study due to adverse events (AEs) regardless of relationship. Of the 22 clinically evaluable pts, the objective response rate was 31.8% (1 CR; 6 PR) and the disease control rate was 86.4%. Median duration on treatment was 24 weeks (range 2 - 84). The most common (≥ 10%) treatment-related AEs of any grade were diarrhea, fatigue, hypertension, decreased appetite, dysphonia, nausea, blood creatinine increased, dry eye, headache, and vomiting. Hypertension was the only treatment-related AE (≥ Grade 3) to occur in > 5% of pts (9.8%) and the only serious AE to occur in more than one pt (3.9%). **Conclusions:** Preliminary results from the study demonstrate that X4P-001 + axitinib is clinically active in pts with advanced clear cell RCC and well tolerated with a manageable safety profile. Enrollment in the Ph 2 portion is near-completion and updated study results will be reported. Clinical trial information: NCT02667886.

4511 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Patient-reported outcomes (PROs) in IMmotion151: Atezolizumab (atezo) + bevacizumab (bev) vs sunitinib (sun) in treatment (tx) naive metastatic renal cell carcinoma (mRCC). *First Author: Bernard Escudier, U1015 INSERM, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, France*

Background: The randomized, open-label Phase III IMmotion151 study met its coprimary endpoint in PD-L1+ patients (pts) with improvement in investigator-assessed PFS for atezo + bev vs sun (HR 0.74; median 11.2 vs 7.7 mo, $P = 0.02$). Encouraging efficacy was also observed in the intent-to-treat (ITT) population (HR 0.83; 11.2 vs 8.4 mo) (Motzer, ASCO-GU 2018). PROs were evaluated as secondary and exploratory endpoints to document pt perspective on overall clinical benefit for each tx. **Methods:** Pts received atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w (n = 454) or sun 50 mg PO QD 4 wk on/2 wk off (n = 461). Pts completed the MD Anderson Symptom Inventory (MDASI) and Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (FKSI-19) questionnaires on days 1 and 22 of each 6 wk cycle, at end of tx, and during survival follow-up. Prespecified concepts included symptom burden (MDASI symptom severity and symptom interference with daily living) and bother from tx side effects (FKSI-19 GP5 item). Health-related quality of life (HRQoL) was also assessed (FKSI-19 total). Descriptive analyses included summary statistics for scores (effect sizes [ES] ≥ 0.3 suggest clinically meaningful differences), score changes from baseline (BL), and time to deterioration (TTD; first ≥ 2-point score increase in MDASI interference). **Results:** BL completion in ITT pts was > 80% and ≥ 70% until wk 57. At post-BL visits, pts receiving atezo + bev had milder and more stable symptom severity, less interference (differences in mean score ES: mean 0.3; range 0.1 - 0.5), and better HRQoL (differences in mean score ES: mean 0.4; range 0.1 - 0.6) vs pts receiving sun, who more often reported worsened interference. TTD in interference was also delayed (HR 0.56; 95% CI 0.46, 0.68): median for atezo + bev was 11.3 mo vs 4.3 mo for sun. A greater proportion of atezo + bev-treated pts reported no or little bother from tx side effects vs sun-treated pts. **Conclusions:** PRO data suggest atezo + bev maintained day-to-day functioning with minimal symptom interference and delayed TTD vs sun, further supporting positive benefit-risk for the combination regimen in first-line mRCC. Clinical trial information: NCT02420821.

4512 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

BMS-986205, an indoleamine 2,3-dioxygenase 1 inhibitor (IDO1i), in combination with nivolumab (NIVO): Updated safety across all tumor cohorts and efficacy in pts with advanced bladder cancer (advBC). *First Author: Josep Tabernero, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: NIVO (anti–PD-1) has shown durable responses and manageable safety (ORR, 19.6%; grade 3–4 treatment-related AEs [TRAEs], 18%) in pts with advBC (Sharma P, et al. *Lancet Oncol* 2017), but prolonging survival in more pts requires additional approaches to overcome tumor evasion mechanisms. IDO1 allows tumor escape through kynurenine (KYN) production, which stimulates development of regulatory T cells and suppresses effector T-cell proliferation. Anti–PD-1 therapy can upregulate IDO1, supporting the rationale for combining NIVO with an IDO1i. BMS-986205 is a selective, potent, once-daily (QD), oral IDO1i that works early in the IDO1 pathway to reduce KYN production. BMS-986205 + NIVO demonstrated a favorable safety profile and antitumor activity in heavily pretreated pts with select solid tumors (Luke J, et al. SITC 2017; NCT02658890). Updated safety across all tumor cohorts and efficacy in the advBC cohort are reported. **Methods:** Dose-escalation methods of this phase 1/2a, open-label study were previously described; during expansion, pts received BMS-986205 100 or 200 mg QD + NIVO 240 mg IV Q2W or 480 mg IV Q4W. Objectives included safety and ORR by RECIST v1.1 (includes unconfirmed [u] responses). Prior IO therapy was permitted in the advBC cohort. **Results:** As of Dec 15, 2017, 434 pts received BMS-986205 + NIVO. TRAEs were reported in 51% of pts (grade 3–4, 12%), the most common being fatigue (13%) and nausea (10%); 16 pts (4%) discontinued due to TRAEs, and 1 pt died due to a TRAE (myocarditis). With a median follow-up of 17 wk (range, 4–53), the ORR among 29 pts with advBC was 34% (1 u CR, 9 PRs [1 u]), and the disease control rate (DCR) was 48%. Of 29 pts, 26 had no prior IO therapy; ORR in these pts was 38% (1 u CR, 9 PR [1 u]), and the DCR was 54%. ORR in pts with tumor PD-L1 $\geq$ 1% (Dako PD-L1 IHC 28-8 pharmDx assay; n = 15) vs $<$ 1% (n = 11) was 47% vs 27%. **Conclusions:** BMS-986205 + NIVO was well tolerated, with a safety profile similar to that of NIVO monotherapy. Preliminary evidence of efficacy was observed in advBC, supporting further evaluation of BMS-986205 + NIVO. Updated data by dose and subgroup in the advBC cohort will be presented. Clinical trial information: NCT02658890.

4513 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Rogaratinib in patients with advanced urothelial carcinomas prescreened for tumor FGFR mRNA expression and effects of mutations in the FGFR signaling pathway. *First Author: Markus Joerger, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

Background: Activation of FGFR signaling is involved in a variety of malignancies including advanced urothelial cancer (UC). Rogaratinib is an oral pan-FGFR kinase inhibitor. We report here the results from a phase I expansion cohort in UC patients prescreened for FGFR1-3 mRNA expression levels with particular attention to activity in patients (pts) with evidence of activating mutations in potential resistance genes, including PIK3CA and RAS. (NCT01976741) **Methods:** Pts with advanced urothelial carcinomas were selected based on high FGFR1-3 mRNA expression in biopsy specimens. Somatic mutations in FGFR downstream signaling genes were detected by PCR array. Pts were treated with rogaratinib 800mg twice daily until tumor progression, intolerable toxicity, or withdrawal. Tumor response was assessed by RECIST, v1.1. Adverse events were reported using CTCAE v4.03 criteria. **Results:** A total of 219 UC pts were prescreened for FGFR1-3 mRNA expression levels and FGFR3 activating mutations, with 99 samples (45%) found to be FGFR-positive. Of those, 87% of samples were positive for FGFR3 mRNA, 5% for FGFR1 mRNA and 8% were double FGFR mRNA-positive (FGFR1/2, 1/3 or 2/3). Frequency of FGFR3 activating mutations in UC samples was 7%, all of which also had high FGFR3 mRNA. Fifty one pts were evaluable for response. Overall objective response rate (ORR) was 24% (12/51; all PRs) and disease control rate (DCR) was 73% (37/51). Interestingly, 0/12 pts with a PR had a hotspot mutation in either PIK3CA or RAS-encoding genes whereas 7/14 pts with PD revealed such a mutation. ORR in PIK3CA/RAS wild type UC pts is 30.6 %. Ten FGFR-positive UC pts had prior immuno-oncology (I/O) treatment, 9 of whom had progressive disease as best response. For these 10 pts the ORR was 30% and the DCR 80%. **Conclusions:** Selection of pts for treatment with rogaratinib based on FGFR mRNA expression levels was feasible and identified drug-sensitive pts with and without underlying FGFR gene alterations. Rogaratinib had a favorable safety profile and showed promising anti-tumor activity in UC pts, with an ORR of 24%, including pts refractory to prior I/O treatment but not with PIK3CA or RAS mutations. Clinical trial information: NCT01976741.

4514 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

VinCaP: A phase II trial of vinflunine chemotherapy in locally-advanced and metastatic carcinoma of the penis (CRUK/12/021). *First Author: Lisa M. Pickering, St. Georges University Hospitals Foundation Trust and The Royal Marsden Foundation Trust, London, United Kingdom*

Background: Platinum-based combination chemotherapy regimens are active in the treatment of penis cancer, but toxicity limits their value for patients with metastatic disease. VinCaP aims to define both the toxicity and the disease control rate for the non-platinum cytotoxic agent Vinflunine. **Methods:** A phase II single-arm trial was conducted. Eligible patients had measurable, histologically-proven squamous cell carcinoma (SCC) of the penis, staged M1; or M0,Tx,N3; or M0,Tx,N2 and deemed inoperable by multidisciplinary team; or M0, T4 any N, ECOG performance status 0-2 and adequate hepatic and renal function. Treatment was 4x21-day cycles of vinflunine (320mg/m^2). In 22 evaluable patients $\geq$7 responses/stabilisations were required to conclude a clinical benefit rate (CBR(CR/PR/SD)) of at least 40% and exclude a rate of $<$ 15% (p0 = 0.15, p1 = 0.40, α = 0.05, β = 0.80, Fleming-A'Hern exact design). Primary endpoint was CBR after 4 cycles of vinflunine. Secondary endpoints included objective response rate (ORR: CR/PR), safety, tolerability, progression-free survival (PFS) and overall survival (OS). **Results:** 25 patients (median age 68 years) were recruited from 8 UK centres between June 2014 and May 2017. 19 patients were M1. Of 22 patients who received treatment: 15 (68%) experienced grade 3/4 adverse events (AE); neutropenia was the most common AE (n = 5, 23%). Recruitment halted in Sep 2016 to investigate 2 treatment-related deaths (1 sepsis, not neutropenic; 1 neutropenic, not septic); re-opened Nov 2016. 10 patients had clinical benefit, CBR = 45.5%, 95%CI: 24.4-67.8, in the evaluable population (n = 22). ORR: 27.3%, (10.7-50.2) in evaluable population; 35.5%, (14.2-61.7) in measurable population (n = 17). Median PFS: 2.9 months, 95%CI: 1.4-6.4; 12 month PFS: 16.7% (4.6-35.3). Median OS: 8.4 months, (3.2-14.1); 12 month OS: 33.7%, (15.4-53.1). **Conclusions:** CBR exceeded the threshold to recommend further research and ORR was comparable to other recent phase II trials in penis cancer. Toxicity profile in keeping with known profile for vinflunine. Vinflunine is an active agent in the treatment of locally advanced and metastatic SCC of the penis. Clinical trial information: NCT02057913.

4515 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Characterizing tumor immune microenvironment (TME) and outcomes for 409 patients (pts) treated on COMPARZ: Distinct clusters emphasize immune infiltration vs. angiogenesis. *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Growing evidence highlights the critical role of the TME for RCC biology and response to systemic therapy. We used integrated molecular profiling to characterize immune & stromal TME across a large cohort of pts treated on the phase 3 COMPARZ trial. **Methods:** We performed mRNA expression profiling (Affymetrix GeneChip HTA 2.0) and unsupervised consensus clustering from archival paraffin specimens. Clusters were characterized by gene set enrichment analyses (GSEA); transcriptional deconvolution; a 43 gene angiogenesis expression score; immunohistochemistry (IHC) for PD-L1 expression on tumor cells and macrophages; and mutation status for a defined list of genes. Findings were correlated with clinical outcomes using parametric and non-parametric tests. **Results:** mRNA clustering was done for 409 patients (212 sunitinib, 197 pazopanib treated) and revealed 4 biologically distinct clusters (C1-4) with significant differences in median overall survival (OS; P= 2.00E-4) and progression free survival (PFS; P= 0.03). C4 displayed the worst outcomes and highest rate of IMDC poor risk features (45.7% pts); GSEA showed enrichment for inflammation signatures, e.g. IFN-γ responses. Immune deconvolution demonstrated the most immune-infiltrated TME for C4 with enrichment of many immune subsets, especially macrophages (compared to C1-3, P= 0.0015); C4 also had the highest rate of PD-L1 expression on tumor cells and macrophages (P= 3.50E-7). Pts in C3 had the most favorable outcomes and displayed the highest angiogenesis gene expression levels (P= 2.20E-16). An integrated model of molecular and IMDC variables compared to IMDC risk stratification alone improved the c-index for OS from 0.63 to 0.69 and PFS from 0.60 to 0.65. **Conclusions:** mRNA-based analyses revealed four distinct molecular subgroups of RCC associated with varying outcomes on TKI therapy. These data highlight stromal and immune TME, specifically angiogenesis and macrophage infiltration programs, as powerful determinants of clinical course. Further study of these differences will be critical in advancing the field of advanced RCC towards precision-medicine. Clinical trial information: NCT00720941.

4516 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Alterations in key clear cell renal cell carcinoma (RCC) genes to refine patient prognosis. *First Author: Dominick Bossé, Dana-Farber Cancer Institute, Boston, MA*

Background: Genomic alterations (GA) in VHL, PBRM1, BAP1, SETD2, TP53 and KDM5C are frequently present in metastatic RCC (mRCC). We investigated the prognostic value of GA resulting in loss of function (LOF) of these genes in mRCC patients stratified by International mRCC Consortium Database (IMDC) risk group. **Methods:** Patients from 7 US centers and 1 annotated cohort from TCGA who had clear cell mRCC treated with 1st line VEGF tyrosine kinase inhibitor and tumor genomics available were included. Tumors were sequenced using next generation sequencing (institutional and commercial platforms) or whole exome sequencing (TCGA). LOF was defined as presence of pathogenic gene variant or 2 copy deletion. Cox model adjusting for age, IMDC risk group was used to investigate the association between GA and overall survival (OS). The prognostic value of GA was further assessed in IMDC favorable, intermediate and poor risk group. **Results:** In total, 308 patients were analyzed. IMDC risk group distribution was favorable 21%, intermediate 54%, poor 17% and unknown 8%. Patients had GA in VHL 77%, PBRM1 43%, SETD2 29%, BAP1 19%, TP53 11%, KDM5C 11%. GA in BAP1 was associated with worse IMDC risk group (favorable 8%, intermediate 23% and poor 20%, p = 0.023) and worse OS (aHR 1.7; 95%CI 1.1-2.5, p = 0.01). GA in PBRM1 (aHR = 0.6; 95%CI 0.4-0.8, p = 0.001) and KDM5C (aHR = 0.4; 95%CI 0.2-0.8, p = 0.007) was associated with better OS. SETD2, TP53 and VHL were not associated with prognosis (p > 0.4). Co-occurrence of GA in BAP1 and PBRM1 was 3.8%. Patients with tumors PBRM1 wild type and harboring GA in BAP1 had worse OS [37 vs 50 mos, aHR 1.9 (95%CI 1.2-2.8 p = 0.004]. When stratified by IMDC risk group, this tumor genomic profile was prognostic for patients with intermediate risk disease only (Table). **Conclusions:** mRCC tumors which are PBRM1 wild type and with LOF in BAP1 have worse survival. Assessment of GA in these key genes can further prognosticate IMDC intermediate risk patients and be useful to stratify patients in clinical trials.

IMDC risk group	PBRM1 wild type and BAP1 altered	N/ N event	HR*	P-value
Good	No	61/16	ref	
	Yes	4/1	1.17(0.14-9.85)	0.883
intermediate	No	135/66	ref	
	Yes	31/19	1.77(1.05-2.98)	0.032
poor	No	45/25	ref	
	Yes	6/5	1.50(0.56-4.06)	0.422

* adjusted for age

4517 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Prospective phase II multi-center study of individualized axitinib (Axi) titration for metastatic renal cell carcinoma (mRCC) after treatment with PD-1 / PD-L1 inhibitors. *First Author: Moshe Chaim Ornstein, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: Standard of care treatment in mRCC after checkpoint inhibitor (CPI) therapy includes VEGFR TKIs, though no prospective data have been published. Axitinib (Axi) is a VEGF-R inhibitor with prior clinical data supporting increased efficacy with dose titration. The existing titration schema of 5mg BID to 7mg BID to 10mg BID every 4 weeks, however, can lead to toxicity due to the magnitude of dose increases. A prospective, multi-center phase II trial of Axi given on an individualized dosing algorithm in mRCC after treatment with CPI was conducted (NCT02579811). **Methods:** Patients (pts) with clear cell mRCC, adequate organ function and measurable disease whose most recent therapy was anti PD-1 / PD-L1 treatment were eligible. Pts were treated with Axi 5mg BID starting dose with upward dose titration in 1mg BID increments (e.g. 5mg BID to 6mg BID, up to 10mg BID max dose) every 14 days if there was no grade (G) 2 Axi-related mucositis, diarrhea, hand-foot-syndrome, or fatigue. If G2 adverse events (AEs) occurred, pts took a 3-day break then resumed the same dose. Recurrent G2 AEs despite treatment breaks or G3/4 AEs resulted in dose reduction in 1mg BID increments. The primary outcome was progression free survival (PFS) with 38 pts needed to improve PFS from 6.5 months (based on retrospective data of TKI post-CPI) to 9.5 months (a = 0.10; power 80%). **Results:** The trial has completed accrual (n = 38): 74% male, median age 64, 89% KPS ≥80%, 16%/66%/19% IMDC favorable/intermediate/poor risk, 94% prior nephrectomy, 71% ≥ 2 prior therapies. Most recent therapy was 89% anti PD-1 (63% nivolumab monotherapy; 17% ipilimumab/nivolumab; 9% other) or 11% anti PD-L1 (6% atezolizumab; 3% bevacizumab/atezolizumab; 3% durvalumab). In evaluable pts, the estimated median is PFS 9.2 months, with 54% of pts still on Axi. The ORR is 38.7% (best response PR 38.7%, SD 48.3%, and PD 12.9%). The median highest dose per pt was 6mg BID (range, 5-9) and 44% of pts required dose reduction to < 5mg BID. There were no unexpected toxicities related to Axi. **Conclusions:** Axitinib on an individualized titration schema resulted in robust clinical efficacy after checkpoint inhibitor therapy. Clinical trial information: NCT02579811.

4518 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Correlation of degree of tumor immune infiltration and insertion-and-deletion (indel) burden with outcome on programmed death 1 (PD1) therapy in advanced renal cell cancer (RCC). *First Author: Martin Henner Voss, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Mutation load and neoantigen burden predict benefit from anti-PD1 therapy across several cancers but are generally low in RCC. Pan-cancer comparisons highlight RCC for its enriched tumor immune infiltrate and a high proportion of indels, which may be immunogenic. We investigated these phenomena in anti-PD1 treated patients (pts) with comparison to pts receiving tyrosine kinase inhibitors (TKI). **Methods:** Whole exome sequencing (WES) was done for 77 tumors from 2 anti-PD1 treated pt cohorts; 25 pts provided RNAseq data. Overall mutation burden, indels, and predicted neoantigens were quantified. ESTIMATE and CIBERSORT algorithms were used to infer abundances of immune infiltrate and detailed immunophenotypes from RNAseq. We investigated correlation of molecular features with overall survival (OS) and durable clinical benefit (DCB = progression free survival > 6mo). A cohort of TKI-treated pts with no prior anti-PD1, previously analyzed as part of the TCGA, was used for comparison (35 with WES, 33 with RNAseq). **Results:** Higher overall immune infiltration correlated favorably with DCB in the PD1 cohort (stratified Mann Whitney test; p = 0.05) but not in TKI treated pts (p = 0.84). As the two most abundant infiltrating cell types, M2 macrophages (p < 0.001) but not CD8+ T cells (p = 0.22) associated with DCB from anti-PD1 therapy; neither associated with outcomes in TKI pts (p = 0.15, p = 0.76). Expectedly, mutation counts were low (median 68; inter-quartile range 45-93). While neither mutation nor neoantigen burden impacted on OS with anti-PD1 therapy (stratified Cox Proportional HR 1.02; p = 0.6; HR 1.01; p = 0.69, respectively), association with OS was significant for frameshift indel count (HR 0.85; p = 0.006). Correlation was similar but did not reach significance in TKI pts (HR 0.87; p = 0.07). **Conclusions:** In anti-PD1 treated RCC pts, baseline tumor immune infiltration, particularly by M2 macrophages, associated favorably with outcome. In contrast to other cancers, mutation and neoantigen load did not affect treatment outcomes; yet higher indel counts appeared to confer superior OS. Such associations were not seen for TKI treated pts.

4519 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Gut microbiome composition to predict resistance in renal cell carcinoma (RCC) patients on nivolumab. *First Author: Lisa Derosa, U1015 INSERM, Gustave Roussy Cancer Campus, Paris Saclay University, Villejuif, France*

Background: Efforts are ongoing to identify mechanisms driving response/resistance to immune checkpoint inhibitors (ICI) in order to personalize therapy. Recently, we speculated that antibiotics (ATB)-related dysbiosis decreases activity of ICI in cancer pts. We and others reported that outcome with ICI in melanoma and epithelial cancers were influenced by the microbiome composition. Here we evaluated the impact of microbiome in RCC. **Methods:** Within a large cohort of RCC pts (n = 85) treated in the NIVOREN study with nivolumab at Gustave Roussy, we prospectively collected fecal samples (n = 69). Of note, the minority of them received ATB before starting ICI (n = 11). Pts were classified as either primary resistant (PD) or non-PD based on RECIST (outcome, 6 months PFS). Metagenomic (MG) data from whole genome sequencing (WGS) were analyzed by multivariate and pair-wise/fold ratio (FR). Then, ICI-resistant RENCA mice were compensated with fecal microbiota transplantation (FMT) from non-PD pts or with commensals identified by WGS-MG to restore responsiveness to ICI to establish cause-effect relationship between dysbiosis and resistance. **Results:** After a median follow-up of 14 months, 27 (39%) pts were PD and 42 (61%) pts were non-PD, based on best response. Considering pts who received ATB, 8 (73%) were PD and 3 (27%) were non-PD *(p = 0.01)*. The microbiome alfa (intra-sample) and beta (inter-sample) diversity were not significantly different among PD and non-PD RCC pts. However, specific gut MG-fingerprints were related to best responses and/or PFS6. Excluding ATB treated patients, *Akkermansia muciniphila* and *Bacteroides salyersiae* were more abundant in non-PD pts with a FR of 2.65 *(p = 0.01)* and 27.09 *(p = 0.05),* respectively. Finally, we showed that *Bacteroides (B. salyersiae* but not *B. xylanisolvens*) or *A. muciniphila* could restore the efficacy of ICI in "unfavorable/dysbiotic" FMT-recipient tumor bearers, improving by a 43% the prevalence of non-PD. **Conclusions:** This is the largest prospective analysis so far, showing that composition of gut microbiome may predict resistance to anti-PD-1 in RCC pts. Interventions to modulate gut microbiome may represent strategies to improve clinical outcomes with ICI.

4520 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A pilot randomized study evaluating nivolumab (nivo) or nivo + bevacizumab (bev) or nivo + ipilimumab (ipi) in patients with metastatic renal cell carcinoma (MRCC) eligible for cytoreductive nephrectomy (CN), metastasectomy (MS) or post-treatment biopsy (Bx). *First Author: Jianjun Gao, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Since ipi and nivo use distinct mechanisms for T cell activation and bev promotes antigen presentation, we hypothesize that nivo+bev or nivo +ipi would safely lead to measurable immunologic changes and improved clinical activity in MRCC. **Methods:** In this open-label, randomized trial (NCT02210117), adults with MRCC w/o prior immune checkpoint therapy and anti-VEGF therapy were enrolled and randomized 2:3:2 to receive nivo, nivo +bev or nivo+ipi, followed by surgery (CN or MS), or Bx, and subsequent nivo maintenance therapy up to 2 years. Response was assessed at ≥12 weeks. Pre- and post-treatment blood and tumors were obtained for correlative studies. **Results:** One hundred patients have been accrued and 90 are evaluable for responses (table below, W = withdrawal; BOR = Best overall response; BRES = Best Response excluding surgical effect). Clinical trial information: NCT02210117. BOR was 50% complete response (CR) + partial response (PR) nivo, 48% CR+PR nivo+bev, 39% CR+PR nivo+ipi. For patients getting surgery, BOR was: 77% nivo, 93% nivo+bev, and 70% nivo+ipi. Grade 3 or 4 toxicities were 30% for nivo, 45% for nivo+bev (including 18% bev-specific hypertension), and 57% for nivo+ipi. We identified a number of immune signatures in relation to clinical responses. **Conclusions:** Patients able to stay on therapy and receive surgery had BOR ranging from 70%-93%. Combination therapy nivo ± [bev or ipi] plus cytoreductive surgery deserves to be tested in a larger phase 3 trial for MRCC. We will also report correlative biomarker data.

	Nivo (N = 26)					Nivo+Bev (N = 38)					Nivo+Ipi (N = 26)				
	CR	PR	SD	PD	W	CR	PR	SD	PD	W	CR	PR	SD	PD	W
All Patients															
BOR	1 (4%)	12 (46%)	5 (19%)	7 (27%)	1 (4%)	1 (3%)	17 (45%)	7 (18%)	11 (29%)	2 (5%)	1 (4%)	9 (35%)	2 (8%)	13 (50%)	1 (4%)
BRES	0	10 (38%)	8 (31%)	7 (27%)	1 (4%)	0	14 (37%)	11 (29%)	11 (29%)	2 (5%)	0	7 (27%)	4 (15%)	14 (54%)	1 (4%)
Patients with Surgery															
BOR	1 (8%)	9 (69%)	2 (15%)	1 (8%)	0	1 (8%)	11 (85%)	1 (8%)	0	0	1 (10%)	6 (60%)	2 (20%)	1 (10%)	0
BRES	0	7 (54%)	5 (38%)	1 (8%)	0	0	8 (62%)	5 (38%)	0	0	0	4 (40%)	4 (40%)	2 (20%)	0
Patients without Surgery															
BOR	0	3 (23%)	3 (23%)	6 (46%)	1 (8%)	0	6 (24%)	6 (24%)	11 (44%)	2 (8%)	0	3 (19%)	0	12 (75%)	1 (6%)

4521 Poster Session (Board #347), Sat, 8:00 AM-11:30 AM

Pembrolizumab (pembro) versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC): 2-year follow-up from the phase 3 KEYNOTE-045 trial. *First Author: Yves Fradet, CHU de Québec - Université Laval, Québec City, QC, Canada*

Background: Based on interim results from the phase 3 KEYNOTE-045 (NCT02256436) study comparing pembro and investigator s choice of chemotherapy (chemo), pembro was approved for the treatment of locally advanced or metastatic UC that has progressed during or after a platinum-containing regimen. Updated results after 2-year follow-up are presented. **Methods:** Eligible patients (histologically or cytologically confirmed UC, progression after platinum, ECOG PS 0-2, measurable disease per RECIST v1.1, ≤2 lines of systemic therapy) were randomly assigned 1:1 to receive pembro 200 mg Q3W or investigator s choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. Primary efficacy end points were OS and PFS (RECIST v1.1, blinded central review). ORR (RECIST v1.1, blinded central review) was a secondary end point. **Results:** As of Oct 26, 2017, among 542 enrolled patients (pembro, 270; chemo, 272), median follow-up was 27.7 mo. Median OS was significantly longer with pembro vs chemo (10.3 vs 7.3 mo; HR, 0.70; $P< 0.0002$). OS benefit with pembro vs chemo was seen in all PD-L1 expression subgroups (HR; combined positive score [CPS] < 1, 0.82; CPS ≥1, 0.58; CPS < 10, 0.75; CPS ≥10, 0.56) and was maintained regardless of age, ECOG PS, prior therapy, liver metastases, baseline hemoglobin, time from last chemo, histology, risk factor group, and choice of chemo. PFS was not different between arms (2.1 vs 3.3 mo; HR, 0.96; $P= 0.32$). ORR was higher with pembro vs chemo (21.1% vs 11.0%). Median duration of response was longer with pembro (not reached [1.6+ to 30.3+ mo] vs 4.4 mo [1.4+ to 29.9+ mo]), and a greater proportion of responses lasted ≥12 mo (68% vs 35%) per Kaplan-Meier method. Fewer patients with pembro vs chemo experienced a treatment-related adverse event of any grade (62.0% vs 90.6%) and a grade ≥3 adverse event (16.5% vs 50.2%). **Conclusions:** Results observed over 2-year follow-up, including OS benefit and superior safety with pembro vs chemo, were consistent with the interim analyses that led to the approval of pembro in locally advanced or metastatic UC that progressed during or after platinum-based chemotherapy. Clinical trial information: NCT02256436.

4522 Poster Session (Board #348), Sat, 8:00 AM-11:30 AM

Conservative management following clinical complete response to neoadjuvant chemotherapy for muscle-invasive bladder cancer: Contemporary outcomes of a multi-institutional prospective cohort study. *First Author: Patrick M Mazza, Department of Urology, Columbia University Medical Center, New York, NY*

Background: Neoadjuvant platinum-based chemotherapy (NAC) followed by radical cystectomy (RC) is the gold standard treatment for muscle-invasive bladder cancer (MIBC). High morbidity and mortality associated with RC and favorable survival outcomes seen in patients who exhibit a clinical complete response (cCR) to NAC and forego RC has encouraged interest in conservative management of MIBC. We report the outcomes of patients from two institutions who experienced a cCR to NAC and opted for surveillance only. **Methods:** Prospective enrollment and retrospective review of patients occurred at Columbia University Medical Center (CUMC) and Memorial Sloan Kettering Cancer Center (MSKCC) to produce two distinct, IRB-approved databases of MIBC patients who underwent "radical" TURBT (complete resection down to muscularis propria) followed by NAC, exhibited a cCR, and opted for surveillance only from 2001-2017. A cCR was defined as negative "radical" TURBT, urine cytology, and cross-sectional imaging. Patients were followed at 3-6 month intervals with cystoscopy ± biopsy, urine cytology, and cross-sectional imaging, with databases continually updated. **Results:** The 148 patient cohort included 119 (80%) men and 29 women of median age 62 (32-88) years and follow-up 55 (5-145) months. NAC regimens were 31% MVAC, 63% gemcitabine and cisplatin, and 6% other platinum-based regimens. Of the 148, 71 (48%) recurred in the bladder—16 (11%) with MI disease and 55 with non-muscle invasive (NMI). Salvage RC prevented cancer-specific death in 9 of 12 (75%) patients who accepted RC after MI relapse and 13 of 14 (93%) after NMI relapse. 5-year disease-specific, overall, cystectomy-free, and recurrence-free survival rates for the entire cohort were 90%, 86%, 76%, and 64%. **Conclusions:** The favorable outcomes observed in this large, multi-institutional cohort support the efficacy of surveillance only for carefully selected and closely monitored MIBC patients. Future studies should aim to improve patient selection by identifying biomarkers predictive of invasive relapse and developing novel imaging methods for its detection.

4523 Poster Session (Board #349), Sat, 8:00 AM-11:30 AM

Atezolizumab (atezo) in first-line cisplatin-ineligible or platinum-treated locally advanced or metastatic urothelial cancer (mUC): Long-term efficacy from phase 2 study IMvigor210. *First Author: Arjun Vasant Balar, Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: Platinum-based chemotherapy is a standard first-line approach for mUC, but many pts are ineligible for cisplatin, and progression is common. Atezo (anti–PD-L1) was approved for first-line cisplatin–ineligible and platinum-treated mUC pts following IMvigor210 results. Here we present more mature DOR and OS data in both populations. **Methods:** Cohort 1 (NCT02951767) pts were treatment naive for mUC, had ECOG PS ≤ 2 and were ineligible for cisplatin by at least one of the following: GFR > 30 and < 60 mL/min, ≥ G2 hearing loss or peripheral neuropathy or ECOG PS 2. Cohort 2 (NCT02108652) pts progressed after platinum and had ECOG PS ≤ 1 and GFR ≥ 30 mL/min. Atezo 1200 mg IV q3w was given until PD (Cohort 1) or loss of clinical benefit (Cohort 2). We evaluated the following efficacy endpoints: RECIST v1.1 ORR by central review (primary), DOR, OS. **Results:** 119 Cohort 1 pts (median follow-up, 29 mo) and 310 Cohort 2 pts (median follow-up, 33 mo) were evaluable as of July 12, 2017. In Cohort 1, ORR was 24% (95% CI: 16, 32), CR rate was 8%, and median DOR was not reached (95% CI: 30.4 mo to not estimable; 19 of 28 responses ongoing); in elderly pts (≥ 80 y; Cohort 1, n = 25), ORR was 28% (95% CI: 12, 49), and CR rate was 12%. Further characterization of outcomes in pts ≥ 80 y and subgroups with poor prognostic factors will be presented. In Cohort 2, ORR was 16% (95% CI: 13, 21), CR rate was 7%, and median DOR was 24.8 mo (95% CI: 13.8, 30.4). In both cohorts, sustained responses occurred among pts who discontinued atezo for reasons besides PD. In Cohort 1, median OS was 16.3 mo (95% CI: 10.4, 24.5), with 1-y OS of 58% (95% CI: 49, 67) and 2-y OS of 41% (95% CI: 32, 50); in Cohort 2, median OS was 7.9 mo (95% CI: 6.7, 9.3), with 1-y OS of 37% (95% CI: 31, 42) and 2-y OS of 23% (95% CI: 19, 28). **Conclusions:** With > 2 y median follow-up, responses to first-line atezo in cisplatin-ineligible mUC pts, including pts ≥ 80 y, appeared durable, resulting in continued improvement in OS since the primary analysis. For pre-treated pts, ORR and OS were in line with prior data, and taken together with DOR, data were consistent with Ph 3 results (IMvigor211, NCT02302807). Clinical trial information: NCT02951767 and NCT02108652.

4524 Poster Session (Board #350), Sat, 8:00 AM-11:30 AM

Updated efficacy and safety of KEYNOTE-052: A single-arm phase 2 study investigating first-line pembrolizumab (pembro) in cisplatin-ineligible advanced urothelial cancer (UC). *First Author: Jacqueline Vuky, Oregon Health & Science University, Portland, OR*

Background: Based on initial results from the phase 2 KEYNOTE-052 study (NCT02335424), pembro was approved for the treatment of cisplatin-ineligible patients with advanced UC. The results of the long-term follow-up analysis of KEYNOTE-052 are presented. **Methods:** Eligible patients were cisplatin ineligible (ECOG PS 2, CrCl ≥30 to <60 mL/min, grade ≥2 neuropathy/hearing loss, NYHA Class 3 heart failure), had advanced UC, and had received no prior chemotherapy for metastatic disease. Patients received pembro 200 mg IV Q3W for up to 24 months. Imaging was performed at wk 9, then Q6W for 12 months, and Q12W thereafter. The primary end point was confirmed ORR (RECIST v1.1, independent central review). **Results:** Efficacy and safety were assessed in 370 patients. Median age was 74 years; 10.8% of patients were ≥85 years old; 42.2% were ECOG PS 2; and 85.1% had visceral disease. As of the Nov 30, 2017, data cutoff, median (range) follow-up was 11.5 (0.1-31.3) mo. Confirmed ORR was 28.9% (95% CI, 24.3-33.8); 30 (8.1%) and 77 (20.8%) patients had complete response and partial response, respectively. Median duration of response was not reached (NR) (95% CI, 21.4 mo to NR); 82% and 68% of patients had a response of ≥6 and ≥12 mo, respectively. Median OS was 11.5 (95% CI, 10.0-13.3) mo; 6-and 12-mo OS rates were 67.2% and 47.5%, respectively. In patients with a PD-L1 expression combined positive score of ≥10 (n=110), ORR was 47.3% (95% CI, 37.7-57.0) and median OS was 18.5 mo (95% CI, 12.2 mo to NR). Median OS was NR (12.4 mo to NR) in patients with lymph node–only disease (n=51) and was 13.1 (95% CI, 11.0-16.8) mo in patients with ECOG PS 0/1 (n=214) and 9.7 (95% CI, 5.7-11.6) mo in patients with ECOG PS 2 (n=156). Treatment-related adverse events (AEs) occurred in 67.6% of patients; most common (≥15%) were fatigue (18.1%) and pruritus (17.8%). Grade ≥3 treatment-related AEs occurred in 20.3% of patients. Immune-mediated AEs occurred in 24.6% of patients. **Conclusions:** Pembro continues to be well tolerated and elicits clinically meaningful, durable antitumor activity in a broad spectrum of cisplatin-ineligible patients with advanced UC. Clinical trial information: NCT02335424.

4525 Poster Session (Board #351), Sat, 8:00 AM-11:30 AM

Upper tract urothelial carcinoma is non-basal and T-cell depleted. *First Author: Panagiotis J. Vlachostergios, Division of Hematology & Medical Oncology, Weill Cornell Medical College & New York-Presbyterian Hospital, New York, NY*

Background: Urothelial cancer (UC) of the upper urinary tract (UTUC) accounts for 5-10% of UC. Despite sharing a common histology with bladder UC (UCB), staging and prognosis differences have been reported. **Methods:** To dissect the central biological features of UTUC driving its phenotype, we performed an integrated analysis of UTUC tumors using whole-exome (WES) and RNA sequencing (RNAseq). We compared the exome and transcriptome of UTUC to the TCGA UCB and an independent UTUC validation dataset (VALD). **Results:** We performed an integrated analysis of WES (n = 16) and RNAseq (n = 19) from biobanked nephroureterectomy archival specimens of 19 chemotherapy-naïve patients with UTUC. Patients' demographics are as follows: median age 71 (range 46-87); 11 men, 8 women; 11 former/current smokers; 13 renal pelvis, 6 ureteral; 17 high-grade, 2 low-grade; 8 low stage (< pT2), 11 high stage (≥ pT2). Our analyses revealed several insights: 1) UTUC has a significantly lower frequency of TP53 mutations (3/16, 18.7%) compared to UCB patients (198/412, 48%) (p = 0.03) but similar frequency of mutations in chromatin modifying (KMT2C, KMT2D, KDM6A), transcription activation (CREBBP), receptor tyrosine kinase (FGFR3, PIK3CA, ERBB2, KRAS), and cell cycle regulation (RB1) genes. 2) UTUC is characterized by downregulation of the DNA mismatch repair genes (p ≤ 0.05) and APOBEC3A, APOBEC3B genes (p < 0.01) and a lower total mutational burden compared to UCB (2 vs 5 mutations per Mb, p = 0.01). 3) UTUC is intrinsically non-basal. UTUC is predominantly luminal by UNC (18/19, 95%) and the MD Anderson (MDA) (17/19, 89%) criteria, and luminal-papillary (16/19, 84%) by the TCGA criteria. All VALD UTUC tumors (n = 10) clustered with the luminal-papillary subtype. 4) UTUC tumors exhibit a T-cell depleted phenotype (17/19, 89%). 5) FGFR3 expression is a dominant transcriptional outlier in UTUC (7/19, 37%) and is associated with a T-cell depleted phenotype (p < 0.01). **Conclusions:** Our study demonstrates that UTUC is predominantly and intrinsically non-basal. We show that UTUC is characterized by a T-cell-depleted phenotype associated with FGFR3 overexpression. By dissecting the biology of UTUC, we provide the biological rationale for future UTUC-specific therapeutic strategies.

4526 Poster Session (Board #352), Sat, 8:00 AM-11:30 AM

Ramucirumab (RAM) exposure-response (ER) relationship in RANGE, a randomized phase III trial of docetaxel (DOC) with or without RAM in advanced urothelial carcinoma (UC) patients (pts) who progressed on or after platinum therapy. *First Author: Ronald De Wit, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: RAM+DOC improved PFS & had acceptable safety in UC (Petrylak, et al *Lancet*, 2017). RAM ER relationships are reported. **Methods:** Pts received RAM (10 mg/kg) + DOC (75 mg/m^2) or placebo (P) + DOC (Day 1 of a 21 day cycle) until discontinuation criteria were met. Evaluable pts (n = 161) were classed into high *v* low groups at the median observed RAM $C_{min\text{-}1}$ (minimum concentration after first dose) or $C_{min\text{-}1}$ quartiles (Q1 = lowest). Matched case controls (MCC) were based on UC prognostic factors. Cox regression was performed. Exposure (E)-safety data are descriptive. **Results:** Subgrouping by baseline prognostic factors indicated pts with 2-4 Bellmunt risk factors, ≥3 metastatic sites, < 10g/dL hgb or < 3.5g/dL albumin often achieved low $C_{min\text{-}1}$. PFS did not differ between low $C_{min\text{-}1}$ & P+DOC pts. High $C_{min\text{-}1}$ pts had ↑ PFS *v* P+DOC pts in 5 (Table) of the 10 subgroups. From $C_{min\text{-}1}$ Q1-4, ORRs were 10.9%%, 38.3%, 34.8% & 37.5%. In a MCC analysis, pts achieving higher E had ↑ PFS & ↓ HR (Table). From Q1-4, grade ≥3 neutropenia increased, but no clear trends were seen for the other grade ≥3 events- fatigue, hypertension and febrile neutropenia. **Conclusions:** Q1 pts had lower mPFS & ORR *v* Q2-4. The potential association between baseline risk factors & E achieved may confound ER analysis & warrants further exploration. Safety appears manageable across RAM E levels. Clinical trial information: NCT02426125.

	P+DOC		High $ObsC_{min\text{-}1}$			
	N / # events	Median, mo	N / # events	Median, mo	HR	*P*-value
Pure Transitional Cell Histology	174 / 146	2.8	66 / 44	5.5	0.472	0.0075
Hemoglobin ≥10 g/dL	190 / 156	2.8	71 / 48	5.5	0.519	0.014
Primary site is Bladder	138 / 120	2.8	52 / 36	5.5	0.480	0.0163
Albumin > 3.5 g/dL	204 / 168	2.8	77 / 54	5.5	0.552	0.023
Liver metastases absent	166 / 132	2.9	59 / 38	5.6	0.534	0.021

PFS MCC Analysis	P+DOC		RAM+DOC		HR (95% CI)	*P*-value (Wald's)
	N / #events	Median, mo (range)	N / #events	Median, mo (range)		
Q1	40 / 34	2.3 (1.4, 2.8)	40 / 33	4.1 (1.9, 4.3)	0.782 (0.484, 1.265)	0.3166
Q2	40 / 33	2.8 (1.4, 4.3)	40 / 35	5.1 (2.3, 6.0)	0.754 (0.467, 1.218)	0.2487
Q3	40 / 33	2.7 (1.4, 4.3)	40 / 29	4.3 (3.0, 5.8)	0.567 (0.343, 0.936)	0.0266
Q4	41 / 34	2.9 (2.6, 5.3)	41 / 28	5.6 (4.0, 8.1)	0.591 (0.358, 0.976)	0.0399

4527 Poster Session (Board #353), Sat, 8:00 AM-11:30 AM

Comprehensive genomic characterization of urothelial carcinomas. *First Author: Amin Nassar, Brigham and Women's Hospital, Boston, MA*

Background: While the genetic characteristics of muscle-invasive bladder cancer have been studied in detail, there are few reports using the same genetic analysis platform to investigate differences and similarities among urothelial carcinoma (UC) derived from different sites and with differing degrees of invasion. **Methods:** We used targeted exome sequencing with Oncopanel to study 82 low-grade (LG) non-muscle invasive bladder cancer tumors (LG-NMIBC), 127 high-grade (HG) NMIBC, 199 muscle-invasive bladder cancer tumors (MIBC), and 55 HG invasive upper tract urothelial carcinoma (UTUC) tissue samples. Oncopanel assesses 275-447 cancer genes for somatic mutations and copy number alterations without a paired normal. All single nucleotide variants (SNVs) that were considered likely germline were excluded. Clinico-pathological characteristics, mutation frequencies for 238, and tumor mutation burden (TMB) were determined for the 4 types of UC, and were compared using the χ^2 test and Kruskall Wallis Test. Nominal p values were obtained, and the Benjamini-Hochberg fdr correction was employed to determine statistical significance (q < 0.1). **Results:** Key results are shown in the Table. **Conclusions:** In this series of uniformly analyzed UC samples of different kinds, we found that: 1) FGFR3, STAG2 and KDM6A mutations are highly enriched in LG-NMIBC; 2) HG-NMIBC, MIBC, and UTUC all have similar genetic alterations; and 3) TP53 and RB1 mutations are associated with all of the latter 3 types of UC in contrast to LG-NMIBC.

		LG NMIBC		HG NMIBC		MIBC		UTUC		total	q value
Gene		N	%	N	%	N	%	N	%	%	
FGFR3 Alteration	Yes/ No	59/23	72/ 28	33/93	26/ 74	25/ 174	13/ 87	10/45	18/ 82	27/ 73	< 0.0001
TP53 Alteration	Yes/ No	3/79	4/ 96	59/67	47/ 53	118/ 81	59/ 41	26/29	47/ 53	45/ 55	< 0.0001
RB1 Alteration	Yes/ No	0/82	0/ 100	23/ 103	18/ 82	46/ 153	23/ 77	6/49	11/ 89	16/ 84	0.0012
STAG2 Alteration	Yes/ No	25/57	30/ 70	21/ 105	17/ 83	18/ 181	9/ 91	8/47	15/ 85	16/ 84	0.006
KDM6A Alteration	Yes/ No	38/44	46/ 54	47/79	37/ 63	49/ 150	25/ 75	12/43	22/ 78	32/ 68	0.024
FGFR2 Alteration	Yes/ No	1/81	1/ 99	9/117	7/ 93	2/197	1/ 99	0/55	0/ 100	3/ 97	0.072
TMB	Mean	11.47		16.61		14.01		11.78		-	

4528 Poster Session (Board #354), Sat, 8:00 AM-11:30 AM

Clinical efficacy of cabozantinib plus nivolumab (CaboNivo) and CaboNivo plus ipilimumab (CaboNivoIpi) in patients (pts) with chemotherapy-refractory metastatic urothelial carcinoma (mUC) either naïve (n) or refractory (r) to checkpoint inhibitor (CPI). *First Author: Rosa Nadal, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Preliminaryclinical activity of CaboNivo and CaboNivoIpi has been previously reported for mUC pts and other genitourinary tumors. Here, we report longer follow-up data of CaboNivo and CaboNivoIpi in pts with mUC nCPI and safety and preliminary clinical activity of CaboNivo in mUC rCPI **Methods:** This phase 1 dose + expansion cohorts study enrolled mUC nCPI (escalating doses of CaboNivo n = 15 and CaboNivoIpi n = 8) and mUC rCPI (Cabo40-Nivo3mg/kg n = 7) pts until progression/unacceptable toxicity. Objectives: Safety, ORR, DOR, PFS and OS. Tumors were assessed for response q8wks (RECIST 1.1). Adverse events (AEs) were graded (G) by NCI-CTCAE v4.0. **Results:** 30 mUC pts enrolled. Median follow-up: whole cohort: 11.9 months; mUC rCPI: 5.6 months. All G clinical AEs in ≥20% (n = 29): fatigue (83%), diarrhea (72%) and anorexia (62%); laboratory AEs: ALT elevation (55%), AST elevation (48%) and hyponatremia (48%). Common ≥G3 clinical AEs: fatigue (17%), HTN (14%), thromboembolic events (14%); laboratory AEs: lipase elevation (31%), hypophosphatemia (17%), hyponatremia (10%). Immune-related AEs 14% (n = 4): mUC nCPI: CaboNivo: G3 meningitis; G3 pneumonitis; CaboNivoIpi: G3 colitis; mUC rCPI: G2 adrenal insufficiency. For mUC nCPI CaboNivo ORR: 50% (6/12), mDOR: 24.1months(mo) [95% CI: 7.8 mo-not reached (NR)]; mPFS 24.1mo [95% CI:1.6mo-NR] & mOS: NR. For mUC nCPI CaboNivoIpi: ORR: 33% (2/6), mDOR: NR; mPFS 10.1mo [95% CI:1.6 mo-NR] & mOS: NR. For mUC rCPI CaboNivo, ORR: 28% (2/7), SD 57% (4/7) and DOR: 100% at 5mo. **Conclusions:** Both CaboNivo and CaboNivoIpi are safe and active in mUC nCPI pts, CaboNivo is also active in mUC pts previously treated with immunotherapy, suggesting the addition of Cabo to Nivo may aid in overcoming CPI resistance. Clinical trial information: NCT02496208.

4529 Poster Session (Board #355), Sat, 8:00 AM-11:30 AM

Atezolizumab (atezo) in special populations: Analyses from an expanded access program (EAP) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). *First Author: Jean H. Hoffman-Censits, John Hopkins University Sidney Kimmel Cancer Center, Baltimore, MD*

Background: Prior to FDA approval of atezo (anti–PD-L1) for platinum-treated mUC (and later cisplatin-ineligible mUC), a US EAP granted mUC pts access to atezo. The EAP (Bellmunt ASCO 2017) included special populations previously ineligible for Ph II study IMvigor210 (Rosenberg *Lancet* 2016). Here, we evaluate outcomes in pts with impaired baseline renal function or variant histology. **Methods:** This study (NCT02589717) enrolled mUC pts who progressed during or following platinum and had ECOG PS ≤ 2. Pts had predominant TCC histology but no restrictions on CrCl levels. Pts received atezo 1200 mg IV q3w until loss of clinical benefit. ORR (per investigator), DCR (CR+PR+SD) and safety were assessed by CrCl or primary tumor histology. **Results:** 114 pts were response evaluable; responses occurred in most subgroups (Table). All-grade treatment-related AEs (TRAEs) occurred in 46% of 214 safety-evaluable pts. In renal function subgroups, TRAE rates ranged from 35% (CrCl 30-45 mL/min) to 54% (CrCl 45-60 mL/min); no TRAE rate differences by histology were seen (46% each). Similar trends occurred for AEs of special interest. TRAEs leading to discontinuation were uncommon (< 3% across subgroups). Two serious TRAEs (15%) occurred in CrCl < 30 mL/min subgroup (< 8% in other subgroups). **Conclusions:** Responses or SD with atezo were seen in pts with mixed histology or compromised renal function (notably in pts with CrCl 30-45 mL/min), and safety was comparable across subgroups. These results suggest that atezo provides clinical benefit in a broad range of platinum-treated mUC pts. Clinical trial information: NCT02589717.

RECIST v1.1 response by baseline characteristic.

	n	ORR, %	95% CI, %	CR, %	DCR, %	95% CI, %
All	114	15	9, 23	3	49	40, 59
CrCl, < 30 mL/min	6	0	0, 46	0	50	12, 88
30-45	19	21	6, 46	5	63	38, 84
45-60	27	4	0, 19	0	30	14, 50
≥ 60	62	19	10, 31	3	53	40, 66
TCC histology only	102	13	7, 21	2	48	38, 58
TCC with mixed histology[a]	12	33	10, 65	8	58	28, 85

Median follow-up (N = 214): 2.3 mo (range 1.6-3.4).
[a] 1 PR was seen among 2 pts with an adenocarcinoma component and 1 CR + 2 PR among 5 pts with "other" subtype. No responses occurred in 1 pt with sarcomatoid or 4 pts with squamous components; 2 pts with squamous histology and 1 with "other" histology had SD.

4530 Poster Session (Board #356), Sat, 8:00 AM-11:30 AM

Optimization of PD-L1 algorithm for predicting overall survival (OS) in patients with urothelial cancer (UC) treated with durvalumab monotherapy. *First Author: Magda Zajac, AstraZeneca, Cambridge, United Kingdom*

Background: PD-L1 expression is a useful biomarker in predicting response to PD-1 and PD-L1 directed immunotherapies in a variety of tumor types. In UC, studies have implicated PD-L1 expression in tumor cells (TC) and tumor-infiltrating immune cells (IC) as having clinical utility, but the relative importance of each cellular compartment and the most predictive algorithm and PD-L1 expression cutoff remain unclear. **Methods:** PD-L1 expression data (SP263 assay) from 188 patients in the UC cohort from single arm (durvalumab monotherapy) Phase 1/2 Study CD-ON-MEDI4736-1108 (NCT01693562; Oct. 2017 data cutoff) were assessed. Regression models were used to evaluate the impact of PD-L1 expression in TC or IC on OS, progression-free survival (PFS), objective response rate (ORR), best percentage tumor change and tumor shrinkage 15 months after last subject randomization. Kaplan–Meier plots were generated to explore the impact of single biomarker and combined (TC or IC [% PD-L1 positive ICs within IC area]) algorithms on OS. **Results:** Both IC and TC PD-L1 were linked to higher ORR, and IC PD-L1 was associated with better survival in patients treated with durvalumab. IC PD-L1 had a higher impact on response to durvalumab than TC PD-L1, showing significant ($P < 0.05$) association with OS, PFS, ORR, and tumor shrinkage. The best outcomes were obtained when TC and IC algorithms were combined, with TC25%/IC25% proving optimal (Table). **Conclusions:** In UC, the TC25%/IC25% algorithm appears to provide optimal predictive value based on efficacy and prevalence of the biomarker. Additional data from randomized trials are needed to confirm these findings. Clinical trial information: NCT01693562.

	ORR, %		Median OS, months		
Cutoff/algorithm	**PD-L1 high**	**PD-L1 low**	**PD-L1 high**	**PD-L1 low**	**Prevalence of PD-L1 high pts, %**
TC1%	21.6	11.1	8.4	10.9	61.7
TC10%	19.5	16.2	6.9	10.9	41.0
TC25%	23.4	15.6	9.3	10.5	25.0
TC50%	19.4	17.1	9.3	10.5	19.1
IC1%	22.4	5.6	11.6	6.4	71.3
IC10%	22.8	6.6	11.6	6.6	67.6
IC25%	28.4	10.5	22.3	5.5	39.4
IC50%	31.1	13.3	22.3	6.6	23.9
TC1%/IC1%	20.9	0.0	10.8	6.4	84.0
TC10%/IC25%	23.3	7.4	12.5	7.8	63.8
TC25%/IC25%	27.5	5.8	19.8	4.8	54.3
TC50%/IC25%	27.1	7.6	20.0	4.8	51.1

N = 188
IC: % PD-L1 positive ICs within IC area

4531 Poster Session (Board #357), Sat, 8:00 AM-11:30 AM

***FGFR3* Driven Metastatic Urothelial Carcinoma of the Urinary Bladder (mUCB): A Comprehensive Genomic Profiling Study.** *First Author: Jeffrey S. Ross, SUNY Upstate Medical University, Syracuse, NY*

Background: Using comprehensive genomic profiling (CGP), we queried whether *FGFR3*-driven mUCB could be further defined by additional genomic alterations (GA) and biomarkers of response to immunotherapies. **Methods:** DNA from FFPE tissues of 1,576 mUCB underwent hybrid-capture based CGP to evaluate all classes of genomic alterations. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined by principal components analysis of optimal homopolymer loci. **Results:** 385 (24%) of the 1,576 UCB featured GA affecting *FGFR1-4*. Of the *FGFR3* GA identified in mUBC (*FGFR3*mut), 77% were SV, 2% were amplifications, 18% were fusions/rearrangements, and 4% had more than 1 GA type. When compared with a cohort of 1,275 *FGFR3* WT mUCB, the GA/tumor and frequency of *TERT* GA were similar. GA in *TP53* and *RB1* were more common in *FGFR3* WT than *FGFR*mut, whereas cell cycle GA (e.g., *CDKN2A)* were more common in *FGFR3*mut tumors. Genes associated with DNA repair were altered in both groups, with *ARID1A* GA more frequent in *FGFR3* WT, *KDM6A* GA more frequent in *FGFR3*mut, and *BRCA1/2* GA less frequent overall and similar in both groups. Targetable *ERBB2* GA were significantly more common in *FGFR3* WT cases. Targets in the MTOR pathway, including GA in *PIK3CA* and *TSC1,* were also more common in *FGFR3*mut mUBC. MSI-High status was extremely rare in both groups. The median TMB was higher in *FGFR3* WT, and samples more often had TMB of ≥10 mut/Mb or ≥20 mut/Mb. **Conclusions:** CGP reveals both similarities and differences in the genomic landscapes of *FGFR3*mut and *FGFR3* WT mUBC. In the 2% of mUBC with *FGFR3* driver GA, other targetable GA affecting kinases or the MTOR pathway are present. As evidenced by TMB, the opportunity for immunotherapies remains significant.

	***FGFR3* WT**	***FGFR3*mut**	**Significance**
Cases	1,275	301	
Median age (years)	67	67	NS
Male/Female	75/25	72/28	NS
GA/tumor	7.3	8.3	NS
TERT	67%	73%	NS
TP53	64%	27%	P < 0.0001
CDKN2A	30%	60%	P < 0.0001
RB1	24%	3%	P < 0.0001
ARID1A	24%	17%	P = 0.001
KDM6A	20%	37%	P < 0.0001
BRCA1	3%	1%	NS
BRCA2	3%	3%	NS
PIK3CA	20%	27%	P = 0.001
ERBB2	18%	6%	P < 0.0001
TSC1	6%	17%	P < 0.0001
MSI	< 1%	1%	NS
Median/Mean TMB (mut/Mb)	7.2/10.7	6.3/9.3	NS
TMB > 10 mut/Mb	38%	28%	P = 0.0008
TMB > 20 mut/Mb	13%	9%	NS

4532 Poster Session (Board #358), Sat, 8:00 AM-11:30 AM

Patient-reported outcomes (PROs) in patients with urothelial carcinoma (UC) treated with durvalumab (second-line or above) in phase 1/2 dose-escalation study 1108. *First Author: Peter H. O'Donnell, University of Chicago Comprehensive Cancer Center, Chicago, IL*

Background: In Study 1108, durvalumab showed meaningful clinical activity in patients with UC, with an objective response rate (ORR) of 17.8% (PD-L1–positive patients: 27.6%) [Powles 2017, *JAMA Oncol*]. We report PRO results. **Methods:** Phase 1/2, open-label, dose escalation study 1108 (NCT01693562) enrolled patients with locally advanced/metastatic UC and prior platinum-based treatment. Patients received durvalumab 10 mg/kg Q2W for 12 months, and were asked to complete Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BL), European Organisation for Research and Treatment of Cancer Quality of Life (QoL) Questionnaire (EORTC QLQ-C30) and a pain questionnaire at baseline (D1) and days 29, 43, 57, 85 and 113 (D113). Changes in PROs were analyzed descriptively. Improvement/deterioration from D1 was based on minimum important difference: $^1/_2$ baseline standard deviation (SD) for FACT-BL (range 0–156), 10-point difference for EORTC QLQ-C30 (total range 0–100). **Results:** In the full analysis set (n = 182), overall questionnaire completion rate at baseline was 99% and 81% at D113. Pain total mean (SD) score (range 0–10) tended to decrease over time, from 3.4 (2.8) on D1 to 1.9 (2.4) at D113. Mean (SD) FACT-BL total scores improved over time, from 107.5 (23.0) on D1 to 115.4 (22.6) on D113, with similar increases in bladder cancer subscale (BLCS) and trial outcome index (TOI) mean scores. FACT-BL total score improved over time in 32.6% of patients (48.8% no change, 18.6% deterioration); 34.9% showed an improvement in FACT-BLCS, and 32.6% in FACT-TOI. EORTC QoL mean (SD) score improved from 57.1 (24.8) on D1 to 69.0 (21.4) at D113. Improvements in EORTC QLQ-C30 functional domains were seen in 26.3–37.8% of patients, while 57.6–73.1% showed improvements in symptom domains, with largest responses in pain, fatigue, physical and role domains (improvement: 73.1, 57.6, 37.8 and 32.4%; no change: 0.0, 27.3, 46.0 and 41.2%; deterioration: 26.9, 15.2, 16.2 and 26.5%, respectively). **Conclusions:** Overall, the mean scores (domain or total) for pain, FACT-BL and EORTC QLQ-C30 improved over time in patients with UC treated with durvalumab in the phase 1/2 study 1108. Clinical trial information: NCT01693562.

4533 Poster Session (Board #359), Sat, 8:00 AM-11:30 AM

Immune profiling in a randomized phase II trial of acalabrutinib and pembrolizumab (PA) versus pembrolizumab (P) for patients with metastatic urothelial cancer (mUC). *First Author: Tian Zhang, Duke University Medical Center, Durham, NC*

Background: Response rates for checkpoint inhibitors (CPIs) in cisplatin refractory mUC range from 15% to 21%. Thus, biomarkers are needed to predict for treatment responses. We conducted a Ph2 clinical trial in patients with mUC, randomized to P or PA (NCT02351739). From this trial, we performed the first correlation analysis of circulating immune cells with clinical outcomes in mUC patients receiving CPI therapy. **Methods:** 75 patients with cisplatin refractory mUC were treated with P or PA. Pre- and on-study flow cytometry was performed on peripheral blood mononuclear cells for these markers: CD3, CD4, CD8, PD-1, PD-L1, PD-L2, B7-H3, CTLA-4, ICOS, LAG3, TIM3, Ki-67, CD45RA, CCR7, CD38, CD14, HLA-DR, CD16/CD56, CD19/CD20, CD25, CD127, CD39, and CCR4. Single and selected double marker positivity was analyzed on CD4 and CD8 T-cells and monocytes (M). Mean ($\pm$ SD) of relative cell subset frequency (RCSF) was calculated and associated with clinical responses (best radiographic response as defined per RECIST 1.1 criteria). Unadjusted p-values were derived from Kruskal-Wallis testing, with responses as outcomes and RCSF or delta RCSF as correlatives. **Results:** Clinical responses (PR+CR) did not differ between treatments (P = 25% vs. PA = 20%); therefore, pooled results from all treated patients were used for analysis. Baseline RCSF (n = 57) or changes in RCSF from baseline to week 4 (n = 51) were correlated with responses. Patients who had CR had lower expression of LAG3, PDL2, CTLA4 and B7H3 on M at baseline. Among T-cells, lower levels of CTLA4+, PD1+, and ICOS+ CD4 T-cells; and higher CD28-/TIM3- CD8 cells were also associated with CR. Changes from baseline to week 4 were observed for actively proliferating CD4 or CD8 T-cells, CD8 T-cells that co-express TIM3 with CD28 or PD-1, and for TIM3-expressing M subsets, suggesting that early increases in immune cell activation (Ki-67, CD28, PD-1) and interferon response (TIM3) are associated with clinical responses. **Conclusions:** Immune profiling in patients with mUC showed activation and interferon response markers on subsets of T-cells and monocytes that were associated with treatment responses to CPI therapy.

4534 Poster Session (Board #360), Sat, 8:00 AM-11:30 AM

FIERCE-21: Phase 1b/2 study of docetaxel + b-701, a selective inhibitor of FGFR3, in relapsed or refractory (R/R) metastatic urothelial carcinoma (mUCC). *First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients with locally advanced or metastatic urothelial carcinoma (mUCC) have a poor prognosis. FGFR3 is frequently overexpressed in UCC and 15-20% of patients with mUCC have FGFR3 gene mutations or fusions (M/F). B-701 is a fully human monoclonal antibody against FGFR3 that blocks activation of the wildtype and genetically activated receptor. FIERCE-21 is a Phase 1b/2 study designed to evaluate B-701 alone or in combination with docetaxel (D). **Methods:** The study consists of a Phase 1b lead-in (P1b) followed by Phase 2 (P2) expansion and a randomized phase. Eligible patients P1b: the study enrolled mUCC R/R excluding prior taxane treatment, and ECOG >1. Treatment: B-701 at 25 mg/kg and D at 75 mg/m^2 q3w. Efficacy was assessed by investigators (RECIST 1.1). Primary objective: Determine P2 dose and evaluate safety and efficacy. **Results:** 19 patients were enrolled in P1b: median age 66 yrs, ECOG 1 = 58%, Hgb <10 gm/dL 5%, liver metastases 26%, ≥ 2 prior regimens 63%, best response to prior therapy PD 52%. Six patients were positive for FGFR3 M/F. Grade ≥ 3 AEs occurring in ≥ 2 patients were typical of D at this dose and schedule [decreased neutrophil count (26.3%), neutropenia (10.5%), decreased WBC (10.5%)]. Two patients had D dose reductions and no subjects had dose reductions of B-701 or discontinued treatment due to AE. Two patients died, 1 with PD and bleeding, and 1 with MAHA associated with infection and recurrent thrombosis. Four subjects are alive (3 M/F). Median OS has not been reached in M/F vs 5.3 months in WT. **Conclusions:** B-701 combined with standard dose D in an every 3 week schedule in patients with mUCC was well-tolerated with expected myelosuppression. Enhanced activity was seen in the FGFR3 M/F compared to WT patients. Phase 2 expansion is currently enrolling FGFR3 M/F patients (B-701 monotherapy vs. combination B-701+D). Clinical trial information: NCT02401542.

4535 Poster Session (Board #361), Sat, 8:00 AM-11:30 AM

Relapse-free survival (RFS) of clinical T2-4N0 urothelial bladder carcinoma (UBC) after radical cystectomy (RC), with or without perioperative chemotherapy (POC): Endpoints for clinical trial design. *First Author: Marco Bandini, Vita-Salute San Raffaele University, Milan, Italy*

Background: Recent data suggests that the full benefit of neoadjuvant therapy may not be captured via pathologic complete response rates. Improved relapse-free survival (RFS) may identify active agents acting though novel mechanisms. **Methods:** Within RISC and San Raffaele databases (1990-2016), we identified 973 cT2-4N0 UBC patients (pts), from 27 centers in the U.S., Europe, Israel, and Canada. A Cox-based nomogram predicting 12-m RFS was built including pt (gender, race), tumor characteristics (histology, pT, pN and surgical margin status [SMS]), and administration of neoadjuvant or adjuvant chemotherapy (CT). Multiple imputation was performed to handle missing data. Validation (2000 bootstrap resamples) was internally tested. Calibration and prognostic ability was assessed comparing estimated versus observed 12-m RFS. **Results:** Overall, 577 (59.3%) and 236 (24.3%) pts had cT2 and cT3-T4, respectively (T unknown and imputated in 160, 16.4%). 125 (12.8%) had mixed UC+other histologies. 275 pts (28.3%) received neoadjuvant CT, 165 (17%) adjuvant CT. On multivariable analyses, pT ($p<0.002$), pN ($p<0.001$) and SMS ($p=0.005$) were associated with higher rate of recurrence. Conversely, use of adjuvant CT (HR = 0.63, $p<0.001$) was associated with lower rate of recurrence. Results were confirmed in sensitivity analyses after removing 61 (6.2%) non-cisplatin POC. Overall, 405 (41.6%) pts relapsed and 375 (38.5%) died. Median RFS and overall survival were 44 months (95%CI, 36-65) and 57 months (95%CI, 50-90), respectively. In POC-treated pts, nomogram-predicted 12-m RFS rates were 91.6% (95%CI, 87-96), 79.7% (95%CI, 73-88) and 53.0% (95%CI, 44-63), across the nomogram-derived tertiles. In pts who did not receive POC, these estimates were 89.8%, 74.8%, and 47.0%, respectively. The bootstrapped c-index of the nomogram was 78% (95%CI: 74-81). **Conclusions:** Nomogram-predicted 12-m RFS may provide data to base future clinical trial designs of novel agents in the perioperative setting.

4536 Poster Session (Board #362), Sat, 8:00 AM-11:30 AM

Prognostic value of genomic alterations of DNA repair genes in advanced bladder cancer (ABC). *First Author: Ming Yin, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: DNA repair defect plays an important role in tumorigenesis, progression, treatment response and outcomes of BC. There is conflicting data on the prognostic & predictive role of DDR gene alterations in ABC patients (pts) treated with platinum-based chemotherapy (Teo *et al.* ASCO 2017; Mendiratta *et al.* GU ASCO 2018). Thus, further validation is needed to understand prognostic implications of DDR genomic alterations in ABC. **Methods:** Exome sequencing data were obtained from 81 ABC pts who received comprehensive genomic sequencing using FoundationOne (315 cancer-related genes). Overall survival (OS) was measured from time of initial diagnosis and metastasis-related survival (MRS) was measured from time of metastatic diagnosis to death or last follow-up. Cox proportional hazard regression analysis was performed to calculate the hazard ratio (HR) and 95% confidence interval (CI). **Results:** In a panel of 28 DDR genes, mutations were present in 74.1% pts (60/81) with18.5% pts carrying mutations in ≥3 DDR genes. Overall, mutations of DDR genes were not significantly associated with OS (HR = 0.76, 95% CI 0.41–1.43, p = 0.397) or MRS (HR = 0.57, 95% CI 0.30–1.08, p = 0.084). Further evaluation showed that most DDR mutations (excluding ATM/RB1) were associated with longer OS (HR = 0.49, 95% CI 0.27–0.87, p = 0.015) and longer MRS (HR = 0.39, 95% CI 0.21–0.70, p = 0.002), while mutations of ATM/RB1 genes were associated with shorter OS (HR 1.87, 95% CI 0.97–3.59, p = 0.06) but not MRS. There was a trend for longer OS and MRS with increased number of DDR mutations in individual pts. Pts carrying ≥3 DDR mutations (excluding ATM/RB1) seemed to have the best prognosis in our cohort (OS: HR 0.36, 95% CI 0.14–0.92, p = 0.03; MRS: HR 0.20, 95% CI 0.07–0.56, p = 0.002). **Conclusions:** Most DDR mutations correlated with improved clinical outcomes in ABC pts. However, ATM/RB1 mutations correlated with poor prognosis. Pts carrying ≥3 DDR (excluding ATM/RB1) mutations had the best prognosis. Further exploration of the deleterious nature and impact of alterations as well as further external validation are critical. Clinical trials evaluating synthetic lethality with DDR inhibitors are ongoing.

4537 Poster Session (Board #363), Sat, 8:00 AM-11:30 AM

A novel, robust multiplex urine-based immunoassay for bladder cancer detection. *First Author: Hideki Furuya, University of Hawaii Cancer Center, Honolulu, HI*

Background: Bladder cancer (BCa) is among the most commonly diagnosed malignancies worldwide, and due the high rate of post-operative disease recurrence, it is one of the most prevalent in many countries. The development of non-invasive molecular assays that can accurately detect and monitor BCa would be a major advance, benefiting both patients and healthcare systems. We have previously identified a urinary protein biomarker panel that is being developed for application in at-risk patient cohorts. Here, we investigated the potential utility of the multiplex assay in a prospective study. **Methods:** The study cohort collected from urology clinics at two institutions was comprised of a total of 145 subjects. The protein biomarker panel (IL8, MMP9, MMP10, ANG, APOE, SDC1, A1AT, PAI1, CA9, VEGFA) was monitored in voided urine samples collected prior to cystoscopy using a custom multiplex ELISA assay. The diagnostic performance of the biomarker panel was assessed using receiver operator curves (ROC), predictive modeling and descriptive statistics. **Results:** Urinary biomarker concentrations were significantly elevated in cases versus controls, and in cases with high-grade and muscle-invasive tumors. The AUC for the 10-biomarker assay was 0.901 (95% confidence interval, 0.850–0.934), with an overall diagnostic sensitivity specificity of 0.90 and 0.91, respectively. **Conclusions:** Urinary levels of a 10-biomarker panel enabled discrimination of patients with BCa. The multiplex urinary diagnostic assay will continue in prospective study. Clinical trial information: NCT03193528.

4538 Poster Session (Board #364), Sat, 8:00 AM-11:30 AM

Bladder cancer gene expression subtypes (60 gene signature) to define prognosis, differential immune response, and biomarker associations. *First Author: Gregory M. Mayhew, GeneCentric, Research Triangle Park, NC*

Background: Gene expression subtypes provide valuable insight into tumor biology and potential therapeutic response. Differential expression of immune infiltrating cells and biomarkers, tumor mutation burden, therapeutic targets, and overall survival were examined in Muscle Invasive Bladder Cancer (MIBC) subtypes, luminal, luminal infiltrated, basal, and neuronal. **Methods:** Multiple MIBC datasets were assembled including TCGA (n = 408) and 2 other gene expression datasets (n = 305, n = 93). A reduced 60-gene subtyping signature was developed and subtype calls were compared to TCGA clustering. Signatures of multiple immune cells, single immune-biomarkers, drug target genes, proliferation, and mutation burden were examined for differential expression using the Kruskal-Wallis test. Differences in gene mutation distributions were evaluated using Fisher's exact test. Survival differences were assessed using stratified cox models and Kaplan Meier plots. **Results:** Immune cell expression was significantly different across the subtypes in multiple datasets (T cells $p < 0.001$ and *CD274*(PD-L1) $p < 0.002$). The luminal subtype as compared to other subtypes showed lower immune expression for most markers. In the TCGA dataset, drug target genes were differentially expressed (*FGFR2*, *FGFR3*, and *ERBB2* $p < 1e\text{-}05$), as was proliferation ($p < 1e\text{-}20$), and patterns were reproducible across datasets, with luminal and luminal-infiltrated subtypes showing higher expression of *FGFR2*, *FGFR3*, and *ERBB2* and lower proliferation. Mutation frequencies of *FGFR3* and *RB1* varied across subtypes (p = 1e-05 and p = 0.0005), whereas mutation burden did not (p = 0.16), despite marked differences in immune infiltration. In the TCGA dataset, significant differences in survival were observed (p = 0.0385 adjusting for stage), with luminal and luminal-infiltrated, as defined by the 60 gene signature, showing better survival and basal worse survival. **Conclusions:** Biologic gene expression subtypes of MIBC using a reduced 60-gene signature reveal key differences in prognosis, immune cell expression, and drug targets. Subtypes provide potential biomarkers for targeted and immunotherapy response.

4539 Poster Session (Board #365), Sat, 8:00 AM-11:30 AM

Model combining genomic and clinical factors to predict clinical benefit from PD1/PD-L1 inhibitors for advanced UC. *First Author: Amin Nassar, Brigham and Women's Hospital, Boston, MA*

Background: Tumor mutational burden is associated with response to PD1/PD-L1 inhibitors in advanced UC. We explored the ability of copy-number variants (CNVs) and specific genomic alterations to complement single-nucleotide variants (SNVs) to predict clinical benefit in patients (pts) with advanced UC receiving PD1/PD-L1 inhibitors. **Methods:** Targeted exome sequencing (238 genes) was performed on archival tumors from metastatic UC pts treated with PD1/PD-L1 inhibitors at our institution. Clinical Benefit (CB) was defined as any objective reduction in tumor size, and no clinical benefit (NCB) was defined as any objective increase in tumor size by RECIST 1.1. Associations between clinical and genomic features and clinical benefit were assessed using univariate and multivariate logistic regression modeling. **Results:** 61 pts were evaluable, with CB in 24 pts and NCB in 37 pts. The prognostic factors associated with NCB on univariate analysis were neutrophil/lymphocyte ratio (NLR) ≥5, ECOG-PS ≥1, hemoglobin (Hb) < 10 gm/dl, liver metastasis, CDKN2B homozygous deletion, high CNV count and low SNV count. On multivariate analysis, a low SNV count and a high CNV count were associated with NCB. There was a strong trend for association of NCB with liver metastasis and NLR ≥5 (Table). **Conclusions:** A new model combining 2 genomic factors, low SNV and high CNV counts, and 2 clinical factors, high NLR and liver metastasis, appeared associated with NCB in pts with advanced UC receiving PD1/PD-L1 inhibitors. Validation of these hypothesis-generating results is warranted.

Risk factors	Adjusted OR	*p* value
Liver metastasis	7.78 (0.84–71.85)	0.070
CDKN2B homozygous deletion	4.61 (0.24–90.06)	0.314
NLR ≥ 5	9.17 (1.00–84.33)	0.050
ECOG-PS ≥ 1	0.76 (0.12–4.92)	0.775
Hb < 10 gm/dl	7.60 (0.22–258.88)	0.260
CNV count ≥ 1 (median)	8.80 (1.02–76.39)	0.049
SNV count < 8 (median)	12.39 (1.65–92.85)	0.014

4540 Poster Session (Board #366), Sat, 8:00 AM-11:30 AM

Association of circulating tumor (ct)-DNA genomic alterations (GA) with outcomes in metastatic urothelial carcinoma (mUC). *First Author: Petros Grivas, University of Washington, Seattle, WA*

Background: Cell-free ctDNA profiling enables noninvasive identification of GA in mUC. We hypothesized that ctDNA GA correlate with outcomes and signify therapy targets. **Methods:** 477 patients (pts) with UC who underwent ctDNA analysis for potentially actionable GA via Guardant360 were identified. A 73-gene ctDNA next generation sequencing (NGS) panel from CLIA-licensed, CAP-accredited laboratory (Guardant Health, Inc.) offers complete exon sequencing in 19 cancer genes, critical exons in 54 genes, amplifications (18 genes), fusions (6 genes) & indels (23 genes) from 10 mL of peripheral blood. KM method was used to estimate overall survival (OS) and failure-free-survival (FFS) since therapy initiation. Cox proportional hazards regression was used to assess the association of ctDNA GA present in $>10\%$ of pts and clinical factors with OS and FFS in univariable analyses. All tests were 2-sided, $p \leq 0.05$ was significant. We also evaluated GA in serial samples to assess genomic evolution. **Results:** 124 pts had available clinical data, of whom 65 had received prior platinum, 21 prior taxane and 10 prior PD1/PD-L1 inhibitor; ≥ 1 GA was detected in 112 pts. Median age at time of ctDNA collection was 72 and median (range) number of GA per sample was 4 (0-80); 110 pts had ≥ 1 SNV & 39 pts ≥ 1 CNV. Most commonly altered genes were TP53 (55%), PIK3CA (24%) and ARID1A (23%). 1-year OS and FFS were 69% and 35%, respectively. ARID1A (HR 0.49, $p = 0.052$) & BRAF (HR 0.24, $p = 0.048$) GA were associated with longer FFS, while BRCA1 (HR: 2.36, $p = 0.016$) GA with shorter FFS; no GA were significantly associated with OS. After ctDNA collection, 32 pts received platinum, 43 anti-PD1/PDL1, 24 other and 25 no therapy. There was no significant effect of post-ctDNA therapy on OS ($p = 0.91$) or FFS ($p = 0.29$); post-ctDNA therapy did not interact with clinical factors. Serial samples showed new and resolution of some GA. **Conclusions:** ctDNA GA were detected in most pts with mUC and appeared similar to those from prior tumor tissue NGS studies. BRAF & ARID1A GA correlated with longer and BRCA1 GA with shorter FFS suggesting that synthetic lethality with DNA damage repair inhibitors may be clinically useful. Serial sample analysis revealed genomic evolution.

4541 Poster Session (Board #367), Sat, 8:00 AM-11:30 AM

Combined checkpoint immunotherapy and cytotoxic chemotherapy: Further results from a phase Ib/II trial of pembrolizumab and docetaxel or gemcitabine in patients with advanced or metastatic urothelial cancer. *First Author: Mamta Parikh, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: We previously reported tolerability of pembrolizumab plus either docetaxel or gemcitabine in platinum-treated metastatic urothelial cancer patients (pts), given the hypothesis that chemotherapy might enhance tumoral neoantigen expression and modulate immunogenicity of tumor cells, potentially enhancing the response to anti-PD-1 therapy. Herein we report further results from an expansion cohort. **Methods:** Eligible pts had Zubrod PS 0-1, adequate end-organ function, with progression following up to 2 prior lines of chemotherapy (at least one platinum based). Patients were treated with pembrolizumab 200 mg IV on D1 q3weeks plus either docetaxel 75 mg/m2 IV on D1 (Arm A) or gemcitabine 1000 mg/m2 IV on D1 & D8 (Arm B). Primary endpoint was safety; secondary endpoints were overall response rate (RR) and progression free-survival (PFS). **Results:** A total of 20 pts have enrolled, 9 in Arm A, 11 in Arm B. Mean age was 66 (range 31-84). Most common AEs $\geq$ Grade 3 were hyponatremia (8/20), anemia (5/20), fatigue (5/20), neutropenia (4/20), leukopenia (4/20) acute kidney injury (3/20), hypophosphatemia (3/20). There were no treatment-related deaths; 13 died from disease progression. In total, 1 pt had complete response (CR), 5 pts had partial responses (PR), 3 pts had minor responses (MR), 4 had stable disease (SD), and 7 progressed; overall RR was 45% and Disease Control Rate (DCR) was 65%. Arm A had overall RR of 44%, DCR 56%. Arm B had overall RR of 45%, DCR 73%. Median PFS (overall, Arm A & Arm B) were 7, 13.3, and 5.9 months. **Conclusions:** The combination of pembrolizumab with either docetaxel or gemcitabine is tolerated with no unexpected adverse effects, with evidence of efficacy. Expanded cohorts continue to enroll. Clinical trial information: NCT02437370.

4542 Poster Session (Board #368), Sat, 8:00 AM-11:30 AM

A subgroup analysis of the East Asia population in RANGE: A randomized phase 3 study of docetaxel (DOC) with or without ramucirumab (RAM) in platinum-refractory advanced or metastatic urothelial carcinoma (UC). *First Author: Nobuaki Matsubara, National Cancer Center Hospital East, Chiba, Japan*

Background: RANGE (NCT02426125) is a global, randomized, double-blind, placebo-controlled, phase 3 study to evaluate the efficacy and safety of RAM in combination with DOC in patients (pts) with platinum-refractory advanced or metastatic UC. Here we report the results of RAM in combination with DOC in the East Asia population (EA). **Methods:** 530 pts were randomized (1:1) to DOC with either RAM 10 mg/kg or placebo (PL) on day 1 of a 21-day cycle (RAM/DOC or PL/DOC). EA pts (n = 110) received DOC 60 mg/m^2; other pts received DOC 75 mg/m^2. Primary endpoint was investigator-assessed progression free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival, safety, quality of life (QOL), and pharmacokinetics (PK). **Results:** PFS outcomes (investigator-assessed and blinded centrally reviewed) among EA remained consistent with the intention-to-treat population (ITT) (Table). Improvements in ORR and 6/12 month PFS rates for EA were in line with those for ITT. The most common grade ≥ 3 adverse events in EA, neutropenia and leukopenia, were observed at a similar frequency in both arms. Mean scores for global QOL in EA stayed largely stable over time without a clear difference between arms. Plasma concentrations of DOC for pts in the 60 mg/m^2 group were similar to those for pts in the 75 mg/m^2 group. **Conclusions:** The DOC PK profile for EA pts receiving 60 mg/m^2 was consistent with non-EA pts receiving 75 mg/m^2. Results in EA were consistent with the improved clinical outcomes and manageable safety profile observed with RAM/DOC in ITT. Clinical trial information: NCT02426125.

	ITT (first 437 pts)			EA**		
	RAM/DOC (N = 216)	PL/DOC (N = 221)	HR (95% CI)*	RAM/DOC (N = 53)	PL/DOC (N = 57)	HR (95% CI)*
Median PFS (month) (Investigator assessed)	4.07	2.76	0.757 (0.607-0.943)	3.02	2.99	0.928 (0.597-1.444)
6 month PFS rate (%)	28.5	18.9		30.6	24.8	
12 month PFS rate (%)	11.9	4.5		14.9	7.1	
Median PFS (month) (blinded centrally reviewed)	4.04	2.46	0.672 (0.536-0.842)	3.32	2.69	0.793 (0.513-1.225)
ORR (%)	24.5	14.0		26.4	15.8	

* Cox PH model (Stratified by ECOG PS at Baseline, Visceral Metastases, Geographical Region) ** All EA pts were included in the first 437 pts of ITT

4543 Poster Session (Board #369), Sat, 8:00 AM-11:30 AM

Preliminary results from an ongoing phase 2a study of RX-3117, an oral nucleoside analogue to treat advanced urothelial cancer (aUC). *First Author: Jacob Adashek, Western University of Health Sciences, Los Angeles, CA*

Background: RX-3117 is an oral small molecule nucleoside analogue (cyclopentyl pyrimidyl nucleoside) that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder cancer. Preliminary data from Stage 2 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with advanced urothelial cancer (aUC) is described below. **Methods:** The efficacy of oral RX-3117 was evaluated in eligible patients (aged $\geq$ 18 years) with refractory aUC in a Phase 2a study. Primary objectives include safety and efficacy of 700 mg of administered orally RX-3117 for 5 consecutive days followed by 2 days off per week in each 4-week cycle for 4 continuous weeks. The primary endpoint is a $\geq$ 20% rate of progression free survival (PFS) benefit (i.e., proportion of subjects with stable disease for at least 4 months) and/or 10% of evaluable patients with a partial or better response by RECIST criteria. **Results:** As of February 2018, 27 patients (19 males, 8 females) with aUC were treated with RX-3117. The median age was 67 years and ECOG performance status was $\leq$ 1. Prior treatment with gemcitabine or immunotherapy was 85% or 67% of patients, respectively. Five patients achieved stable disease for 4 cycles of RX-3117 treatment; one patient received treatment for 315 days and another patient continues treatment beyond 4 months. One patient achieved a partial response after 2 cycles. Four patients have shown a tumor reduction ranging from 13.9 to 20% as measured by RECIST. All reductions occurred after 1 cycle of RX-3117 treatment, except for one patient's reduction, which occurred after 4 cycles. The most frequent related adverse events were G1/2 diarrhea (14%), fatigue (9%), nausea (9%), vomiting (9%), G1/G2 anemia (7%), and G3 thrombocytopenia (7%). **Conclusions:** RX-3117 is safe and well tolerated and shows preliminary evidence of anti-tumor activity in heavily pretreated patients. The study continues to enroll subjects with aUC in Stage 2. Clinical trial information: NCT02030067.

4544 Poster Session (Board #370), Sat, 8:00 AM-11:30 AM

SPEAR-bladder (study informing treatment pathway decision in bladder cancer): First- through third-line time to treatment failure in the US. *First Author: Gurjyot K. Doshi, US Oncology Network, McKesson Specialty Health, Houston, TX*

Background: Immune-oncology (IO) regimens have improved the clinical outlook for patients with locally advanced or metastatic urothelial carcinoma (mUC). This analysis aimed to assess time to treatment failure (TTF) among patients with mUC treated with systemic chemotherapy and IO regimens in the US community oncology setting. **Methods:** This is a retrospective study of patients with mUC receiving treatment from January 2015 to April 2017, with follow-up through June 2017 using the US Oncology Network electronic health records database. TTF was defined as the interval between treatment initiation in the first (1L), second (2L), or third line (3L) and discontinuation for any reason. TTF was compared between the chemo and IO cohorts using Kaplan-Meier and Cox proportional hazard modeling. **Results:** 523 patients initiated 1L treatment (median age, 72 years; 76.5% male), 241 2L (median age, 69 years; 75.9% male) and 50 3L (median age, 67 years; 74.0% male). Of patients receiving 1L platinum-based combinations (n = 497, 95%), 27.7% were treated with carboplatin/gemcitabine, followed by 26.0% with cisplatin/gemcitabine, and 7.3% with carboplatin/paclitaxel. IO regimens were received by 56.8% of patients in 2L and 68.0% in 3L. In the 2L setting, patients treated with IO regimens had a significantly longer TTF than those treated with systemic chemotherapies ($P < 0.0001$) (Table). **Conclusions:** These findings provide important insights into patterns of care and outcomes among patients with mUC in the community oncology setting. Comparisons between the chemo and IO cohorts were limited due to utilization of heterogenous chemotherapy regimens and small sample sizes. Patients in the IO cohort stayed on therapy for longer periods than chemotherapy-treated patients. Future real-world research may determine generalizability of the results seen in this study.

TTF

Line of Therapy	Chemo, median, weeks	IO, median, weeks	Hazard Ratio (95% CI)	*P*-Value
1L	n = 497 11.3	n = 26 15.1	0.570 (0.346-0.939)	0.0274
2L	n = 104 9.1	n = 137 12.1	0.552 (0.406-0.749)	< 0.0001
3L	n = 16 9.9	n = 34 22.9	0.461 (0.213-0.997)	0.0490

4545 Poster Session (Board #371), Sat, 8:00 AM-11:30 AM

Efficacy of split schedule (SS) vs conventional schedule (CS) neoadjuvant cisplatin-based chemotherapy for muscle-invasive bladder cancer (MIBC). *First Author: Chelsea K. Osterman, University of Pennsylvania, Philadelphia, PA*

Background: Neoadjuvant cisplatin (70mg/m2) based chemotherapy (NAC) prior to cystectomy is standard of care for MIBC. Many patients (pts) cannot receive cisplatin due to impaired renal function. In pts with borderline renal function (eGFR 40-60mL/min), administration of cisplatin 35mg/m2 day 1+8 or 1+2 (i.e., split schedule) is a commonly used alternative. No prior studies have directly compared the effectiveness of SS to CS cisplatin in NAC for MIBC. **Methods:** We conducted a retrospective multi-institutional matched cohort study of MIBC pts receiving either SS or CS cisplatin containing NAC from 2013 -2017. Pts were matched 1:1 on chemotherapy regimen (GC or AMVAC), number of cycles, tumor histology, and clinical stage. All pts had confirmed MIBC, cT2-T4a, with eGFR ^{3} 40mL/min. Primary outcomes included complete (pT0) and partial (< pT2) pathologic response. Comparisons of matched pairs (SS vs. CS pts) were made using the McNemar test and conditional logistic regression. **Results:** 80 matched pts were identified (Table 1). pT0 rates were 17.5% (95% CI, 7 - 33%) and 32.5% (95% CI, 19 - 49%) in SS and CS cisplatin pts, respectively (p = .21),corresponding to an odds ratio for pT0 of 0.45 (95% CI, 0.16 – 1.31). Similarly, rates of < pT2 were 27.5% (95% CI, 15 - 44%) in SS and 45% (95% CI, 29 - 62%) in CS pts (p = 0.21). **Conclusions:** Split schedule cisplatin was associated with numerically but not statistically significant lower pathologic response rates relative to full dose. Limitations of the study include small sample size and treatment selection bias. Although split scheduling of cisplatin is a reasonable alternative to the conventional schedule, larger studies with greater statistical power are required to detect whether true differences exist between these alternative strategies.

Baseline pt characteristics.

	CS (n = 40)	SS (n = 40)	p value
Median age	65.5	71	0.007
Male	82.5%	65%	0.08
Urothelial cell carcinoma	80%	77.5%	0.78
cT stage			0.37
T2	70%	62.5%	
T3	20%	27.5%	
T4	10%	15%	
Median GFR	74.7 (64.0 – 85.5)	63.5 (51.4 – 73.0)	0.003
Median NAC cycles	3	3	0.84
Completed planned NAC	77.5%	70%	0.58
Creatinine 1.5x baseline during NAC	35%	40%	0.64

4546 Poster Session (Board #372), Sat, 8:00 AM-11:30 AM

Correlation between gene expression and prognostic biomarkers in small cell bladder cancer (SCBC). *First Author: Vadim S. Koshkin, Cleveland Clinic Taussig Cancer Insitute, Cleveland, OH*

Background: SCBC is a rare malignancy with poorly understood biology. TCGA data in BC underscores the presence of a neuronal subtype possibly misclassified by conventional histopathology. Increased small cell component (SC%) and protein expression (expr) of DLL3 and CD56 were previously shown to correlate with worse outcomes in SCBC. The association of gene expr data with available biomarkers has potential to improve risk stratification and inform treatment decisions. **Methods:** 63 patients (pts) at Cleveland Clinic diagnosed between 1993 and 2015 had SCBC histology independently reconfirmed. All pts had SC % quantified and 52 pts had immunohistochemistry (IHC) for DLL3 and CD56. A further subset of 39 pts had gene expr analysis using HTG EdgeSeq OBP. Expr of genes relevant in neuroendocrine tumors was evaluated with a panel including CHGA, DLL1, DLL3, DLL4, ENO1, HES1, HES5, HEY1, NCAM1, NOTCH1, NOTCH2, NOTCH4, RB1, SYP, and TP53. Associations between DLL3 and CD56 protein expr, SC%, and expr of relevant genes were assessed to identify biomarkers pertinent to molecular diagnostics (Spearman correlation, $p < 0.05$). Using these as seed-genes in a network-based approach we sought to develop a prognostic gene expression signature in SCBC. **Results:** Among 52 pts with IHC data, 79% had SC% > 50%, and protein expr of DLL3 and CD56 (> 1% of tumor cells) was 68% and 81%, respectively. DLL3 protein expr correlated positively with mRNA expr of DLL3 (r = 0.70), CHGA (r = 0.55), DLL4 (r = 0.45), and negatively with NOTCH1 (r = -0.47), RB1 (r = -0.48) and ENO1 (r = -0.34). CD56 protein expr correlated positively with mRNA expr of NCAM1 (r = 0.61), DLL4 (r = 0.38), HEY1 (r = 0.42) and SYP (r = 0.34) and negatively with NOTCH1 (r = -0.34) and HES5 (r = -0.35). SC% correlated positively with DLL3 (r = 0.38) and NCAM1 (r = 0.41) and negatively with HES1 (r = -0.34). **Conclusions:** Expression of genes implicated in the pathophysiology of SC tumors correlated with protein expr of DLL3, CD56 and SC%, which were previously shown to be prognostic in SCBC. This supports a prognostic role for a novel gene expr signature in SCBC. Multi-institutional validation of this signature in external BC cohorts as well as comparison with BC TCGA and SC lung cancer datasets are ongoing.

4547 Poster Session (Board #373), Sat, 8:00 AM-11:30 AM

Apache: An open label, randomized, phase 2 study of durvalumab (Durva), alone or in combination with tremelimumab (Treme), in patients (pts) with advanced germ cell tumors (GCT): Results at the end of first stage. *First Author: Daniele Raggi, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: The prognosis of chemorefractory GCT pts is dismal. Durva is an anti-PD-L1 monoclonal antibody (mAb). Treme is anti-CTLA4 mAb. We aimed to investigate the activity of Durva, alone or with Treme, in these pts. **Methods:** Apache (NCT03081923) is an open-label, randomized, 3-stage, phase 2 study. Pts who have failed ≥2 chemotherapy (CT) regimens receive Durva, 1.5 gr q4w, x 13 cycles (arm A) or Durva plus with Treme, 75 mg q4w, x 4 cycles, followed by Durva alone x total 13 cycles (arm B). Serum tumor markers (STM), and radiologic assessments are repeated q8 weeks. The primary endpoint is the modified objective response-rate (mORR = RECIST 1.1 complete or partial response [PR] or stable disease [SD]+STM reduction > 10%). H0: mORR rate ≤10%, H1: mORR ≥25%, type I and II error rates at 10%. The total sample size of 120 pts is split into 3 stages: in stage 1, according to Gehan's rule, each arm is terminated whenever no response is observed. Biomarker analyses include: IHC PD-L1 expression on immune cells (Ventana SP142) and genomic sequencing with FoundationOne assay (Foundation Medicine Inc., Cambridge, MA, USA). Results of first stage are presented. **Results:** From 02/17-11/17, 18 pts were enrolled (17M, 1F), 9 per arm. 14 had gonadal and 4 extragonadal GCT, 15 had received ≥3 prior CT regimens. Median tumor mutational burden (TMB) was 4 mutations (mut)/mb. One pt (5.6%) had reversible G3 irAE (pneumonitis) in arm B. In arm A, 100% of pts had disease progression (PD), all with features of hyperprogression (hyper-PD): 4 had clinical PD and death before restaging, median increase in sum of tumor diameters (RECIST 1.1) was 146%, median increase in the elevated STM was 462%. In arm B, 2 responses (22.2%, 1 RECIST-PR in seminoma and 1 SD with STM reduction in nonseminoma) were observed. PD features were similar to arm A. PD occurred in both arms regardless of PD-L1 expression and TMB (PR case: PD-L1 negative and 4 mut/mb). **Conclusions:** Single-agent durvalumab should not be pursued further in GCT; conversely, combination immunotherapy showed signals of activity and will be expanded to 2nd stage. Response biomarkers are urgently required. Clinical trial information: NCT03081923.

4548 Poster Session (Board #374), Sat, 8:00 AM-11:30 AM

Use of 18F-FDG PET/CT to select candidates for active surveillance: Results of the SEMITEP trial of PET-directed strategy for stage 1 seminoma. *First Author: Yohann Loriot, Institut Gustave Roussy, Villejuif Cedex, France*

Background: Stage I seminoma patients (pts) run a relapse risk of 15-20% without further adjuvant treatment. Pts are usually offered active surveillance or an adjuvant treatment with a risk of overtreatment of about 80%. There is no robust prognostic factor associated with the risk of relapse. 18F-FDG PET/CT (PET) demonstrates high diagnostic accuracy for restaging pts with metastatic seminoma. Our hypothesis was that PET scanning accurately detects micro-metastasis and may help better select patient for therapy. **Methods:** In the SEMITEP trial (NCT01887340), pts with newly diagnosed stage 1 seminoma underwent PET scanning before any decision for adjuvant treatment. PET scans were assessed by a local nuclear physician but were centrally retrospectively reviewed. A PET was interpreted as positive if any non-physiological 18F-FDG uptake was observed. Pts with negative PET findings were assigned to a surveillance protocol with no further adjuvant treatment and alleged surveillance work-up; pts with positive PET findings were recommended to receive immediate therapy (preferentially 2 cycles of carboplatin at a dose of AUC = 7). The first endpoint was the proportion of pts in whom an adjuvant therapy could be omitted. The secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. **Results:** A total of 169 pts were recruited, and 166 patients underwent PET. The PET findings were negative in 160 of these pts (96%), 150 (94%, 95% confidence interval [CI], 90 -98) of whom were assigned to surveillance. PET was positive in 6 pts, 5 of whom were treated with immediate treatment. At a median follow-up of 2.5 years 22/150 (15%) pts with PET-negative experienced a relapse. No relapse occurred among the 15 pts treated with immediate treatment. There was one chemotherapy-related death. The 2-year PFS and OS rates were 88 % (95% CI, 81.7-92.1) and 99.4 % (95% CI, 96.6-99.9), respectively. **Conclusions:** Post-orchidectomy treatment can be avoided in a majority of pts with stage 1 seminoma. PET may help identifying about one fifth (6/28) pts with disseminated seminoma that are not detected by CT-scan. Surveillance remains necessary in men with negative PET. Clinical trial information: NCT01887340.

4549 Poster Session (Board #375), Sat, 8:00 AM-11:30 AM

Circulating miR-371a-3p for the detection of low volume viable germ cell tumor: Expanded pilot data, clinical implications and future study. *First Author: Lucia Nappi, Vancouver Prostate Centre and SWOG AYA, Prevention and Surveillance and SWOG YI Award, Vancouver, BC, Canada*

Background: Determining the histology of borderline enlarged nodes in clinical stage I (CSI) or post-chemotherapy residual disease (PCRD) patients (pts) with germ cell tumor (GCT) is challenging, especially when classic tumor markers are negative. Currently, accurate assessment requires clinical follow-up with imaging to establish patterns of growth or pathological confirmation. A blood-based approach to reliably identify patients with non teratoma viable GCT (NTVGCT) would be valuable. **Methods:** miR-371a-3p (miR371) extracted from plasma of pts with GCT was analyzed by RT-PCR and relative expression calculated by the 2-ΔΔCt method with appropriate negative and positive controls. The sensitivity and specificity of miR371 were calculated correlating miR371 expression to the presence of relapsed/residual NTVGCT. **Results:** 74 samples were analyzed in 56 patients: 24 CSI; 32 metastatic, of whom 21 had PCRD. Among CSI patients, 8 relapses occurred and miR371 was positive in 6/8 relapses. Among the CSI patients that did not relapse, 7 had borderline enlarged nodes but negative miR371. For the metastatic pts, miR371 was positive in 16/18 pts pre-chemotherapy and became negative in all post-chemotherapy. 3 miR371 negative pts (1 CSI and 2 metastatic) had pathologically confirmed primary teratoma. miR371 was negative in all the pts with PCRD (n = 21) and no residual NTVGCT was detected in those pts by either pathology (n = 13) or clinical follow-up (n = 8). Sensitivity and specificity were 93.3% and 100%, respectively across the entire cohort of samples in detecting the presence of relapse or residual NTVGCT. Both internal and external validation studies have been performed with excellent concordance. **Conclusions:** Detectable plasma levels of miR371 have excellent correlation with the presence of NTVGCT. More rational selection of adjuvant therapy in CSI, reduction in imaging and more precise post-chemotherapy evaluations are among the more obvious settings in which biomarker-based decision making can improve GCT management. These and other data informed the development of two large US/Canadian intergroup studies to define the role of miRNA clusters in management of GCT.

4550 Poster Session (Board #376), Sat, 8:00 AM-11:30 AM

Etoposide and cisplatin (EP) for metastatic good-risk germ cell tumors (GCTs): The Memorial Sloan-Kettering Cancer Center (MSKCC) experience in 944 patients (pts). *First Author: Samuel Funt, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Standard of care for pts with metastatic, good-risk GCTs consists of either 3 cycles of bleomycin, etoposide, and cisplatin (BEPx3) or 4 cycles of EP (EPx4). EPx4 avoids both pulmonary and vascular bleomycin toxicity. **Methods:** 944 pts with good-risk GCTs (LDH modified to $<$ 3 x upper limit of normal) were treated with EPx4 at MSKCC from1982 to 2015. EP consisted of cisplatin 20mg/m2 and etoposide 100mg/m2 on days 1 to 5 at 21-day intervals. Response, post-EP surgical findings, and survival were obtained for 655 pts treated from 2000 to 2015 and compared with the same outcomes plus updated follow-up for 289 pts treated from 1982 to 2002 previously reported by Kondagunta et al. (JCO, 2005). **Results:** Of the recent 655 pts, median age was 33 (range, 15-77), nonseminoma comprised 65%, seminomas 35%, AFP elevated in 27%, HCG 53%, and LDH 31% with 7.6% of nonseminoma with LDH 1.5 - 3 times upper limit of normal. 97% pts completed 4 cycles of EP. Of 655 pts, 313 underwent post-EP retroperitoneal lymph node dissection (RPLND): 59.1% necrosis or fibrotic debris, 38.0% pure teratoma, 2.6% viable, non-teratomatous GCT, 1 patient unclassified. Febrile neutropenia and thromboembolic events occurred in 15.9% and 8.9%, respectively. In the combined group of 944 pts, 927 (98.2%) achieved a favorable response (CR or PR-negative markers); there was 1 treatment-related death. With median follow up for the combined 944 pt group of 6.8 years, five-year PFS and OS rates were 93.4% and 97.9%, respectively. Outcomes summarized in the table. **Conclusions:** In the largest series of good-risk pts treated with EPx4 ever reported, our results confirm that this regimen is highly effective and well-tolerated. EPx4 remains a standard treatment option for good-risk GCT and remains the preferred regimen at MSKCC.

	JCO 2005	Current	Updated Total (%)
Number of Pts	289	655	944
Favorable Response (%)	282 (98)	645 (98)	927 (98)
Viable, non-teratomatous GCT at Post-EP Surgery (%)*	11/134 (8)	8/313 (3)	19/447 (4)
Relapse (%)	18 (6)^	26 (4)	44 (5)
Died of Disease (%)	10 (3)^	4 (1)	14 (2)

*JCO 2005 includes any post-EP surgery. Current limited to RPLND.
^1 pt relapsed and died of disease post-publication

4551 Poster Session (Board #377), Sat, 8:00 AM-11:30 AM

Retroperitoneal cancer viability after postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) in good risk germ cell tumors (GCTs). *First Author: Fadi Taza, Division of Hematology and Oncology, Indiana University Simon Cancer Center, Indianapolis, IN*

Background: Four cycles of etoposide and cisplatin (EP $\times$ 4) or 3 cycles of bleomycin, etoposide, and cisplatin (BEP $\times$ 3) is the current standard of care for patients with good-risk testicular cancer. We sought to examine the differences in the tumor viability for patients treated with EP x 4 vs BEP x 3 in the (PC-RPLND) specimens. **Methods:** The Indiana University (IU) Testicular Cancer Database was queried to identify IGCCCG good-risk patients who received EP $\times$ 4 or BEP $\times$ 3 induction chemotherapy followed by PC-RPLND. The primary endpoint was PC-RPLND cancer viability vs teratoma presence. **Results:** A total of 291 patients treated between 1988 and 2017 met the inclusion criteria. Median age was 28 (14.6-70.8) years. Primary histology was non-seminoma in 92.8%. Induction chemotherapy consisted of EP $\times$ 4 in 45 (15.5%) patients and BEP $\times$ 3 in 246 (84.5%). One hundred and sixty-six patients (57.2%) received chemotherapy outside the IU and were subsequently referred for PC-RPLND. Using a logistic regression model after accounting for age and time to surgery, patients who received EP x 4 have approximately 2.5 times the odds of having residual cancer viability in the PC-RPLND (Odds ratio 2.548, 95% CI 1.130-5.744, p = 0.024) and no significant difference in the odds of having teratoma (Odds Ratio 0.669, 95% CI 0.343-1.303, p = 0.237). **Conclusions:** Our retrospective study has shown differences in pathological outcomes for good risk GCT patients treated with EP x 4 vs BEP x 3. Patients who received BEPx3 had less residual cancer in the RP specimen at the time of PC-RPLND compared to EPx4 after adjusting for age and time to surgery. We prefer to use BEPx3 as first line chemotherapy in good-risk patients unless there is a contraindication for bleomycin.

4552 Poster Session (Board #378), Sat, 8:00 AM-11:30 AM

Adjuvant etoposide plus cisplatin (EP) for pathologic stage (PS) II nonseminomatous germ cell tumor (NSGCT). *First Author: Deaglan Joseph McHugh, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The risk of relapse after primary retroperitoneal lymph node dissection (RPLND) for patients (pts) with PS IIA NSGCT is 10-20% and increases to over 50% for pts with PS IIB NSGCT. Cisplatin-based chemotherapy reduces the risk of relapse to approximately 1%. Standard adjuvant chemotherapy regimens consist of 2 cycles of EP or 2 cycles of bleomycin plus EP (BEP). **Methods:** From March 1989 to April 2016, 156 pts with PS II NSGCT seen at Memorial Sloan Kettering Cancer Center and assigned to two cycles of EP chemotherapy following RPLND were included. Pts from a prior analysis (Kondagunta, JCO, 2004) were included with updated survival outcomes and expanded histopathologic parameters. Each treatment cycle consisted of cisplatin 20mg/m^2 and etoposide 100mg/m^2 administered on days 1 to 5 at 21-day intervals. Demographics, histopathologic features, therapeutic and survival outcomes were recorded. **Results:** Median age was 28 years (range 15-52). 30 pts (19%) had pN1 disease, 122 (78%) pN2 disease and 4 (3%) pN3 disease. Median number of positive lymph nodes was 3 (range 1-37) and median size of the largest positive node was 2.0cm (range 0.4-7.0cm). 69 pts (45%) had extranodal tumor extension. Embryonal carcinoma, seminoma, mature teratoma and yolk sac were the predominant histological subtypes in the RPLND pathology in 115 (90%), 8 (6%), 4 (3%) and 1 (1%) pts respectively. 150 pts (96%) received 2 cycles of EP, 5 (3%) received 1 cycle of EP and one received 4 cycles of EP due to a transient marker increase following his first cycle. Dose delays occurred in 54 (38%) pts, mostly as a result of neutropenia (44/54 delays). With a median follow-up of 9 years, two pts (1 pN2 and 1 pN3) relapsed; both achieved a CR to TIP and are NED at 65 and 143 months respectively. 3 pts died, all unrelated to GCT or treatment, for 10-year relapse-free and overall survival rates of 98% and 99%, respectively. **Conclusions:** This is the largest series reported to date on adjuvant chemotherapy with EP for PS II NSGCT and confirms that 2 cycles of EP is highly effective in reducing recurrence with disease-specific survival of 100% and acceptable toxicity. These data suggest that inclusion of bleomycin (e.g., BEP) in this setting is not necessary.

4553 Poster Session (Board #379), Sat, 8:00 AM-11:30 AM

The prognostic value of teratoma in the primary tumor and postchemotherapy retroperitoneal lymph node dissection (PC-RPLND) specimens in patients with germ cell tumors (GCTs). *First Author: Fadi Taza, Division of Hematology and Oncology, Indiana University Simon Cancer Center, Indianapolis, IN*

Background: A retrospective study using an institutional database from MSKCC [ASCO 2017, abstract # 4555] on 231 patients, showed that the presence of teratoma (T) in the primary testicular cancer was proposed to be an important clinical predictor of long-term outcome in men with GCT. We hypothesized that neither the presence nor the absence of T predicts the long-term survival in GCT patients. **Methods:** Metastatic non-seminoma (NSGCT) patients who received chemotherapy and had a primary testicular cancer (PTC) specimens available were included in this retrospective study. The cohort was divided into two groups according to the presence or absence of T in the primary tumor. The Indiana University Testicular Cancer Database was reviewed and survival data were correlated with the histopathological findings. Differences in overall survival (OS) and progression free survival (PFS) between the two groups were evaluated using log-rank test **Results:** PTC specimens were available from 1224 pts diagnosed between 1990-2016. Median age was 27.3 years (range 13.1-70.8) and median follow-up 1.9 y (range 0.1-30.1) since the initiation of chemotherapy. The element of T was present in 689 pts vs 535 without T. At the start of chemotherapy, 61.5%, 14.1% and 24.4% of pts were stratified as good, intermediate, and poor IGCCCG risk. The 5-year PFS in pts with the T present vs. absent was 61.9% (95% CI, 57.1% to 66.2%) and 63.1% (95% CI, 58.0% to 67.8%); *P*= 0.66, respectively. The 5-year OS in pts with the T present vs. absent was 82.2% (95% CI, 77.9% to 85.8%) and 81.4% (95% CI, 76.5% to 85.3%); *P*= 0.91, respectively. We then evaluated 503/1224 who underwent PC-RPLND, 327 had pure T and 146 had only necrosis in the resected lymph nodes. Five-year OS for pts with T vs necrosis was 90.3% (95% CI, 83.6% to 94.4%) and 93.4% (95% CI, 85.8% to 97.0%) respectively, P = 0.21. **Conclusions:** The presence of teratoma in primary tumor and PC-RPLND was not a prognostic factor in this retrospective study of patients with NSGCT.

4554 Poster Session (Board #380), Sat, 8:00 AM-11:30 AM

Psychological stress in long-term survivors of testicular cancer: A Danish nationwide cohort study. *First Author: Michael Kreiberg, Rigshospitalet, Copenhagen, Denmark*

Background: Survival in cancer is generally increasing and in case of testicular cancer (TC) the majority of patients become long-term survivors (TCS). The aim of the present study was to investigate if long-term TCS experience a higher level of psychological stress than the Danish male general population (GP) and whether psychological stress is influenced by treatment modality. **Methods:** In 2014-2016, 2409 TCS with a mean time since diagnosis of 18 years (range 7-33 years) answered a questionnaire covering psychological stress (Perceived Stress Scale (PSS)), sociodemographic factors and physical health variables. In PSS, scores are summed up with 0 representing the least stressed and 40 the most stressed. PSS scores were compared with the GP (n = 67151) from The Danish National Health Survey 2013. Age adjusted linear regression with TCS who had been treated with orchiectomy alone serving as reference explored the effect of treatment modality on PSS score. **Results:** In TCS $<$ 65 years of age we found a higher mean PSS score than in the GP ($p < 0.01$) (table 1), while TCS $>$ 65 years of age had a lower PSS score than the GP ($p = 0.043$) There was no association between treatment modality and PSS score. **Conclusions:** Long-term TCS $<$ 65 years of age were more stressed than the general population, while treatment modality did not influence the levels of psychological stress. Research is needed to clarify if screening and treatment programs for psychological stress should be part of the follow-up for TCS.

Perceived stress scale (PSS) scores in long-term testicular cancer survivors (TCS) and a male danish general population (GP).

		GP (N = 67151)	TCS (N = 2409)	p-value
Age group mean PSS scores, (No.)	$<$ 45	11.02 (21680)	12.94 (508)	$<$ 0.001
	45-54	10.87 (12668)	11.53 (803)	0.008
	55-64	10.28 (13584)	11.81 (690)	$<$ 0.001
	$>$ 65	10.36 (19218)	9.68 (408)	0.043
Treatment mean PSS scores, (No.)	Surveillance		11.35 (1138)	
	3-4 courses of BEP		11.95 (876)	
	Abdominal RT		11.37 (312)	
	More than one line of treatment		12.07 (83)	

Age group mean PSS Scores were analysed with independent t-test between GP and TCS.
Abbreviations: BEP, bleomycin, etoposide, cisplatin; RT, radiotherapy.

4555 Poster Session (Board #381), Sat, 8:00 AM-11:30 AM

Comprehensive genomic characterization of chemotherapy-resistant testicular germ cell tumors (TGCT). *First Author: Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy*

Background: Although both seminomatous (Sem) and nonseminomatous (NS) TGCT have a favorable response to platinum-based chemotherapy (CT), a small proportion of them are chemorefractory. Therapeutic options for these patients (pts) are limited, and relevant therapeutic targets are lacking. **Methods:** The database of Foundation Medicine Inc. was searched, integrated with relevant clinical data. Archival tissues from 108 CT-treated and relapsed TGCT pts (22 Sem and 86 NS) underwent hybrid-capture based comprehensive genomic profiling (CGP) to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and reported as mutations (mut) per megabase (Mb) and microsatellite instability (MSI) was determined on 114 loci. **Results:** Sem pts were older than NS ($p = 0.007$). All pts had failed at least 1 CT regimen for metastatic disease. The mean GA/tumor frequency was 4.1 mut/tumor for NS and 3.1 for Sem ($p = 0.08$). *KRAS* alterations (mainly amplifications) were the most frequent GA (47% and 36% in Sem and NS). *TP53*, *CCND2* and *FGF6/23* GA frequencies were similar in both Sem and NS. GA in *KIT* (21% vs 2%), *PIK3CA/MTOR* (10% vs 0%), *PTEN* (5% vs 0%) and *BRCA2* (5% vs 0%) were more frequent in Sem than NS whereas *BRAF* (2%) and *ERBB2* (1%) GA were found in NS only. Among pts with *MTOR* alterations, one Sem was treated based on genomic profiling and had an exceptional response to everolimus, after CT and immunotherapy (IT) failure. MSI-High status was not identified in Sem cases and was found only in 2% of NS. The median TMB for the Sem cases was 2.5 mut/Mb and for NS was 2.7 mut/Mb. TMB levels of $\geq$10 mut/Mb were not encountered in Sem. Higher levels of TMB were more frequent in NS with 5% of NS having $\geq$10 mut/B and 1% $\geq$20 mut/Mb. **Conclusions:** Clinical trials in molecularly-selected pts are warranted for refractory TGCT, particularly the high frequency of *KRAS* amplification may portend activity of MEK inhibitors. Overall, the GA found in refractory Sem and NS differ significantly. Sem features lower GA frequency with slightly higher potential for targeted therapies in KIT and PI3K/MTOR pathways. Based on rare high TMB and MSI-High status, IT may be of benefit in a small subset of NS.

4556 Poster Session (Board #382), Sat, 8:00 AM-11:30 AM

Quality-adjusted time without symptoms or toxicity (Q-TWiST): Analysis of cabozantinib (Cabo) vs sunitinib (Sun) in patients with advanced renal cell carcinoma (aRCC) of intermediate or poor risk (Alliance A031203). *First Author: Ronald C. Chen, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: CABOSUN (NCT01835158), a randomized, open-label phase II trial, demonstrated significant improvement in progression-free survival with Cabo (8.6 months) versus Sun (5.3) months) in the first-line treatment of patients with intermediate- or poor-risk clear cell aRCC. To evaluate the overall treatment difference, we conducted a post hoc analysis using a quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) methodology. **Methods:** Each patient's overall survival was partitioned into 3 mutually exclusive health states: time with grade 3/4 toxicity (TOX) before progression; time without symptoms of disease progression or grade 3/4 toxicity (TWiST); and time after progression or relapse (REL). Time spent in each state was weighted by a health-state utility associated with that state and summed to calculate Q-TWiST. A threshold utility analysis was used, applying utilities across a range of 0 (death) to 1 (perfect health). **Results:** The analysis period was 650 days (d) (median survival follow-up period). Mean time spent with TWiST was 121 d (95% confidence interval, 43–199) longer for Cabo compared with Sun. Mean time spent with TOX was 8 d longer for Cabo; mean time spent with REL was 104 d shorter for Cabo. In the threshold utility analysis, the difference in Q-TWiST ranged from 129 d (TOX = 1, REL = 0) to 17 d (TOX = 0, REL = 1) in favor of Cabo across all utility combinations. When considering relative utility weights consistent with those observed in aRCC patients (TOX = 0.5, REL = 0.5), the difference in Q-TWiST was 73 d in favor of Cabo. **Conclusions:** Treatment with Cabo was associated with longer Q-TWiST compared with Sun, primarily due to longer time without symptoms of disease or grade 3/4 toxicities. This analysis, which accounts for disease control efficacy, treatment toxicity and health-related quality of life, provides clinicians with a measure of Cabo and Sun treatment differences on the quality of survival to help with clinical decision-making. Support for CaboSun: U10CA180821, U10CA180882; funding for present study: Ipsen. Clinical trial information: NCT01835158.

4557 Poster Session (Board #383), Sat, 8:00 AM-11:30 AM

Interim data analysis of the ADAPT trial using the modified intent to treat (mITT) population re-evaluates Rocapuldencel-T for clinical benefit over standard of care. *First Author: Robert A. Figlin, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: The Phase 3 ADAPT trial evaluates overall survival (OS) of Rocapuldencel-T (Roca) in combination (combo) with standard-of-care (SoC) for the treatment of newly diagnosed mRCC compared to SoC alone. At a February 2017 interim analysis, the study was judged unlikely to demonstrate statistically significant improvement in OS. However, the ITT patients included 39 patients (combo) that did not receive Roca and 14 SoC patients not treated. Therefore, additional analyses for the modified ITT (mITT) was evaluated for OS and immune response (IR) in patients receiving therapy. **Methods:** The mITT includes 268 combo patients who received $\geq$1 dose of Roca + sunitinib and 141 SoC patients that received $\geq$1 cycle of sunitinib. Median OS was calculated by log-rank analysis and correlated with IR measured over 1 year Roca dosing. Also, the potency of Roca product administered (measured by level of IL-12 secretion) was correlated with OS. IR and IL-12 levels were assayed by flow cytometry and correlations were analyzed by the Spearman's rank correlation coefficient method. **Results:** The mITT combo arm had a median OS of 30.4 months (mo) vs. 32.4 mo in the SoC arm (HR 0.97 95%CI 0.72, 1.33), however, $>$ 50% of patients were censored at the time of analysis. To test for delayed effects of Roca, we stratified patients based on follow-up time from randomization. For patients in the 1st quartile (longest follow-up time), OS was 35.5 mo for the combo arm (n = 66, 32% censored) and 22.5 mo for SoC (n = 35, 15% censored). As the percentage of censored subjects increased and follow-up time decreased, the OS advantage in the combo arm diminished (3.5 months, 1st 50% randomized and 3.1 months, 1st 75% randomized). Also, the magnitude of anti-tumor IR after 7 doses of Roca correlated with OS ($r = 0.4$, $p < 0.0001$) and IL-12 levels correlated with both IR ($r = 0.4$, $p < 0.0001$) and OS ($r = 0.27$, $p < 0.0002$). **Conclusions:** The mITT combo subjects, all of whom received Roca therapy, are anticipated to be the population that could benefit from this treatment. This analysis demonstrated correlations between Roca mechanism of action and OS and longer follow-up time is warranted to assess potential efficacy of Roca. Clinical trial information: NCT01582672.

4558 Poster Session (Board #384), Sat, 8:00 AM-11:30 AM

Phase ib and phase II studies of pembrolizumab (P) with bevacizumab (B) for the treatment of metastatic renal cell carcinoma (RCC): BTCRC-GU14-003. *First Author: Arkadiusz Z. Dudek, University of Illinois at Chicago, Chicago, IL*

Background: Hypoxic regions of RCC, impede homing of cytotoxic T cells into tumor. In addition, tumor angiogenesis enhances immunosuppressive activity of MDSC and TAM. Antiangiogenic therapy decreases the number of MDSC and changes polarization of TAM to an immunostimulatory phenotype. We hypothesized that therapy with B will potentiate the immune antitumor activity of P. We, therefore, performed phase 1b for safety of P and B, followed by phase 2. **Methods:** Study population included subjects (age $>$ 18 y) with metastatic clear cell RCC after failure of at least one systemic therapy (phase 1b) or treatment naïve (phase 2). In phase Ib, P (200 mg dose q 3 weeks) was given with B (either at 10 or 15 mg/kg q 3 weeks). Primary endpoint for phase 2 was response rate (RR) (PR or CR) using RECIST v1.1. With assumption of 80% power to detect a 55% improvement in RR of P and B, over historic data with single P activity in RCC (RR of 27%), and an a error of 0.1, 48 subjects were to be accrued to detect RR of 42%. **Results:** 13 subjects (ages 33-68, median 55) were enrolled to phase 1b study; 11 males. No dose-limiting toxicity have been reported. Best responses (BR) were 5 PR, 6 SD, 1 PD. Median time on treatment was 130 (21-659) days. 200 mg of P and 15 mg/kg of B, given q 3 weeks, was determined to be safe and used in phase 2. 48 subjects (ages 42-84, median 61); 33 males were accrued to phase 2 study. Primary endpoint of RR was reached at 60.9 % (95% CI = 45.4%, 74.9%) with median time on treatment 298 (range 21-741) days. BR: 28 PR, 18 SD, 2 UN. Progression occurred in 20 (41.7%) patients. Median PFS time was 17.0 months (95% CI = 11.3, 24.8). Median OS has not been reached. 12 (25%) died. Most common grade 3 toxicity were hypertension (21%), hyponatremia, proteinuria (9%), adrenal insufficiency, dehydration 6 %), pneumonitis, skin toxicity, weakness, nausea and vomiting (4%), diarrhea, and arthralgia (2 %). There were 2 grade 4 toxicities (hyponatremia and hyperglycemia). There was 1 grade 5 toxicity (heart failure). Presence of tumor infiltrating T cells, but not PD-L1 expression correlated with PR. **Conclusions:** The 200 mg of P and 15 mg/kg dose of B, given every 3 weeks, is safe and active in metastatic RCC. Clinical trial information: NCT02348008.

4559 Poster Session (Board #385), Sat, 8:00 AM-11:30 AM

Comprehensive molecular and immunohistochemical analysis of advanced renal cell carcinoma patients treated with mTOR inhibitors. *First Author: JesÃ̲os GarcÃa-Donas, Fundacion Hospital de Madrid, Madrid, Spain*

Background: The development of new combinations with mTOR inhibitors and the description of meaningful responses in cases with mutations in the mTOR pathway have raised the interest on these compounds. Predictive biomarkers of activity are crucial to ensure patients likely to benefit are properly treated. **Methods:** Through an observational prospective study by the Spanish Oncology Genitourinary Group (SOGUG), FFPE tumor samples were collected from 77 RCC patients treated with temsirolimus or everolimus. Patients with partial response (by RECIST), or stable disease for at least 6 months were classified as responders. Immunositochemistry (IHC) was performed in 64 patients for p-S6, p-S6K1, p-AKT, p21, BAP1 and PBRM1. Mutational analysis of key genes in mTOR pathway was performed through Next Generation Sequencing in tumor DNA. The association between expression of the proteins and response to mTOR inhibitors was analyzed through logistic regression. **Results:** The 77 patients studied had been treated with everolimus (79%) or temsirolimus (21%); 87% had ccRCC histology, 60% had intermediate, 39% good prognosis, and 1% poor prognosis (MSKCC); 29 patients were responders, 47 non-responders and 1 could not be classified. Among the five cases with mTOR pathway activating mutations (1 *TSC1* (p.P333HfsTer5), 1 *TSC2* (p.L826M); and 3 *MTOR* mutations (p.S2215_L2216delinsF, p.Y1974H, p.E773D)), three were responder patients and two non-responders. Regarding p-S6 staining, two responder patients and one non-responder had positive staining, while one responder had negative staining and one non-responder was not evaluable. In the full series, negative IHC expression for BAP1 and PBRM1 was associated with better mTOR inhibitor response (OR = 4.0, 95%CI = 1.4-11.9, P = 0.011 and OR = 3.9, 95%CI = 1.2-12.8, P = 0.025, respectively, multivariable analysis). However, no association between for p-S6, p-S6K1, p-AKT and p21 staining and mTOR inhibitor response was observed. **Conclusions:** *TSC1, TSC2* and *MTOR* mutations only partially correlated with response. Lack of BAP1 and PBRM1 expression was associated with improved response to mTOR inhibitors.

4560 Poster Session (Board #386), Sat, 8:00 AM-11:30 AM

Lenvatinib + pembrolizumab in patients with renal cell carcinoma: Updated results. *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib, a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors and other targets, has been approved in combination with everolimus to treat advanced renal cell carcinoma (RCC) after 1 prior VEGF-targeted therapy. We report results for the RCC cohort of a phase 1b/2 trial of lenvatinib + pembrolizumab in patients (pts) with selected solid tumors (NCT02501096). **Methods:** In this multicenter, open-label study, pts with metastatic clear cell RCC and measurable disease per immune-related RECIST (irRECIST) received oral lenvatinib 20 mg daily + pembrolizumab 200 mg IV every 3 weeks. Tumor assessments were performed by study investigators using irRECIST, and retrospectively by independent radiographic review (IRR) per irRECIST and RECIST 1.1. The phase 2 primary endpoint was objective response rate at 24 weeks (ORRWK24). **Results:** 30 Pts were enrolled: 12 (40%) pts had 0 and 18 (60%) pts had ≥1 prior anticancer therapy; 16 (53%) pts received ≥1 prior VEGF-targeted therapy. At data cutoff of August 1, 2017, median follow-up for progression-free survival (PFS) was 13.8 mos (95% CI, 11.9–15.7). ORRWK24 was 63.3% (95% CI, 43.9–80.1) by investigator review, per irRECIST. ORR by IRR using RECIST 1.1 was 66.7% (95% CI, 47.2–82.7), and median PFS was 17.7 mos (95% CI, 9.6–NE). Efficacy outcomes are summarized in the table. Grade 3 or 4 adverse events (AEs) occurred in 21 (70%) pts; however, 4 (13%) discontinued treatment due to AE. The most common AEs were diarrhea (83%), fatigue (70%), hypothyroidism (67%), stomatitis (63%), and nausea (60%). **Conclusions:** The combination regimen of lenvatinib + pembrolizumab showed promising antitumor activity with manageable AEs, and no new safety signals were identified. A phase 3 trial of lenvatinib + pembrolizumab and lenvatinib + everolimus versus sunitinib for the first-line treatment of advanced RCC is underway (NCT02811861). Clinical trial information: NCT02501096.

	N = 30		
	Independent radiographic review		Investigator review
Outcome	RECIST 1.1	irRECIST	irRECIST
ORR*, n (%)	20 (66.7)	20 (66.7)	21 (70.0)
95% CI	47.2–82.7	47.2–82.7	50.6–85.3
Median duration of response, mos	16.3	NE	18.4
95% CI	8.9–NE	14.9–NE	10.3–NE
Median PFS, mos	17.7	17.7	19.8
Median PFS, mos 95% CI	9.6–NE	10.2–NE	11.6–NE

*Overall ORR. NE, not estimable.

4561 Poster Session (Board #387), Sat, 8:00 AM-11:30 AM

Comparison of clinical outcomes with first-line pazopanib in clinical trial eligible and non-clinical trial eligible patients with renal cell carcinoma. *First Author: Eric Jonasch, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although pazopanib (PAZ) has been evaluated in clinical trials of patients (pts) with renal cell carcinoma (RCC), limited real-world data on the effectiveness and safety of PAZ exist. The PRINCIPAL study (NCT01649778) assessed the effectiveness and safety of first-line PAZ in a real-world setting. **Methods:** In this nonrandomized, prospective study, pts with advanced and/or metastatic clear cell RCC were enrolled in PRINCIPAL within 30 days of initiating first-line PAZ. Data on progression, survival, and safety were collected approximately every 3 months (mos) until death, consent withdrawal, or loss to follow-up, for up to 30 mos. Pts in PRINCIPAL were separated into two groups based on key eligibility criteria from the Phase III COMPARZ trial (Motzer et al. *NEJM.* 2013;369:722). Key clinical trial eligible (CTE) criteria included no prior systemic therapy, presence of measurable disease per RECIST 1.1, Karnofsky performance status ≥70, adequate organ system function, no history or clinical evidence of central nervous system metastases, and no coronary or cerebral artery disease at baseline. CTE pts were compared to non-CTE (NCTE) pts. Clinical effectiveness (ie, median overall survival [mOS], median progression-free survival [mPFS], and overall response rate [ORR]), adverse event (AE) measures, and relative dose intensity (RDI) were assessed in both pt populations. **Results:** Of the 657 enrolled pts who received ≥1 dose of PAZ, 97 (14.8%) were CTE and 560 (85.2%) were NCTE. RDI ≥85% was achieved in 70.1% and 56.6% in the CTE and NCTE populations, respectively. Effectiveness was similar in the CTE and the NCTE populations (mPFS, 9.6 *vs* 10.7 mos; ORR, 33.0% *vs* 29.8%; mOS, 26.3 *vs* 32.9 mos). Serious AEs were reported by 23.7% of CTE and 28.2% of NCTE pts. AEs led to dose adjustment/interruption in 83.5% and 95.2%, respectively, and AEs led to treatment discontinuation in 8.2% of the CTE and 15.5% NCTE pts. **Conclusions:** The results of the PRINCIPAL study suggest that first-line PAZ for pts with advanced or metastatic RCC remains effective and safe in a real-world setting, showing similar outcomes to those reported in large randomized clinical trials. Clinical trial information: NCT01649778.

4562 Poster Session (Board #388), Sat, 8:00 AM-11:30 AM

Neutrophil-to-lymphocyte ratio as a potential prognostic factor of disease-free survival in high-risk renal cell carcinoma: Analysis of the S-TRAC trial. *First Author: Anup Patel, London, London, United Kingdom*

Background: Sunitinib significantly improved disease-free survival (DFS) vs placebo (PBO) in patients (pts) with loco-regional renal cell carcinoma (RCC) at high risk of recurrence post nephrectomy. Neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammatory response. A post hoc exploratory analysis of the S-TRAC trial evaluated NLR as a potential prognostic factor in the RCC adjuvant setting. **Methods:** Sunitinib- and PBO-treated pts from S-TRAC were categorized into baseline (BL) NLR < 3 and ≥ 3 subgroups to explore the association between BL NLR (post nephrectomy) and DFS. Subgroups were based on low NLR (< 3) being associated with long-term response in metastatic RCC. Associations between DFS and change in NLR from BL at Wk 4 were explored. Kaplan–Meier estimates were provided and Cox proportional analysis was performed. **Results:** In all, 605 pts from S-TRAC with BL NLR values were analyzed: 465 with NLR < 3 and 140 with NLR ≥ 3. At BL, significant differences between NLR < 3 vs ≥ 3 subgroups were seen for age (median 56.0 vs 60.0 y; $P = .0161$) and race (white [81.9% vs 90.0%], black [0.6% vs 0.7%], asian [14.6% vs 5.7%], other [2.8% vs 3.6%]; $P = .0226$). NLR < 3 vs ≥ 3 was statistically significant in the univariate analyses of DFS (hazard ratio [HR] 1.39; $P = .0418$); median 5.84 y (NLR < 3) vs not reached (NLR ≥ 3). A lower BL NLR was associated with shorter DFS. NLR < 3 vs ≥ 3 was also statistically significant in a multivariate analysis of DFS (HR 2.29; $P = .0348$). More pts treated with sunitinib (73%) had ≥25% decrease in NLR at Wk 4 vs PBO (20%). A ≥25% decrease in Wk 4 NLR showed a trend towards longer DFS vs no NLR change (HR 0.744; $P = .0729$), while a ≥25% increase in NLR at Wk 4 showed a trend towards shorter DFS vs no change (HR 1.112; $P = .6771$). NLR change from BL at Wk 4 was associated with treatment (sunitinib vs PBO; $P < .0001$). **Conclusions:** In S-TRAC, lower BL NLR might be a prognostic factor of shorter DFS. A ≥25% decrease in Wk 4 NLR showed a trend towards prolonged DFS. Additional data on CD8, neutrophils and lymphocytes will be presented. Clinical trial information: NCT00375674.

4563 Poster Session (Board #389), Sat, 8:00 AM-11:30 AM

A randomized phase II trial of pazopanib (PAZ) vs. temsirolimus (TEM) in patients (pts) with advanced clear-cell renal cell carcinoma (accRCC) with intermediate or poor-risk disease (the TemPa trial). *First Author: Amado J. Zurita, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TEM has level 1 evidence in aRCC with poor-risk disease. No previous trial compared a VEGFR-TKI with TEM as first-line (1L) therapy. **Methods:** We randomly assigned (1:1) treatment-naïve pts with accRCC and > = 3 risk factors (Hudes et al., NEJM 2007) to receive PAZ 800 mg po qd or TEM 25 mg iv qw. The primary endpoint was progression-free survival (PFS), and the secondary endpoints were overall survival (OS), objective response rate (ORR) and safety. A blinded radiologist assessed the radiographic response using RECIST v1.1. A sample size of 90 pts was based on an assumption of improved median PFS from 3.8 mo (TEM) to 6.1 mo (PAZ). Pts were stratified by prior nephrectomy (Nx) and prior cytokine therapy. The Kaplan-Meier method was used for PFS/OS analysis, and the Fisher's exact test for comparison of ORR between PAZ and TEM. **Results:** TemPa was closed to new patient enrollment in Sept. 2017 after the results of CheckMate 214 and CABOSUN were released. A total of 69 pts were eligible and evaluable (median age 61, 52 males [75%], 44 [64%] with poor-risk by IMDC criteria). Thirty pts (43%) had prior Nx and 3 pts prior IL-2. Thirty-five pts received PAZ (intermediate-risk 15, poor-risk 20) and 34 pts TEM (intermediate-risk 10, poor-risk 24). Of the 69 pts, 67 had progressive disease or died. The median PFS was 5.2 mo (95% CI: 3.6 –7.4) for PAZ and 2.6 mo (95% CI: 1.9 –4.2) for TEM (p = 0.16). However, PFS was significantly longer with PAZ in IMDC intermediate-risk pts after adjustment for IMDC risk group (7.3 *v* 3.7 mo, HR 0.38, p = 0.03). Fifty-nine pts have died. The median OS was 12.0 mo (95% CI: 8.3–20.1) for PAZ and 7.3 mo (95% CI: 5.8–17.4) for TEM (p = 0.56). Sixty-eight pts were evaluable for response: 9/35 pts (26%) who received PAZ and 2/33 pts (6%) who received TEM had partial response (p = 0.046). Adverse events were consistent with the known safety profiles of PAZ and TEM, and resulted in treatment discontinuation in only 2 pts in each. Circulating biomarker analysis will be presented. **Conclusions:** PAZ extended PFS, particularly in intermediate-risk, and yielded a higher ORR than TEM as 1L therapy in pts with accRCC and poor prognosis features. Clinical trial information: NCT01392183.

4564 Poster Session (Board #390), Sat, 8:00 AM-11:30 AM

Patterns of relapse and implications for post-nephrectomy surveillance for patients with high-risk non-clear cell renal cell carcinoma: Subgroup analysis of the phase 3 ECOG-ACRIN E2805 trial. *First Author: Vivek Narayan, University of Pennsylvania, Philadelphia, PA*

Background: Non-clear cell renal cell carcinomas (non-ccRCC) comprise a diverse subgroup, with biology and clinical behavior that is distinct from clear cell RCC (ccRCC). However, the natural history of non-ccRCC remains poorly defined, and clinical practice relies on consensus guidelines largely intended for ccRCC. We evaluated the patterns of relapse and the implications for post-nephrectomy surveillance for patients with non-ccRCC enrolled on the first and largest randomized trial of adjuvant anti-angiogenic therapy for high-risk RCC. **Methods:** Retrospective subgroup analysis of patients with non-ccRCC enrolled on E2805. For recurrence rates (RR) by site, the cumulative incidence was estimated accounting for competing risks. Gray's test was used to compare the incidence between groups. The 2017 NCCN recommendations were used to evaluate the adequacy of strict adherence to post-nephrectomy surveillance guidelines. **Results:** 403 non-ccRCC patients were enrolled (37% papillary, 28% chromophobe, 21% mixed, 14% unclassified). 144 recurrences were detected over a median follow-up of 6.2 years. 5-year RRs (95% CI) were 22% (11, 28) and 49% (41, 56) for Int-High and Very-High UISS risk groups, respectively. Abdominal recurrences were most frequently identified, including lymph node (39%), nephrectomy bed (17%), and liver (13%). While overall 5-year RRs were comparable between non-ccRCC and ccRCC patients (34.6% vs 39.5%), non-ccRCC patients were significantly more likely to develop abdominal site relapse (5-yr RR 26.4% vs 18.2%, p = 0.0008) and less likely to relapse in the chest (5-yr RR 13.7% vs 20.9%, p = 0.0005). Surveillance imaging for 5.3 years would be required to capture 95% of abdominal non-ccRCC recurrences. **Conclusions:** This is the largest, standardized evaluation of the natural history of non-ccRCC following curative-intent nephrectomy. Our findings demonstrate that non-ccRCC exhibits a distinct pattern of relapse when compared to conventional ccRCC, and emphasize the importance of continued long-term imaging for patients with high-risk resected non-ccRCC.

4565 Poster Session (Board #391), Sat, 8:00 AM-11:30 AM

Disease-free survival in patients at highest risk of recurrent renal cell carcinoma in S-TRAC. *First Author: Alain Ravaud, Department of Medical Oncology, Hôpital Saint-André, University of Bordeaux-CHU, Bordeaux, France*

Background: Sunitinib (SU) is FDA-approved for adjuvant treatment of patients (pts) at high risk (≥T3, any Fuhrman grade and/or nodal involvement [N+]) of recurrent renal cell carcinoma (RCC) post nephrectomy, based on the phase 3 S-TRAC trial that showed significant improvement with SU vs placebo (PBO) in disease-free survival (DFS) based on blinded independent central review (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.59–0.98; *P*= 0.03). The definition of high risk in S-TRAC included both objective (T stage and Fuhrman grade) and more subjective (pre-nephrectomy Eastern Cooperative Oncology Group performance status [ECOG PS]) prognostic parameters. To delineate the highest risk pts from S-TRAC purely based on objective parameters, we performed an additional analysis classifying pts at highest risk of recurrence post nephrectomy, defined as T3 and Fuhrman grade > 2 or T4 or N+ and any T. **Methods:** DFS analyses were conducted using Cox proportional hazard model. **Results:** In S-TRAC, 398 (65%) patients were classified at highest risk. The results indicated a treatment benefit in DFS by independent review for SU vs PBO in this highest risk group (HR 0.73; 95% CI 0.54–0.97; *P*= 0.03), consistent with the HR for DFS previously reported in the S-TRAC trial for the T3 higher (HR 0.74; 95% CI 0.55–0.99; *P*= 0.04) group defined as T3 with Fuhrman grade ≥2 and ECOG PS ≥1 or T4 with any ECOG PS or N+ with any T, any ECOG PS, as well as with the overall population. Safety data did not identify major differences between the highest risk group vs overall S-TRAC pts. Incidence of key adverse events with SU was similar in highest risk group vs overall study pts (diarrhea: 58.2% vs 56.9%; palmar-plantar erythrodysesthesia syndrome: 51.5% vs 50.3%; hypertension: 35.7% vs 36.9%; fatigue: 37.2% vs 36.6%; hypothyroidism: 15.3% vs 18.3%). **Conclusions:** The clinically meaningful treatment benefit observed in pts at highest risk of recurrence and the overall S-TRAC population, together with a consistent safety profile between these groups, support the favorable benefit/risk assessment of SU as an adjuvant treatment option for pts with RCC at high risk of recurrence post nephrectomy. Clinical trial information: NCT00375674.

4566 Poster Session (Board #392), Sat, 8:00 AM-11:30 AM

Replication stress response deficiency (RSRD) and response to immune therapy in clear cell renal cell carcinoma (ccRCC). *First Author: Patrick Glen Pilie, University of Michigan, Ann Arbor, MI*

Background: Despite treatment advances with immune therapy (IO), advanced stage ccRCC still has poor prognosis, due in part to a lack of predictive biomarkers. Replication stress (RS) is a hallmark of ccRCC initiation, contributing to genomic instability. However, cancer evades death from instability via deficient DNA damage repair (DDR) and RS response (RSR). The ATM/ATR and CHK2/CHK1 axes are critical to DDR and RSR; and deficiencies in these axes may activate innate immune signaling and lead to improved IO response. In this study, we assessed protein signaling changes in early ccRCC patient tumors, performed *in silico* analysis of ccRCC cohorts for the presence of a novel RSR deficient (RSRD) score, and evaluated the prognostic and predictive value of this RSRD score in ccRCC. **Methods:** We performed reverse phase protein microarray (RPPA) on 12 stage I ccRCC tumors vs 12 normal kidney tissues. We analyzed the Cancer Genome Atlas (TCGA) for a novel gene expression score of RSRD, and its impact on OS. We assessed immune cell infiltrate in TCGA tumors using CIBERSORT. We assessed RNA data from previously published cohort of 28 ccRCC patients treated with IO (*Miao et al, Science 2018*) and clinical outcomes based on RSRD score. **Results:** Early ccRCC tumors already showed loss of p-ATM/p-CHK2 and p-ATR/p-CHK1 protein signaling with increased IRF1 and ADAR1 expression ($p < 0.05$). From TCGA, RSRD-high tumors were more likely to be advanced stage and had significantly worse OS in multivariate analysis. *In silico* analysis revealed RSRD-high tumors had significantly higher T cell infiltrate compared to RSRD-low tumors. In the *Miao et al* IO-treated ccRCC cohort, 11/33 tumors were RSRD-high, with 73% of RSRD-high showing clinical benefit compared to only 18% of the RSRD-low and 36% of the bulk study population even when controlling for PBRM1 mutation. **Conclusions:** RSR and DDR signaling are dysregulated in ccRCC and may activate innate immune pathways. A novel RSRD score has potential as both prognostic and predictive biomarker for IO response. Further studies are warranted to validate the predictive power of this biomarker and understand how DDR and RSR deficiencies in ccRCC may impact immune activation.

4567 Poster Session (Board #393), Sat, 8:00 AM-11:30 AM

A meta-analysis of randomized controlled trials for efficacy and safety of vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) adjuvant therapy in high-risk renal cell cancer (RCC). *First Author: Irbaz Bin Riaz, Mayo Clinic, Rochester, MN*

Background: Three large randomized placebo controlled trials (RCTs) (ASSURE, S-TARC, PROTECT) with adjuvant VEGF-TKIs in high risk RCCs have provided variable results for improving disease free survival (DFS) with concerns for increased toxicity. We performed a meta-analysis of these trial results to asses a risk-benefit for adjuvant post-op treatments in high risk RCC patients by assessing reported disease free survival (DFS) and toxicity endpoints. **Methods:** A generic variance weighted random effects model was used to derive estimates for DFS and common side effects in the three trials. A separate analysis was performed for Sunitinib alone because of its FDA approval. Heterogeneity was assessed with Cochrane Q -statistic and was quantified with I^2test. $I^2 > 75\%$ was consistent with a high degree of heterogeneity. **Results:** The three RCTs involved 4096 patients. Adjuvant therapy with TKIs yielded no significant improvement in DFS or OS as compared to placebo (DFS HR = 0.92, 95% CI 0.82-1.04 and OS HR = 1.00, 95% CI 0.86-1.17). Separate analysis of DFS in sunitinib vs placebo did not show any benefit (2 studies, N = 1909; HR = 0.90, 95% CI 0.67-1.19). Use of TKIs was associated with significantly increased risk of drug toxicity. Increased risk of grade 3 or 4 adverse events (RR = 2.73, 95% CI 2.51-2.97), diarrhea (RR = 14.57, 95% CI 7.93-26.79), fatigue (RR = 3.63, 95% CI 2.13-6.18), hypertension (RR = 3.95, 95% CI 3.18-4.91) and palmar/plantar dysesthesia (RR = 21.4, 95% CI 12.91-35.47) was observed. **Conclusions:** No OS or DFS benefit for VEGF TKIs including for Sunitinib was observed in this meta-analysis, while there was a significantly increased risk of toxicity in greater than half of the patient population. Subgroup analyses based on age, sex, pharamacokinetics, pharmacogenomics may help to identify potential candidates. Analysis from ongoing adjuvant TKI trial results (SORCE,ATLAS,2810) and immunotherapy (IMMotion,Keynote-564,checkmate 914) are awaited and may provide more refinement in selecting high risk RCC candidates with favorable benefit-risk ratios for post op drug therapies.

4568 Poster Session (Board #394), Sat, 8:00 AM-11:30 AM

Evaluation of the spectrum selective RTK inhibitor sitravatinib in clear cell renal cell carcinoma (ccRCC) refractory to anti-angiogenic therapy (AAT). *First Author: Shubham Pant, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sitravatinib (MGCD516) is an oral, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including the TAM family (AXL, MER), split RTKs (VEGFR2, PDGFR, KIT), RET and MET. Because of the importance of sitravatinib targets in the pathogenesis of ccRCC and putative roles for MET and AXL in intrinsic and acquired resistance to anti-angiogenic agents, sitravatinib was evaluated in patients (pts) with ccRCC after failure of AAT. **Methods:** Study 516-001 is a Phase 1/1b study of sitravatinib in pts with advanced solid tumors. After determination of the MTD in Phase 1, pts with ccRCC after failure of AAT and pts with qualifying genetic alterations in sitravatinib targets were enrolled into distinct Phase1b cohorts using respective multi-stage designs. Pts received 150mg sitravatinib once daily in continuous 21-day cycles and were evaluated for safety, PK and clinical activity. Here we report on the completion of Stage 2 enrollment of the Phase1b ccRCC cohort. **Results:** 89 pts (50 men/39 women; median age 67 years; range 36-84) with advanced solid tumors were enrolled in Phase1b cohorts, including 28 pts (20 men/8 women; median age 67.5 years; range 47-77) in the ccRCC cohort who received a median of 3 prior treatment regimens. Prior AAT included sunitinib (n=17), pazopanib (n=13) and axitinib (n=9); 12 pts received ≥2 prior angiogenesis inhibitors. One partial response (PR) among the first 10 evaluable ccRCC pts in Stage 1 met criteria for enrollment of a total of 20 evaluable pts for Stage 2, where 4 confirmed PRs were observed and an unconfirmed PR in a pt who had received 4 prior AATs. Prolonged stable disease for at least 24 weeks was observed in an additional 5 pts. Treatment-related AEs (>20% of pts; Grades 1-3) included diarrhea, hypertension, nausea, vomiting, fatigue and decreased appetite. **Conclusions:** Stage 2 enrollment of the Study 516-001 Phase1b cohort of ccRCC refractory to AAT was completed. Sitravatinib treatment resulted in 4 confirmed PRs in a heavily pre-treated patient population and demonstrated a manageable safety profile. Further evaluation of sitravatinib in ccRCC is warranted. Clinical trial information: NCT02219711.

4569 Poster Session (Board #395), Sat, 8:00 AM-11:30 AM

A FARETES study of the efficacy and safety of testosterone in metastatic renal cell carcinoma patients with fatigue. *First Author: Ilya Tsimafeyeu, Kidney Cancer Research Bureau, Moscow, Russia*

Background: Fatigue is a frequent symptom of metastatic renal cell carcinoma (mRCC), and most common adverse event of treatment with tyrosine kinase inhibitors. The aim of this multicenter randomized phase 2 study was to determine efficacy and safety of testosterone undecanoate (T) in mRCC patients with fatigue developed during targeted therapy. **Methods:** Sixty male patients with clear cell mRCC, normal PSA level, low testosterone level and no evidence of hypothyroidism receiving first-line sunitinib or pazopanib with fatigue were randomly assigned (1:1) to either T and targeted therapy or targeted therapy alone (control group). T (1,000 mg) was injected intramuscular deeply on Day 1 of a new treatment cycle. The primary endpoint of the study was the difference in mean change of fatigue according to Functional Assessment of Cancer Therapy-Fatigue (FACIT-F). Secondary endpoints were safety, FKSI-19 score, testosterone serum concentrations, red blood cells (RBC) count and hemoglobin level. The assessments were performed at baseline and Day 28 of a treatment cycle. **Results:** T was well tolerated. No unexpected toxicity was observed. The health-related quality-of-life scores in the T group were better than those in the control group (Table). The current study did achieve its primary endpoint based on the significant differences favored T over targeted therapy alone regarding fatigue (all P≤0.012). Clinical trial information: NCT03379012. **Conclusions:** Male patients with mRCC receiving targeted therapy had significantly less fatigue and better symptom control with T. There was non-significant positive trend in hemoglobin level between 2 groups. T therapy was safe. Long-term outcomes will be reported.

	Baseline		Day 28	
	T group, N=30	Control group, N=30	T group, N=30	Control group, N=30
Age (years), mean (range)	52 (33-71)	55 (42-69)	-	-
Sunitinib, N(%)	28 (93)	28 (93)	-	-
IMDC poor risk factors, 0-2, N(%)	21 (70)	22 (73)	-	-
FACIT-F, mean (SD)	37 (4.7)	35.3 (3.1)	20.3 (8.1)	42.5 (8.4)
FKSI-19, mean (SD)	46.5 (12.2)	44.2 (9.4)	27.5 (12.5)	39.9 (9.8)
Total testosterone serum, nmol/l, mean (SD)	6.21 (1.78)	8.56 (2)	33.2 (14.3)	-
RBC, 10^{12}/l, mean (SD)	3.7 (0.5)	3.9 (0.2)	4.4 (0.4)	3.6 (0.15)
Hemoglobin, g/l, mean (SD)	124.5 (11.7)	119 (10.4)	133 (13.5)	108 (17)

4570 Poster Session (Board #396), Sat, 8:00 AM-11:30 AM

Patient-reported frustrations in renal cell carcinoma (RCC) care delivery: Results of a joint European Association of Urology (EAU)/KCCure survey. *First Author: Cristiane Decat Bergerot, City of Hope Comprehensive Cancer Center, Monrovia, CA*

Background: A joint survey was developed by the EAU RCC Guidelines Panel and KCCure, a non-profit patient advocacy group, to ascertain patient perceptions towards adjuvant therapy for RCC (Battle D *et al* ASCO GU 2018). This survey included open-ended questions pertaining to sources of frustration in cancer-related care, the results of which are summarized herein. **Methods:** An online survey was conducted from April to June, 2017, publicized through social media and patient networking platforms. The survey obtained basic clinicopathologic, treatment related information, and open-ended questions asking for common sources of frustration in cancer-related care. Patients were also asked how they might reconcile these sources of frustration. Each response was analyzed and categorized into descriptive categories. The Kruskal-Wallis test was used to define associations between baseline characteristics and sources of frustration. **Results:** Among 450 patients with RCC, median age was 56, and 56% were female. The majority was diagnosed with clear cell histology (85%) and most patients had non-metastatic disease (73%). The most common sources of frustration were related to poor communication (20%), lack of confidence in diagnosis (18%), fear of recurrence/progression (14%) and financial issues (9%). Practical sources of frustration (e.g., lack of information, financial issues) were more common among patients with non-clear cell histology (P = 0.05) and older age (P = 0.01). In contrast, emotional sources of frustration (e.g., fear of recurrence/progression) were more common in females (P = 0.001). Patients posited that care could be improved if physicians demonstrated greater compassion (21%), spent more time supplying information (20%) and if they could circumvent financial issues (11%). **Conclusions:** RCC patients have varied and multiple concerns around care delivery. Based on this findings, practitioners should aim to better inform patients and should be cognizant of psychosocial issues surrounding their care. Certain baseline characteristics (age, gender and histology) can be considered in individualizing care delivery to minimize patient frustration.

4571 Poster Session (Board #397), Sat, 8:00 AM-11:30 AM

Anxiety and patients: Perspectives on surveillance and adjuvant therapy in renal cell carcinoma. *First Author: Dena Battle, KCCure, Alexandria, VA*

Background: Until recently there has been no approved adjuvant therapy (AT) for renal cell carcinoma (RCC). Surveillance after nephrectomy is carried out with various modalities without clear recommendations from guidelines. In the S-TRAC trial, sunitinib improved disease-free survival (DFS) for high risk RCC patients (pts). Overall survival (OS) data is immature. Data on pts perception of AT vs surveillance are missing. The purpose of this study was to assess pts anxiety and perspectives regarding AT vs surveillance in RCC. **Methods:** We conducted a survey-monkey survey in n = 450 pts with RCC. The survey was promoted via kccure.org, Facebook and smartpatients.com. Questions focused on pts attitude towards AT. **Results:** Baseline pts characteristics include: median age 55.6 years (17-82 years); 56.4% female; 73.6% post-nephrectomy, 22.0% post-partial nephrectomy; 76.4% clear cell; 39.1% pts with RCC recurrence; 35.3% receiving systemic therapy for RCC. Median NCCN distress score was 6.39 in the majority of the pts. Main drivers of anxiety were cancer recurrence (74.4%), fear of the loss of renal function (38.7%), contrast media harming the kidney (27.1%) and exposure to radiation (20.7%). No differences in anxiety levels ranged between stage, age, gender, and type of surgery. Systemic therapy increased NCCN distress score (6.87, $p < 0.0001$). 63.1% of pts would use AT if it prolonged OS; 60.1% if AT prolonged DFS; 42.7% if AT demonstrated acceptable toxicity; 36.7% if guaranteed insurance coverage and efficacy. Use of systemic therapy correlated with a wish for a prolonged OS ($p < 0.0001$). Pts on systemic therapy had a significant higher acceptance of toxicity ($p < 0.0001$). **Conclusions:** Anxiety is a key driver for pts decisions and is unrelated to stage. Most pts are willing to use AT based on DFS benefits alone and place lower emphasis on toxicity. These data provide an important perspective on pts perceptions with RCC and the need for pts education on risks of AT.

4572 Poster Session (Board #398), Sat, 8:00 AM-11:30 AM

Real world experience and biomarkers of nivolumab in dutch advanced renal-cell carcinoma patients. *First Author: Saskia Lisa Verhaart, VU University Medical Center, Amsterdam, Netherlands*

Background: Although nivolumab, a programmed death 1 inhibitor, has been approved as a second line treatment for advanced renal-cell carcinoma (RCC) in Europe since 2016, its real-world experience is currently unknown. **Methods:** Efficacy, toxicity and potential biomarkers (histology, performance score, lactate dehydrogenase [LDH], eosinophils, neutrophils and lymphocytes) of nivolumab were retrospectively evaluated in Dutch RCC patients, who were consecutively registered in a national database between March 2016 and May 2017. **Results:** Data of 264 patients in 24 hospitals was analyzed. Twenty-one (9%), 122 (49%) and 104 (42%) patients were categorized in favorable, intermediate and poor MSKCC risk groups, respectively. Median overall survival (OS) was 18.7 months (95% CI, 13.7 – 23.7) and time to treatment failure (TTF) 6.0 months (95% CI, 5.1 – 6.8). Overall, 46 grade 3 or 4 adverse events (AEs) in 39 patients (15%) and two nivolumab related deaths were reported. After a median follow-up of 12.3 months, 78% (38 of 49) of responding patients had an ongoing response. Clear-cell histology patients had a median OS of 17.6 months (95% CI, 14.6 – 20.6) and TTF of 5.6 months (95% CI, 4.8 – 6.3) while non-clear-cell histology patients had a median TTF of 3.3 months (95% CI, 1.4 –5.1). Patients with a WHO performance score ≤ 1 had a better OS and TTF as compared to patients with a performance score of ≥ 2; median OS 18.7 months (95% CI, not estimable) *vs.* 5.4 months (95% CI, 1.2 – 9.6) and TTF 6.0 months (95% CI, 5.0 – 6.9) *vs.* 2.4 months (95% CI, 1.5 – 3.3). In patients with normal baseline LDH, median OS was not estimable and median TTF 6.7 months (95% CI, 5.2 – 8.2), while a decreased efficacy (median OS 9.7 months (95% CI, 7.5 – 11.9) and TTF 2.9 months (95% CI, 2.1 – 3.6) was observed in patients with elevated LDH at baseline. An increase in absolute eosinophil count between week 0 and 8 was related to improved OS (HR = 0.41; 95% CI, 0.23 – 0.73, P = 0.003) and TTF (HR = 0.65; 95% CI, 0.46 – 0.92, P = 0.015). **Conclusions:** In this real-world population, efficacy and safety of nivolumab are comparable to the results reported in the pivotal phase III trial. Remarkably, increase in eosinophil count during treatment with nivolumab predicts improved efficacy and survival.

4573 Poster Session (Board #399), Sat, 8:00 AM-11:30 AM

Safety and activity of hydroxychloroquine and aldesleukin in metastatic renal cell carcinoma: A cytokine working group phase II study. *First Author: Leonard Joseph Appleman, University of Pittsburgh, Pittsburgh, PA*

Background: Aldesleukin (recombinant human interleukin-2, IL-2) has been an FDA-approved treatment for mRCC since 1992 with a 5-10% rate of durable complete response. Hydroxychloroquine (HCQ) inhibits cellular autophagy, a protective mechanism that enables cells to survive metabolic stress. In murine models, the combination of IL-2 and HCQ was associated with diminished toxicity and increased efficacy. We hypothesized that this combination would be tolerable and active in patients with metastatic renal cell carcinoma (mRCC). **Methods:** The Cytokine Working Group studied high-dose IL-2 in combination with oral HCQ for patients with mRCC. Subjects received IL-2, 600,000 International Units/kg, every 8 hours up to 14 doses/cycle. HCQ was administered daily by mouth, starting 2 weeks prior to the first dose of IL-2 and continued up to one year. The initial HCQ dose was 600 mg daily, with a planned dose escalation to 1200 mg daily. Subjects were monitored for safety and tolerability as well as response per RECIST 1.1. **Results:** 30 patients (9F, 22M) received study treatment, and 29 were evaluable for response. MSKCC prognostic group: good- 38%; intermediate- 55%; poor- 11%. Five subjects were treated at 600 mg daily HCQ with no unexpected toxicity. Thirteen subjects were then treated at HCQ 1200 mg. Of these, 2 experienced hypotension and tachycardia, and 1 patient died from pulmonary emboli. The cardiac events, consistent with IL-2 toxicity, were observed earlier in the course of treatment than anticipated. HCQ dose was therefore de-escalated to 600 mg daily, and 12 additional subjects were enrolled with no unexpected toxicity. There were 3 confirmed complete responses and 3 partial responses (1 confirmed); the median overall survival has not been reached. Surprisingly, median progression-free survival was 5 months for the 1200 mg cohort and $>$ 17 months for the 600 mg group, 3-4x the historical duration. High baseline levels of serum hepatocyte growth factor $>$ median predicted for inferior overall survival. Soluble LAG-3 levels increased with IL-2 therapy. **Conclusions:** IL-2 plus HCQ was well tolerated and clinically active with encouraging PFS of 17 months at the 600 mg HCQ dose. Clinical trial information: NCT01550367.

4574 Poster Session (Board #400), Sat, 8:00 AM-11:30 AM

Prospective, multinational, observational study of real-world treatment outcomes with pazopanib in patients with advanced or metastatic renal cell carcinoma (PRINCIPAL study). *First Author: Manuela Schmidinger, Medical University of Vienna, Vienna, Austria*

Background: PRINCIPAL (NCT01649778) was the largest prospective real-world effectiveness and safety study of pazopanib (PAZ) in patients (pts) with renal cell carcinoma (RCC). **Methods:** Pts with advanced and/or metastatic clear cell RCC were enrolled within 30 days of initiating first-line PAZ. Follow-up data on progression, survival, and safety was collected approximately every 3 months until death, consent withdrawal, or loss to follow-up, for up to 30 months. Primary efficacy end points were median overall survival (mOS), median progression-free survival (mPFS), and overall response rate (ORR). Safety measures included frequency of adverse events (AEs), serious AEs, and AEs of special interest. **Results:** Among 657 pts who received $\geq$1 dose of PAZ, 76.3% completed the study (33.0% completed 30 months of follow-up and 43.2% died). Median enrollment age was 66 years, with 57.2% aged $\geq$65 years. 4.1%, 62.6%, and 33.3% of pts were grouped as favorable, intermediate, or poor risk by Heng criteria, respectively. Most pts (84%) initiated treatment at 800 mg, and the median treatment time with or without dose interruption was 6.9 and 7.6 months, respectively. mPFS and mOS are shown in the Table. Among the measurable disease population (n = 168), ORR was 30.3%, median duration of response was 11.0 months (95% confidence interval [CI] 8.6-14.6), and time to response, evaluated every 3 months, was 3.0 months (95% CI 2.9-3.1). Most pts had an AE (74.0%) that led to dose adjustment/interruption in 49.3% and treatment discontinuation in 14.6%. The most frequent ($>$ 10%) drug-related AEs were hypertension (20.9%), diarrhea (11.3%), and increased alanine aminotransferase (11.0%). **Conclusions:** Real-world effectiveness and safety outcomes in the PRINCIPAL study were consistent with clinical trials and support the first-line use of PAZ across all risk groups of pts with advanced or metastatic RCC. Clinical trial information: NCT01649778.

	mPFS, months (95% CI)	mOS, months (95% CI)
All pts	10.4 (9.3-12.0)	29.9 (24.7-NR)
Heng risk group		
· **Favorable**	16.1 (11.6-26.0)	NR (28.6-NR)
· **Intermediate**	12.5 (10.3-15.4)	32.9 (32.9-NR)
· **Poor**	6.7 (5.8-9.1)	14.8 (12.2-19.5)

NR, not reached.

4575 Poster Session (Board #401), Sat, 8:00 AM-11:30 AM

Comparative transcriptomic profiling of renal medullary carcinoma (RMC) to determine distinct signatures and pathways associated with response to chemotherapy. *First Author: Pavlos Msaouel, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: RMC is a highly aggressive renal cell carcinoma (RCC) with poor prognosis and variable response to chemotherapy. It is often treated with cytotoxic regimens used for collecting duct carcinoma (CDC) and upper tract urothelial carcinoma (UTUC). We analyzed the transcriptomic profile of RMC samples and compared it with that of CDC, UTUC, clear-cell renal cell carcinoma (ccRCC), papillary RCC (pRCC), and chromophobe RCC (chRCC). **Methods:** RNA sequencing (RNA-seq) was performed in primary tumor tissues from treatment-naïve patients with RMC (n = 11), CDC (n = 9), and UTUC (n = 22). We compared these profiles to ccRCC, pRCC, and chRCC samples (n = 20 each) randomly selected from The Cancer Genome Atlas (TCGA). Gene ontology (GO) analysis was performed using DAVID. *In vitro* cell proliferation was assessed using the MTT assay. **Results:** Unsupervised hierarchical clustering and principal component analyses showed that 9/11 RMC samples formed a distinct cluster while 2 samples overlapped with CDC (p = 0.0003). There was no overlap between RMC and UTUC, ccRCC, pRCC, or chRCC. Five patients with RMC showed at least partial response to subsequent chemotherapy (4/5 received a paclitaxel-based regimen) and their pre-treatment samples demonstrated upregulation of 62 genes (FDR $<$ 0.05) compared with the other patients. GO analysis revealed that these genes are associated with transmembrane transport pathways (enrichment score 3.87). The most upregulated gene ($>$ 3-fold) was guanine deaminase (GDA), a regulator of microtubule assembly normally expressed in human kidney collecting ducts. *In vitro* siRNA knockdown of GDA in the paclitaxel-sensitive RCC cell lines HCR-59 and UOK-146 conferred resistance to paclitaxel but not to drugs that do not target microtubules such as gemcitabine, doxorubicin, or platinum agents. **Conclusions:** RMC displays a unique transcriptomic signature that is closer to CDC than to UTUC or to other RCC subtypes. RMC tumors more likely to respond to chemotherapy show upregulation of genes such as GDA. Our results provide the first evidence that GDA may be a biomarker of response to microtubule-targeting agents in RMC.

4576 Poster Session (Board #402), Sat, 8:00 AM-11:30 AM

Functional biomarkers of homologous repair (HR) deficiency to guide novel DNA damage response targeted therapy in clear cell renal cell carcinoma (ccRCC). *First Author: Patrick Glen Pilie, University of Michigan, Ann Arbor, MI*

Background: Treatment for advanced ccRCC has rapidly evolved; however, responses are not uniform and synthetic lethal treatments with associated predictive biomarkers are still lacking. We previously reported that HR deficiency (HRD) is an early event in ccRCC, and that an HRD signature predicts for loss of RAD51 protein expression and improved OS. HRD has been shown to predict response to DNA damage response (DDR) inhibitors (DDRi) across many tumor types. In this current study, we posited that HRD positive RCC is sensitive to DDRi, that a stage dependent increase in phosphoinositide-3-kinase (PI3K) activation drives resistance to DDRi, and this resistance can be overcome with PI3K pathway inhibitors. **Methods:** We performed reverse phase protein microarray (RPPA) on 12 patient-derived stage I ccRCC tumors and 12 normal kidney tissues. We analyzed differential protein expression in HRD versus HR intact (HRI) ccRCC samples from the Cancer Genome Atlas (TCGA). We assessed apoptotic activity and colony formation in HRD (ACHN) and HRI (786-O) RCC lines with and without CHK1 inhibitor (CHK1i) and/or mammalian target of rapamycin (mTOR) inhibitor (mTORi). **Results:** Early ccRCC had loss of protein expression of FOXO3a, p-ATM, p-CHK2, p53 ($p < 0.05$) compared to normal, reflecting early defective ATM signaling. In TCGA, 75% of stage I ccRCC had an HRD signature, which decreased to less than 50% in stage IV tumors. HRI tumors had significantly higher protein expression of RAPTOR, CMYC, and PI3K than HRD tumors. In a preclinical model, HRD ACHN was sensitive to CHK1 inhibitor, whereas HRI 786-O was resistant. Adding mTORi overcame resistance to CHK1 inhibition in 786-0. **Conclusions:** Early stage ccRCC has defective DDR protein signaling with loss of ATM pathway activation. Increased oncogenic signaling, including in the mTOR/PI3K/AKT pathway, may alter HR gene activity and sensitivity to DDRi. The addition of mTORi to DDRi overcomes resistance to DDRi in HRI ccRCC. This study provides rationale for future biomarker-driven clinical trials of DDR inhibitors in advanced ccRCC patient populations.

4577 Poster Session (Board #403), Sat, 8:00 AM-11:30 AM

Single-center analysis of 109 patients (pts) with metastatic chromophobe renal cell carcinoma (ChRCC): Differences in outcomes by histologic variant. *First Author: Yasser Ged, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ChRCC constitutes 5-10% of all RCC cases, and is generally associated with better prognosis including benefit from approved targeted agents (*Armstrong, Lancet Onc, 2016*). Presence of sarcomatoid features (SF) have previously been proposed as an adverse prognostic marker, but data for systemic therapy is limited. We assessed therapeutic outcomes for pts with metastatic ChRCC with and without SF. **Methods:** Retrospective chart reviews of pts with newly diagnosed metastatic ChRCC evaluated at Memorial Sloan Kettering Cancer Center (MSKCC) between 2002-17. MSKCC pathology reports determined presence/absence of SF to categorize pts. Evaluated endpoints included overall survival, time to treatment (TTF) for pts who initiated first line therapy at MSKCC and time to recurrence (TTR) post nephrectomy with metastatic disease. OS between the 2 groups was compared using log-rank analysis. A subset of pts had next generation sequencing (NGS) with MSK-IMPACT. **Results:** 109 pts with newly diagnosed metastatic ChRCC were identified (80 without SF, 29 with SF). Pts with SF were more likely to present with IMDC poor risk status (31% vs 10%) and de novo metastatic disease (48% vs 19%). 52 pts initiated first line therapy at MSKCC (35 without SF, 17 with SF). First line agents included VEGF tyrosine kinase inhibitors (60%), mTOR inhibitors (13%), cytokines (6%) and other investigational agents (21%). Outcomes are summarized in table below. NGS was performed in 22 pts, of which 64% and 45% harbored TP53 and PTEN alterations. **Conclusions:** Pts with metastatic ChRCC with SF had significantly worse outcomes compared to pts without SF. Median TTR < 3 months for this subgroup supports close surveillance following nephrectomy for localized tumors. The lack of benefit observed across various classes of systemic agents warrants study of underlying biology and investigating novel agents.

Outcome (Median)	All pts N = 109 Months (95% CI)	ChRCC without SF N = 80 Months (95% CI)	ChRCC with SF N = 29 Months (95% CI)	Log-rank
OS	25 (12, 33)	38 (26, 51)	7.5 (4.2, 10.7)	HR 4.7 (95% CI: 2.7, 8.2) $p < 0.001$
TTF	5.1 (2.7, 8.0)	8.0 (5.1, 13.0)	1.8 (0.9, 2.7)	-
TTR	25.5 (23.4, 58.3)	48.8 (30.8, 80.7)	2.7 (0.7, 6.9)	-

4578 Poster Session (Board #404), Sat, 8:00 AM-11:30 AM

Overall survival (OS) by clinical risk category for high dose interleukin-2 (HD IL-2) treated metastatic renal cell cancer (RCC): Data from PROCLAIM. *First Author: Mayer N. Fishman, Moffitt Cancer Center, Tampa, FL*

Background: Clinical risk factors continue to separate mRCC patient survival outcomes regardless of therapy. **Methods:** International Metastatic RCC Database Consortium (IMDC) risk criteria were utilized to assess survival among 939 mRCC patients in the PROCLAIM data base, with dates of treatment from 2006 to present. 810 patients (pts) had data for all 6 IMDC criteria and are described here. Median follow-up is 23.4 months (range 0.2 – 124 mo). Patients are grouped by prior or no prior therapy, IL-2 alone, or subsequent therapy. Some patients are in two groups. **Results:** The majority of patients were treatment-naïve and intermediate risk. Of the 249 patients with favorable risk, the median OS is 63.3 mo and the 2-year OS is 77.6%. Of 480 patients with intermediate risk, median OS is 42.4 mo, 2-year OS 68.2%, and of 81 patients with poor risk, median OS 14 mo, 2-year OS 40.4%. **Conclusions:** Among mRCC pts treated with HD IL-2, all risk groups have median and 2-year survival consistent with or better than recent reports of checkpoint or targeted therapies for RCC. Favorable and intermediate risk (by IMDC) patients treated with HD IL-2 have better OS compared with that of poor risk patients, with highest OS in favorable risk patients. Favorable risk patients treated with HD IL-2 alone have a 2-yr OS of 74%. These data continue to support a recommendation for HD IL-2 for patients with mRCC.

Patient Group (numbers)	Favorable	Intermediate	Poor
All patients (810)	249	480	81
Therapy prior to IL-2 (89)	17	57	15
No prior therapy (365)	113	220	32
Therapy post IL-2 (414)	122	254	38
IL-2 alone (356)	119	203	34
2-year Overall Survival			
All patients (810)	77.6%	68.2%	40.4%
No Prior Therapy (365)	83.6%	71.6%	53.3%
Post-IL-2 Therapy (414)	81%	72.0%	46.8%
IL-2 Alone (356)	73.8%	63.7%	39.8%

4579 Poster Session (Board #405), Sat, 8:00 AM-11:30 AM

Cabozantinib (Cabo) in advanced non-clear cell renal cell carcinoma (nccRCC): A retrospective multicenter analysis. *First Author: Nieves Martinez Chanza, Dana-Farber Cancer Institute, Boston, MA*

Background: Cabo shows robust clinical activity in advanced clear cell RCC. nccRCC, a heterogeneous mix of diseases, have been underrepresented in clinical trials and effective systemic therapy is lacking. We retrospectively characterized the clinical activity and toxicity of cabo in nccRCC. **Methods:** Medical records from advanced nccRCC patients (pts) treated with cabo across 18 institutions were reviewed. We captured baseline characteristics, clinical outcomes and genomic alterations by next-generation sequencing (NGS). Objective response rate (ORR) was assessed by RECIST. Clinical benefit (CB) included ORR or stable disease. Time to treatment failure (TTF) and overall survival (OS) were estimated by Kaplan-Meier. **Results:** We identified 80 pts with nccRCC: papillary (59%), chromophobe (10%), collecting duct (5%), Xp11.2 translocation (15%) or unclassified (11%). The majority were IMDC intermediate/poor risk (88%) and received cabo $\geq 3^{rd}$ line (53%). Median exposure was 4 months(mos) (range: $<$ 1-23). 48% remained on cabo while 42% had discontinued for progression and 5% for toxicity. Most common adverse events were fatigue (51%) and rash (33%). In 66 pts on cabo $\geq$8 weeks, ORR was 27.3%. 71% had CB; with 64% durable CB $\geq$6 mos. Median OS was 11 mos (95%CI 9-NR). TTF was 6.9 mos (95%CI 4.8-9.9). Subset analyses in Table. Most frequently altered genes in 43 pts with NGS were MET (21%) and CDKN2A (19%). Of the 7 evaluable papillary RCCs with MET alterations, 5 (71%) achieved CB. **Conclusions:** Cabo is safe and active in nccRCC. Support of ongoing (e.g.NCT02761057) and future prospective studies in nccRCC encompassing all histologies is warranted.

	ORR (%) N = 66	CB (%) N = 66	Median TTF (mos) N = 80	Median OS (mos) N = 80
HISTOLOGY(n)*				
-Papillary(38)	11(28.9)	24(63.2)	6	11
-Chromophobe(7)	3(42.9)	5(71.4)	5.8	8
-Collecting(3)	1(33.3)	2(66.7)	10.6	NR
-Xp11.2(10)	2(20)	9(90)	8.3	16
-Unclassified(8)	1(12.5)	7(87.5)	6.7	11
IMDC RISK GROUP(n)*				
-Good(6)	4(66.7)	5(83.3)	NR	NR
-Intermediate(41)	8(19.5)	27(65.9)	6	11.2
-Poor(16)	5(31.3)	13(81.3)	5.8	8
TREATMENT LINE(n)*				
-1ST(13)	1(7.7)	10(76.9)	6.7	11.2
-2ND(17)	4(23.5)	11(64.7)	4.8	9
-≥3RD(36)	13(36.1)	26(72.2)	8.1	11

(n)* for ORR/CB

4580 Poster Session (Board #406), Sat, 8:00 AM-11:30 AM

Pilot trial of ibrutinib plus nivolumab in patients with metastatic renal cell cancer (mRCC): results from a dose-finding cohort. *First Author: Primo Lara, University of California, Davis, Sacramento, CA*

Background: Immune checkpoint inhibitor therapy (CIT) has transformed the management of patients (pts) with mRCC, with a fraction experiencing durable tumor responses. However, most eventually develop disease progression after either an initial response to CIT or while on CIT. Newer agents that modulate immune response can possibly potentiate CIT therapy. The ITK/ETK/BTK inhibitor ibrutinib has been reported to inhibit myeloid derived suppressor cells in preclinical models and to potentiate CIT. We conducted an investigator-initiated pilot trial of ibrutinib plus the PD1 inhibitor nivolumab in mRCC pts, particularly in those previously exposed to CIT. Here we report initial safety and efficacy results from the dose-finding cohort. **Methods:** Pts with mRCC of any histologic subtype and who have completed at least one line of prior systemic therapy including prior CIT were eligible. Pts must have acceptable end-organ function and Zubrod PS of 0-2. Treatment consisted of nivolumab 240 mg IV q2 weeks plus ibrutinib 560 mg (dose level 0) or 420 mg (dose level -1) orally once daily. Cycle length was 28 days. Dose limiting toxicity (DLT) was defined as any Grade (Gr) 3+ adverse event (AE) attributable to therapy. **Results:** As of 9/18/17, 12 pts have been enrolled, six to each dose level. Patient characteristics: Mean age = 62 years (range 44-78); Male sex = 7 (58%); White race = 9 (75%); Prior CIT = 11 (92%). Three pts experienced one DLT each in dose level 0 (all Gr3): elevated lipase, hypoalbuminemia, & nausea. Only 1 DLT has been seen thus far in dose level -1 (Gr3 infection). The most common Gr3+ AEs include anemia (n = 5), ALT elevation (4), AST elevation (3), nausea (3), hypoalbuminemia (2), esophagitis, infection, lipase increase, and vomiting (1 each). Two pts with prior CIT had partial tumor response (both confirmed), 1 of which later became a CR. **Conclusions:** Ibrutinib at a dose of 420 mg orally once daily in combination with nivolumab 240mg IV q 2 weeks appears feasible and tolerable in mRCC patients. No unique immune-related AEs have been seen thus far. Anti-tumor activity was seen in 2 pts previously exposed to PD1-targeted therapy. Updated results will be presented. (Supported by Pharmacyclics and UCDCCC). Clinical trial information: NCT02899078.

4581 Poster Session (Board #407), Sat, 8:00 AM-11:30 AM

Active surveillance and deferred medical treatment (ASDT) in metastatic renal cell carcinoma (mRCC): Update of a single center experience and efficacy of medical treatment. *First Author: Philipp Ivanyi, Dept. Hematology, Hemostaseology, Oncology & Stem Cell Transplantation, Hanover Medical School, Hannover, Germany*

Background: ASDT is applicable to a fraction of mRCC patients (pts). We investigated clinical outcome of ASDT and report on efficacy of medical treatment (Rx). **Methods:** Between 4/2000-3/2016 patients (pts) with mRCC were identified from medical records, retrospectively. Pts alive ≥3 months after diagnosis of metastatic disease without Rx for ≥6 months were grouped as ASDT(+), all other pts were deemed ASDT(-). Overall survival (OS) and clinical progression free survival (cPFS) of administered Rx were analysed, as well as time from diagnosis mRCC to initiation of 2nd line treatment or death (= time to failure of treatment strategy [TTFS]). Descriptive statistics, Kaplan-Meier and Log-rank analyses were applied. **Results:** 142/370 (38.4%) mRCC received ASDT for a median duration of 24.1 (95%CI:20.2-28.1) months (mo). ASDT pts showed a superior OS: 67.3 (95%CI:50-84.6) mo vs. ASDT(-): 30.4 (95%CI:25-35.9) mo ($p < .001$). ASDT pts received a median of 1 (range(r): 0-8) lines of Rx compared to ASDT(-) with median 3 (r:1-10) lines of Rx ($p < 0.001$). cPFS in either 1st ($p = .052$), 2nd ($p = .062$) and 3rd ($p. = .067$) line Rx tends to be superior in in ASDT(+) pts compared to ASDT(-). TTFS compared favourably in ASDT(+) vs. ASDT(-) pts with 37.3 (95%CI: 28.2-46.4) mo vs. 10.0 (95%CI: 8.8-11.2) mo. ($p < .001$). **Conclusions:** Clinical selection by expert opinion was able to identify pts with indolent disease and favorable OS. Deferred treatment did not impact efficacy of subsequent Rx in ASDT(+) pts. ASDT is a feasible approach in selected pts in high-volume centers.

4582 Poster Session (Board #408), Sat, 8:00 AM-11:30 AM

Radiofrequency ablation of pathologically proven T1a renal tumors: 15 years follow up—A tertiary cancer center experience. *First Author: Mohamed E. Abdelsalam, Department of Interventional Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: To evaluate the long term oncologic efficacy and overall survival of radiofrequency ablation (RFA) for pathologically proven T1a Renal cell carcinoma (RCC). **Methods:** we retrospectively reviewed our renal ablation data base between January 2001 and December 2014, we included only patients with histologically diagnosed T1a RCC (< 4 cm) who underwent RFA. Patient who underwent cryoablation, those with syndromes, and those with recurrent or bilateral RCC were excluded. For each patient, we recorded: Demographics, tumor size and histology, complications, recurrence at ablation site, development of metastases, history of another malignancy, survival/death and cause of death. Overall survival (OS) was estimated using Kaplan and Meier product-limit estimator. **Results:** Ninety four RFA procedures were performed for 92 lesions in 92 patients (54 males and 38 females, average age 68 years). Average tumor size was 2.7cm (range: 1-3.9 cm). The median follow-up for all subjects was 4.7 years (range: 0.16 – 14.4 years). Total of 7 patients developed complications (7.4%). Three, 1 and 3 patients developed Grades I, II and III (3.2%) complications respectively according to the Clavien-dindo classification. A total of 6 patients (6.4%) developed local recurrence at the ablation site, one patient underwent watchful observation, two underwent repeat ablation and 3 patients underwent partial nephrectomy. One patient had disease recurrence in the other kidney. Fifty four patients (56%) had another non-renal primary malignancy. None of the patients developed metastasis from RCC. The median overall survival was 8.31 years. The overall survival was 68 %, 34% and 21 % at 5, 10 and 14 years respectively. The cancer specific survival (CSS) was 100 %. **Conclusions:** Radiofrequency ablation is a safe and highly efficacious modality for treatment of small renal tumors. Fifteen-year follow up data reveals long standing oncologic control with low recurrence and complication rates.

4583 Poster Session (Board #409), Sat, 8:00 AM-11:30 AM

Outcomes of patients (pts) with metastatic renal cell carcinoma (mRCC) and sarcomatoid dedifferentiation (sRCC) after treatment with immune checkpoint inhibitors (ICI): A single-institution retrospective study. *First Author: Jeremy Aaron Ross, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pts with mRCC and sarcomatoid dedifferentiation (sRCC) have a poor prognosis with approved targeted therapies (Keskin et al. JU 2017). The response to ICIs in mRCC pts with sRCC is unknown. **Methods:** This is a retrospective study of pts with metastatic sRCC who received ICIs (2013-2017). Data collected include tumor histology, demographics, type of ICI, response to ICI, and efficacy outcomes (response, progression-free survival [PFS], and overall survival [OS]). Descriptive statistics were used. **Results:** 33 pts (85%) had clear-cell RCC (ccRCC); 6 pts had variant histology RCC (vhRCC) including chromophobe (2), mucinous tubular and spindle cell carcinoma (1), and unclassified (3). All pts but 2 had intermediate- or poor- risk disease by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. 15 pts (38%) had greater than 50% sarcomatoid component (sarc) in primary tumor of nephrectomy specimen, 5 (13%) had > 80%, and 2 (5%) had 100%. 22 pts (56%) received nivolumab (nivo) as a single agent. 15 pts (38%) received nivo in combination with ipilimumab and 2 pts (5%) received pembrolizumab. 24 pts (62%) responded to treatment with ICIs. Of these, 14 (58%) received ICIs at first-line therapy, 9 pts in second, 1 in fourth. Median PFS was 8.3 months (95% CI 3.6 – 13.1). 5/33 pts with ccRCC (15%) achieved a complete response (CR) and 4 remain in CR at 52, 31, 31, and 22 months from start of ICI. 1 pt was not followed at our institution after 24 months of CR. These pts had 90%, 1%, 30%, 50%, and 90% sarc, respectively. 1 of these patients remains on treatment. 5/6 pts with vhRCC did not respond to therapy; 1 pt with unclassified histology had stable disease for 5 months 28 pts (77%) are alive at time of this analysis. The median OS was not reached. **Conclusions:** In pts with sRCC, ICIs appear to be effective in ccRCC with up to 15% achieving durable CR. The prognosis of vhRCC with sRCC remains poor despite treatment with ICI, underscoring the need to develop more effective therapies for these patients.

4584 Poster Session (Board #410), Sat, 8:00 AM-11:30 AM

Effectiveness and safety of pazopanib (PAZO) and everolimus (EVE) in a changing treatment (Tx) landscape: Interim results of the non-interventional study PAZOREAL. *First Author: Martin Boegemann, University of Muenster Medical Center, Münster, Germany*

Background: The therapeutic landscape for metastatic renal cell carcinoma (mRCC) has evolved rapidly with the approval of targeted therapies like tyrosine kinase-, mTOR-, multikinase-, and immune checkpoint inhibitors. Real-world data are urgently needed to monitor the translation of these approaches into daily practice. **Methods:** PAZOREAL is a prospective, non-interventional study to evaluate efficacy, tolerability, safety, and quality-of-life (QoL) in mRCC patients (pts) treated with first-line PAZO, second-line nivolumab (NIVO) or EVE, or third-line EVE (± lenvatinib) after NIVO. The primary variable was time on drug (TD) in the respective Tx lines. Other endpoints were overall survival (OS), dosing, safety, and QoL. **Results:** Between Dec 2015 and Nov 2017, 421 pts were enrolled. Interim results for 385 pts treated with PAZO in first line are presented here, majority of pts presented with ECOG 0-1 (81.0%) and clear cell carcinoma (80.3%). Median TD was 6.5 months (95%CI, 5.5-8.3). Using commonly applied trial eligibility criteria i.e. Karnofsky PS $\geq$ 70%, normal hemoglobin and clear-cell histology, the median TD in trial-eligible pts (39.5% of 385 pts) was 8.0 months (95%CI, 6.2-11.2). Progressive disease (n = 104/212 pts) was the most common reason for end of PAZO Tx, followed by toxicity (n = 34) and unrelated adverse events (AEs) (n = 20). 75 pts subsequently received NIVO as second-line treatment. Median OS was not reached. Death was reported for 20.8% of pts. Survival follow-up is ongoing. PAZO Tx was well tolerated. Treatment-emergent AEs (TEAEs) were reported for 308 of 378 pts included in the safety analysis, PAZO-related TEAEs for 246 pts (65.1%), and PAZO-related grade 3/4 TEAEs for 75 pts (19.8%). Most commonly reported AEs were diarrhea, nausea, and fatigue. QoL evaluated by EQ-5D-5L remained stable during PAZO Tx. **Conclusions:** The PAZOREAL study demonstrated acceptable efficacy, safety and tolerability of PAZO in the real-world setting. For patients considered trial-eligible, TD was comparable with results from clinical trials. The sequence of PAZO followed by NIVO as second line Tx is commonly applied in Germany.

4585 Poster Session (Board #411), Sat, 8:00 AM-11:30 AM

Nivolumab (nivo) for patients (pts) with metastatic non-clear cell renal cell carcinoma (nccRCC): A single-institution experience. *First Author: Jad Chahoud, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Nivo is approved for refractory metastatic renal cell carcinoma (RCC). However, the clinical activity of nivo in nccRCC is unknown as these patients were excluded from the trial population. **Methods:** We conducted a retrospective study of pts who received at least one dose of nivo for histologically-confirmed nccRCC. We tabulated treatment characteristics, objective response according to RECIST v1.1, adverse events (AEs), progression-free survival (PFS) and overall survival (OS). **Results:** Between 3/2010 and 12/2017, we identified 40 pts with nccRCC; 12 (30%) had papillary histology, 10 (25%) unclassified, 5 (12.5%) chromophobe, 3 (7.5%) translocation, 8 (20%) had ccRCC with rhabdoid component, 1 (2.5%) mucinous tubular and spindle cell carcinoma and 1 (2.5%) sarcomatoid RCC. Median age was 58 years (17-80) and 82.5% were male. The majority of pts had ECOG PS 1 (65%) or 2 (27.5%). At start of nivo therapy, 85% had metastatic disease in $\geq$ 2 sites; 7.5 % had International Metastatic RCC Database Consortium favorable-risk, 72.5% intermediate- and 20% poor-risk disease. Most pts (82.5%) had prior nephrectomy and median number of prior lines of therapy was 2 (0-8) with 60% of pts receiving $\geq$ 2 prior VEGFR-TKIs. The majority received nivo monotherapy (n = 32, 80%), and 20% (n = 8) received a combination of nivo with anti-VEGF or anti-CTLA4 therapy. At a median follow-up of 20 mo (16.2, 29.6), median PFS was 5.4 mo (3.4-10.2), with a 6-mo PFS rate of 45% (31.6%-64.2%). Median OS was 17.3 mo (7.8-NA), and 1-yr OS 60.1% (45.7%-79.1%). Disease control rate for 32 pts evaluable for best response was 78.1% (CR 6.25% + PR 9.37% + SD 62.5%), 12 pts (37.5%) had stable disease $\geq$ 6mo. Most common AEs were diarrhea (10%) and fatigue (17.5%). Nivo was stopped secondary to intolerance in 7 pts, 4 of whom achieved durable disease control. There were no treatment-related deaths. **Conclusions:** Nivo demonstrated clinical benefit and was well-tolerated in pts with nccRCC. Until there is evidence from prospective clinical trials, this retrospective data supports the use of nivo in pts with metastatic nccRCC.

TPS4586 Poster Session (Board #412a), Sat, 8:00 AM-11:30 AM

Pembrolizumab (pembro) plus epacadostat or placebo for locally advanced or metastatic urothelial carcinoma (UC) after failure of first-line platinum-containing chemotherapy: KEYNOTE-698/ECHO-303. *First Author: Thomas Powles, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

Background: Pembro has shown clinical efficacy as monotherapy in locally advanced or metastatic UC in first-line (1L) cis-ineligible and second-line (2L) postplatinum settings. Combination of pembro and epacadostat, a potent and highly selective oral inhibitor of the indoleamine 2,3-dioxygenase 1 (IDO1) enzyme, in the ongoing ECHO-202/KEYNOTE-037 phase 1/2 study (NCT02178722) showed increased ORR compared with data from pembro monotherapy and durable responses in 1L and 2L advanced UC patients. Further evaluation of this combination in a phase 3 randomized trial in advanced/metastatic UC is warranted. **Methods:** KEYNOTE-698/ECHO-303 (NCT03374488) is a global, phase 3, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety of pembro plus epacadostat versus pembro plus placebo in patients with locally advanced or metastatic UC that progressed after prior platinum-containing chemotherapy. Eligibility criteria include age $\geq$18 years; confirmed transitional cell or predominantly transitional cell histology; progression or recurrence of UC after 1 prior platinum-containing chemotherapy regimen for advanced or metastatic UC or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; measurable disease per RECIST v1.1, ECOG 0-1, and good organ function at baseline; and provision of tumor sample for PD-L1 analysis. Eligible patients will be stratified by Bellmunt score (0, 1, $\geq$2) and PD-L1 expression (combined positive score [CPS] $\geq$10 or CPS $<$ 10), and randomly assigned 1:1 to receive pembro 200 mg IV Q3W plus epacadostat 100 mg orally twice daily (continuously) or pembro plus matching placebo. Study treatment will continue until disease progression, unacceptable toxicity, or completion of 35 pembro infusions. Imaging will be performed every 9 weeks for the first 12 months and every 12 weeks thereafter until disease progression. Primary end points include OS and PFS (RECIST v1.1) by investigator assessment. Secondary end points include ORR, patient-reported outcomes, and safety. Approximately 648 patients will be enrolled. Clinical trial information: NCT03374488.

TPS4587 Poster Session (Board #412b), Sat, 8:00 AM-11:30 AM

Phase 3, randomized, double-blind trial of pembrolizumab plus epacadostat or placebo for cisplatin-ineligible urothelial carcinoma (UC): KEYNOTE-672/ECHO-307. *First Author: Arjun Vasant Balar, Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY*

Background: For patients ineligible to receive cisplatin, there is less benefit but still toxicity with alternative first-line cytotoxic chemotherapy. Upregulation of programmed death 1 (PD-1) and indoleamine 2,3- dioxygenase 1 (IDO1) enzyme may be therapeutically relevant in metastatic UC. Pembro is a PD-1 inhibitor effective in treatment of locally advanced/metastatic UC in cisplatin-ineligible and platinum-refractory patients. Epacadostat is a potent and highly selective oral inhibitor of IDO1. A recent phase 1/2 trial of pembro plus epacadostat (ECHO-202/KEYNOTE-037, NCT02178722) yielded encouraging efficacy and safety data in patients with advanced UC. **Methods:** KEYNOTE-672/ECHO-307 (NCT03361865) is a randomized, active-controlled, double-blind, global phase 3 trial conducted to evaluate efficacy and safety of first-line pembro in combination with epacadostat or placebo in cisplatin-ineligible patients with advanced/metastatic UC. Eligibility criteria include age $\geq$18 years; confirmed unresectable/metastatic UC of the urinary tract; ineligible for cisplatin-based therapy; no prior systemic chemotherapy for unresectable/metastatic UC (neoadjuvant/adjuvant treatment with platinum-containing chemotherapy with recurrence $>$ 12 months permitted); ECOG performance status 0-2; and available tumor sample for PD-L1 analysis. Patients will be randomly assigned 1:1 to receive pembro 200 mg IV Q3W plus epacadostat 100 mg orally twice daily (continuously) or pembro plus placebo. Randomization will be stratified by Bajorin risk score (0, 1, 2) and PD-L1 expression (combined positive score $\geq$10 or $<$ 10). Treatment will continue until disease progression, unacceptable toxicity, or completion of 35 pembro infusions. Imaging will be performed every 9 weeks for first 12 months and every 12 weeks thereafter. Adverse events will be assessed per NCI CTCAE, version 4.0. Dual primary end points are progression-free survival per blinded independent central review and overall survival. Secondary end points include objective response rate, patient-reported outcomes, and safety. Target enrollment is 650 patients. Clinical trial information: NCT03361865.

TPS4588 **Poster Session (Board #413a), Sat, 8:00 AM-11:30 AM**

A phase 3, open-label, randomized study of nivolumab plus ipilimumab or standard of care (SoC) vs SoC alone in patients (pts) with previously untreated unresectable or metastatic urothelial carcinoma (mUC; CheckMate 901). *First Author: Matt D. Galsky, Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY*

Background: Cisplatin-containing regimens have been SoC for mUC for nearly 40 years, but durable responses are rare with such treatments. Furthermore, a large proportion of pts with unresectable/mUC are ineligible for cisplatin therapy. Treatment approaches conferring longer-term disease control and extending to broader mUC pt populations are urgently needed. Recently, the programmed death-1 (PD-1) inhibitor, nivolumab, induced durable responses in pts with unresectable/mUC progressing despite platinum-based chemotherapy, and nivolumab combined with ipilimumab (a CTLA-4 inhibitor) demonstrated acceptable safety and clinical activity. This phase 3 study will evaluate nivolumab + ipilimumab and nivolumab + SoC vs SoC in previously untreated pts with unresectable/mUC (NCT03036098). **Methods:** Key inclusion criteria: cisplatin-eligible and -ineligible pts with measurable disease, no prior systemic chemotherapy for unresectable/mUC, and evaluable tumor biopsy. Key exclusion criteria: active brain metastases, autoimmune disease, and prior treatment with drugs specifically targeting T-cell co-stimulation or checkpoint pathways. Cisplatin-eligible and -ineligible pts will be randomized 1:1 to arm A (nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks up to 4 doses, followed by nivolumab 480 mg every 4 weeks until disease progression or unacceptable toxicity) or arm B (gemcitabine-cisplatin or gemcitabine-carboplatin for up to 6 cycles). Additional cisplatin-eligible pts will be randomized to arm C (nivolumab 360 mg + gemcitabine-cisplatin every 3 weeks for up to 6 cycles, followed by nivolumab 480 mg) or arm D (gemcitabine-cisplatin for up to 6 cycles). Stratification factors: PD-1 ligand 1 status, cisplatin eligibility, and liver metastasis. Co-primary endpoints: overall and progression-free survival (OS and PFS) by blinded independent central review (BICR) in cisplatin-ineligible pts receiving nivolumab + ipilimumab vs SoC, and PFS by BICR in cisplatin-eligible pts receiving nivolumab + SoC vs SoC. Enrollment began March 2017 with a target of ~897 pts. Clinical trial information: NCT03036098.

TPS4589 **Poster Session (Board #413b), Sat, 8:00 AM-11:30 AM**

IMvigor130: A randomized, phase III study evaluating first-line (1L) atezolizumab (atezo) as monotherapy and in combination with platinum-based chemotherapy (chemo) in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC). *First Author: Matt D. Galsky, Icahn School of Medicine at Mount Sinai/Tisch Cancer Institute, New York, NY*

Background: Platinum-based chemo is the standard of care for most pts with untreated mUC, although clinical outcomes remain poor. Atezo (anti–PD-L1) was approved in the United States, European Union and elsewhere as monotherapy in both the 1L cisplatin (cis)–ineligible and post-platinum settings based on the single-arm, Phase II IMvigor210 trial. Data from other tumor types (e.g., NSCLC and TNBC) suggest that atezo may be tolerable when combined with chemo. Here we describe IMvigor130, a Phase III trial designed to evaluate the efficacy and safety of 1L atezo given alone or in combination with platinum-based chemo vs placebo and chemo, in pts with locally advanced or mUC. **Methods:** Across 35 countries, IMvigor130 (NCT02807636) is enrolling ≈ 1200 pts with histologically documented advanced or mUC (T4b, any N; or any T, N2-3; M1, stage IV) of the bladder, urethra, renal pelvis or ureters who have not received prior chemo for advanced disease. Eligible pts have measurable disease (per RECIST v1.1), ECOG PS 0-2 and a tissue sample for PD-L1 testing (VENTANA SP142 IHC assay). IMvigor130 was initially designed to enroll only cis-ineligible pts but was amended to include all platinum-eligible pts. Pts are randomized 1:1:1 to: (A) atezo + chemo (gemcitabine [gem] + cis or carboplatin [carbo]), (B) atezo alone or (C) placebo + chemo at the following doses (starting day 1 of a 21-day cycle): atezo (or placebo) 1200 mg IV q3w, gem 1000 mg/m^2 on days 1 and 8, carbo AUC 4.5 q3w, cis 70 mg/m^2 q3w. Atezo and chemo are administered, in the absence of unacceptable toxicity, until RECIST v1.1 progressive disease. Randomization is stratified by PD-L1 status on immune cells, number of Bajorin risk factors or liver metastases and investigator's chemo choice. The co-primary endpoints are PFS and OS in Arm A vs Arm C in the ITT population and OS in Arm B vs Arm C in the ITT population. Key secondary efficacy endpoints include investigator-assessed ORR, DOR and PFS per RECIST v1.1 (for atezo vs placebo + chemo arms). Safety, biomarkers and other exploratory endpoints will also be evaluated. Clinical trial information: NCT02807636.

TPS4590 **Poster Session (Board #414a), Sat, 8:00 AM-11:30 AM**

EV-201 Study: A single-arm, open-label, multicenter study of enfortumab vedotin for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor therapy. *First Author: Jonathan E. Rosenberg, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Most patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC) treated with checkpoint inhibitor immunotherapy (CPI) will fail to achieve a durable response regardless of treatment setting (post-platinum or first-line cisplatin-ineligible). Enfortumab vedotin (EV), an antibody-drug conjugate, delivers the microtubule-disrupting agent monomethyl auristatin E to tumors expressing Nectin-4, which is overexpressed in mUC. Preliminary results from an ongoing phase 1 study of EV (Petrylak ASCO-GU 2018) showed that EV (1.25 mg/kg) was well-tolerated in pts with CPI-treated mUC (n = 67). Fatigue (55%), nausea (48%), and decreased appetite (45%) were the most commonly reported treatment-related AEs. Hyponatremia (n = 4, 6%) was the only AE grade ≥3 (regardless of attribution) in > 5% of the cohort; vomiting (n = 2, 3%) was the only treatment-related AE grade ≥3 occurring in ≥2 pts. Hyperglycemia, a new safety finding, emerged post-database cutoff; the protocol was revised. EV showed a confirmed objective response rate (ORR) of 31% in 55 of 67 evaluable pts (23.5% in pts with baseline liver metastases, n = 17) with most responses ongoing as of 02-Oct-2017. Nine pts with unconfirmed PR are pending response assessment. These encouraging results warrant further investigation in this population. **Methods:** This single-arm, open-label, multicenter phase 2 study (NCT03219333) evaluates the antitumor activity and safety of EV monotherapy in ~120 pts with la/mUC. Pts must have previously received a CPI and either have received prior platinum or be cisplatin-ineligible. Pts must have histologically or cytologically documented transitional cell carcinoma of the urothelium that progressed during or following receipt of most recent therapy. The primary objective is to determine antitumor activity as measured by ORR. Secondary objectives include assessment of duration of response, disease control rate, PFS, OS, and safety/tolerability. Pts must have tumor tissue available for exploratory analyses. Response is assessed per RECIST v1.1. Study enrollment began in Sep 2017. Clinical trial information: NCT03219333.

TPS4591 **Poster Session (Board #414b), Sat, 8:00 AM-11:30 AM**

Phase II randomized study of first line avelumab with carboplatin-gemcitabine versus carboplatin-gemcitabine alone in patients with metastatic urothelial carcinoma ineligible for cisplatin-based therapy. *First Author: Alejo Rodriguez Vida, Hospital del Mar, Barcelona, Spain*

Background: Cisplatin-based chemotherapy is standard first line treatment for metastatic urothelial carcinoma (mUC). However, around 50% of patients are ineligible for cisplatin due to poor performance status or comorbidities. For these cases, carboplatin-based combinations are valid alternative options, although they are associated with inferior survival. Additional new strategies for cisplatin-ineligible patients are therefore urgently needed. Recently, excellent clinical activity has been reported with immune checkpoint inhibitors as monotherapy for cisplatin-ineligible patients. The purpose of this study is to test the safety and efficacy of avelumab (anti PD-L1 therapy) given pre-emptively and combined with carboplatin-gemcitabine (carbo/gem) followed by maintenance avelumab. Priming the chemotherapy response giving immunotherapy first could enhance the overall response of the combination and prevent the detrimental effect of chemotherapy on immune cells. Up regulation of PD-L1 by chemotherapy could also enhance the immunotherapy efficacy. **Methods:** This is a multicenter, randomized, open label phase II study evaluating safety and efficacy of sequencing 2 cycles of induction avelumab prior to combining carboplatin-gemcitabine plus avelumab for 6 cycles, followed by avelumab maintenance, compared to carbo/gem alone. Eligibility criteria include patients with mUC, no prior systemic therapy, ineligibility for cisplatin and adequate organ function. Patients will be stratified by the presence/absence of visceral metastasis and ECOG 0-1 versus 2. Primary endpoint of the study is objective response rate (ORR). Secondary endpoints include progression free survival, overall survival and safety. Exploratory endpoints include potential immunologic and genomic predictive biomarkers. For sample size calculation, we hypothesized that the ORR with the combination will be ≥45%, compared to 30% with standard carbo/gem. A sample of 80 patients will provide a probability of 0.9 of confirming our hypothesis, based on a Simon randomised phase II design. The trial is open to accrual. Clinical trial information: NCT03390595.

TPS4592 **Poster Session (Board #415a), Sat, 8:00 AM-11:30 AM**

ATLAS: A phase 2, open-label study of rucaparib in patients (pts) with locally advanced or metastatic urothelial carcinoma (mUC). *First Author: Petros Grivas, University of Washington, Seattle, WA*

Background: There are limited treatment options for pts with mUC that has progressed during or after platinum-based chemotherapy and/or immune checkpoint inhibitors (ICIs), emphasizing the need for new therapies. Analysis of The Cancer Genome Atlas bladder cancer dataset suggests that approximately 60% of bladder cancer tumors have homologous recombination deficiency (HRD). Poly(ADP-ribose) polymerase inhibitors (PARPis) have demonstrated activity in tumors with HRD. In the United States, the PARPi rucaparib is approved for the treatment of pts with deleterious *BRCA* mutation (germline/somatic) associated advanced ovarian cancer treated with ≥2 chemotherapies. We hypothesize that PARP inhibition may have antitumor activity in mUC, particularly in tumors with HRD. The ATLAS (NCT03397394) trial will evaluate the efficacy and safety of rucaparib in pts with locally advanced or mUC previously treated with platinum-based chemotherapy and/or ICIs. **Methods:** Eligible pts must have measurable disease per RECIST v1.1, adequate organ function, and radiographic progression after 1–2 prior standard-of-care regimens. Confirmation of HRD status before enrollment is not required, but fresh tumor tissue or recently obtained archival tissue is mandatory for HRD profiling. Prior PARPi treatment is an exclusion. All pts will receive 600 mg rucaparib orally BID until disease progression or other reason for discontinuation. The primary endpoint is confirmed objective response rate (investigator-assessed per RECIST v1.1) in both HRD-positive (signature based on tumor genomic loss of heterozygosity) and intent-to-treat populations. Secondary endpoints include overall survival, progression-free survival, response duration, safety, and pharmacokinetics. Exploratory endpoints include evaluation of molecular biomarkers associated with response and resistance to rucaparib, including changes in plasma and tumor samples, and circulating tumor DNA. Patients are being enrolled in 6 countries, with a target enrollment of 200 pts. The study has > 90% power to reject the null hypothesis (P= 0.10) at a 5% significance level if the true response rate for rucaparib is 20%. Clinical trial information: NCT03397394.

TPS4593 **Poster Session (Board #415b), Sat, 8:00 AM-11:30 AM**

A phase I-II study to evaluate safety and efficacy of the combination of niraparib plus cabozantinib in patients with advanced kidney/urothelial carcinoma. *First Author: Daniel E. Castellano, Hospital 12 de Octubre, Madrid, Spain*

Background: Niraparib (N) is an orally available and selective poly(ADP-ribose) polymerase (PARP)-1/-2 inhibitor approved for maintenance treatment of patients (pt) with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to platinum-based chemotherapy (CT). Cabozantinib (C) is a tyrosine kinase (TK) inhibitor with activity against TKs including VEGFR2, MET and AXL, approved on kidney cancer pt after TK failure, that has demonstrated clinical activity in heavily pretreated, advanced UC pt. c-Met receptor TK is activated in urothelial carcinoma (UC) cells. c-Met activity can decrease response to PARP inhibitors, whereas treatment with c-Met inhibitors renders cells more sensitive to PARP inhibition. UC pt with tumors overexpressing c-Met may benefit from the combination of c-Met and PARP inhibitors. This multicenter, open-label phase (ph) I-II study (NCT03425201) is to explore the maximum-tolerated dose (MTD) of N + C combination in pt with advanced genitourinary malignancies (UC and kidney cancer) follow by a preliminary efficacy of the combination in advanced UC. **Methods:** Eligible pt have confirmed histopathology of UC or clear cell renal cell carcinoma, advanced or metastatic disease, age ≥18 years, ECOG PS ≤1, progressive disease after platinum-based CT, measurable lesions, no prior therapy with PARP or c-Met inhibitors and adequate bone marrow, liver and renal functions. The ph I portion is enrolling ≈24 pt to identify the MTD proposed to use in a ph II (RP2D). Pt will receive N and C p.o. once daily in 28-day cycles: Dose level 1 (DL1) N/C 100/20 mg; DL2 200/20 mg; DL3 200/40 mg; DL4 200/60 mg. Pt will be accrued to each dose level in cohorts of 6 pt until the MTD is achieved (the highest dose at which ≤1 out of 6 pt experience a dose-limiting toxicity [DLT]). DLT will be evaluated during the first 2 cycles. The ph 2 portion will enroll 51 UC pt to receive the RP2D. Tumors will be assessed per RECIST v1.1. Endpoints of the ph 2 are 6-month PFS (primary), overall response rate, disease control rate, duration of response, PFS and OS. Tissue and plasma sample will be collected for translational study. Clinical trial information: NCT03425201.

TPS4594 **Poster Session (Board #416a), Sat, 8:00 AM-11:30 AM**

SPIRE: A phase Ib/randomised IIa open label clinical trial combining guadecitabine (SGI-110) with cisplatin and gemcitabine chemotherapy for solid malignancies including bladder cancer. *First Author: Simon J. Crabb, Southampton Experimental Cancer Medicine Centre, Southampton, United Kingdom*

Background: Cisplatin based chemotherapy is a standard of care therapy for urothelial bladder cancer for palliative first line treatment of advanced/metastatic disease or radical neoadjuvant treatment of localized muscle invasive disease. However, cisplatin resistance, associated with disease progression or relapse, is common and remains a critical barrier to therapeutic advance. Pre-clinical data suggest cisplatin resistance in bladder cancer, and other cancers, might be avoided by co-administration of a DNA hypomethylating agent. **Methods:** SPIRE is a phase Ib/IIa trial evaluating whether the DNA methyltransferase inhibitor SGI-110 (guadecitabine), in combination with gemcitabine and cisplatin chemotherapy (GC), is safe and biologically effective. It incorporates a dose escalation phase in advanced/metastatic solid tumors, including bladder cancer, followed by a randomized dose expansion phase as neoadjuvant treatment prior to cystectomy for bladder cancer (T2-4a N0 M0). The primary objective is to determine a recommended phase II dose (RP2D) of SGI-110 in combination with GC, using pre-defined dose limiting toxicity criteria assessed by CTCAE v4.03, and a biologically effective dose based on serum DNA LINE-1 methylation and hemoglobin F re-expression status. Dose Escalation Phase: Treatment comprises GC (G 1000 mg/m^2, IVI, days 8 and 15; C 70 mg/m^2, IVI, day 8), and SGI-110 (SC, days 1-5), for up to 6 cycles of 21 days. Up to 6 patients are enrolled in each of up to 4 SGI-110 dose level cohorts utilizing a 'rolling 6' design. Dose Expansion Phase: 20 patients will be randomized 1:1 to GC, or GC + SGI-110 at the established RP2D, to expand safety and pharmacodynamic endpoint data. SPIRE is coordinated by the CRUK Southampton Clinical Trials Unit and is currently recruiting to a 3rd dose escalation cohort through the UK Experimental Cancer Medicine Centre (ECMC) network. It was developed through the CRUK Combinations Alliance. Funding: Cancer Research UK (C9317/A19903) and Astex Pharmaceuticals. Sponsor: University Hospital Southampton NHS Foundation Trust. Clinical trial information: ISRCTN16332228.

TPS4595 **Poster Session (Board #416b), Sat, 8:00 AM-11:30 AM**

PECULIAR: An open label, multicenter, single-arm, phase 2 study of neoadjuvant pembrolizumab (PEM) and epacadostat (EPA), preceding radical cystectomy (Cy), for patients (pts) with muscle-invasive urothelial bladder cancer (MIUBC). *First Author: Andrea Necchi, Istituto Nazionale dei Tumori, Milan, Italy*

Background: MIUBC is a systemic disease and > 40% of pts develop recurrence after Cy. Despite neoadjuvant chemotherapy yields Level 1 evidence, it is underutilized worldwide and a small survival improvement is deemed over Cy alone. PEM is an EMA and FDA-approved therapy for metastatic UC after platinum failure or for cisplatin-ineligible pts. EPA, an anti-IDO1 agent, combined with PEM, safely improved the response-rate in UC in phase 1 trial. Our hypothesis is that PEM+EPA, given neoadjuvantly, could further improve downstaging MIUBC. **Methods:** Pts with T2-T3b N0 UC with residual disease after transurethral resection of the bladder (TURB, surgical opinion, cystoscopy or radiological presence) will receive 3 cycles of PEM 200mg intravenously, q3 weekly. EPA will be orally taken at the dose of 100 mg BID, from d1 until 10 days before Cy. Cy should be performed within 3 weeks of the last PEM dose. Computed tomography (CT) scan, ^{18}FDG-PET/CT scan, and multiparametric bladder MRI (mpMRI) will be done during screening and before Cy to stage and evaluate response. After Cy, pts will be managed according to EAU guidelines. Adjuvant anti PD-1 therapy is not allowed. PD-L1 status will be assessed using Dako anti-PD-L1 antibody (clone 22C3), relying on the combined positivity score (CPS). Pathologic complete response (pT0) is the primary endpoint. All pts enrolled who receive at least 1 cycle of study drug will be included in the ITT analysis. The H_1 is pT0≥25% and H_0 pT0≤15%. A MinMax 2-stage design will be used to estimate the number of pts required. Out of 71 total pts, with the first stage of 43 pts, ≥6 pT0 will be required in the first stage, and ≥14 pT0 in the whole study population. Correlative research on blood samples will include immune-cell profiling and cytokine assessment. In tumor samples, genomic analyses will be done with FoundationONE test (Foundation Medicine Inc.). Tumor mutational burden (TMB) will be determined on 1.1 Mbp of sequenced DNA and reported as mutations (mut) per megabase (Mb) and microsatellite instability (MSI) will determined on 114 loci (EudraCT number 2017-002379-24). Clinical trial information: 2017-002379-24.

TPS4596 Poster Session (Board #417a), Sat, 8:00 AM-11:30 AM

P3BEP (ANZUP 1302): An international randomised phase 3 trial of accelerated versus standard BEP chemotherapy for adult and paediatric male and female patients with intermediate and poor-risk metastatic germ cell tumours (GCTs). *First Author: Peter S. Grimison, Chris O'Brien Lifehouse, Sydney, Australia*

Background: Bleomycin, etoposide, cisplatin (BEP) given 3-weekly x 4 remains standard 1st line chemotherapy for metastatic GCTs. Acceleration of standard regimen with shorter cycle lengths has improved cure rates in other cancers. This is the first international randomised clinical trial for intermediate and poor-risk metastatic extracranial GCTs involving both adult and paediatric age group males and females. We aim to determine if accelerated BEP is superior to standard BEP. **Methods:** DESIGN: Open label, randomised, stratified multicentre, 2 stage, phase 3 trial. Primary endpoint for stage I (n = 150) is complete response rate (RR), and for entire trial (n = 500) is progression free survival (PFS). SAMPLE SIZE: 150 and 500 patients gives > 80% power to detect a 20% improvement in RR and 7% absolute improvement in 2yr PFS, respectively. POPULATION: Males and females aged 11-45 years with intermediate or poor-risk metastatic GCTs of the testis, ovary, retroperitoneum or mediastinum for 1st line chemotherapy. TREATMENT: Randomisation 1:1 to 4 cycles of "standard BEP" or "accelerated BEP": cisplatin 20mg/m^2 IV D1-5; etoposide 100mg/m^2 IV D1-5; bleomycin 30000 IU IV weekly; and pegylated G-CSF SC D6 or Filgrastim daily; given every 3 weeks or every 2 weeks respectively. Accelerated BEP arm receives 4 additional weekly doses of bleomycin. ASSESSMENTS: Response assessments at 30 day safety assessment, and 6 months from randomisation or after all post-chemotherapy intervention is completed. Regular follow-up up to 5 years, then annually. Archival tumour tissue and baseline blood collected for translational substudies. STATUS: 25 sites open in ANZ, 4/21 sites open in UK (led by Cambridge Clinical Trials Unit), 46 patients recruited by February 2018. International collaboration with USA (led by Children's Oncology Group) is confirmed with sites expected to open by mid2018 and more sites sought for stage 2. Clinical trial information: NCT02582697.

TPS4597 Poster Session (Board #417b), Sat, 8:00 AM-11:30 AM

PROSPER: A phase III randomized study comparing perioperative nivolumab (nivo) vs. observation in patients with localized renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN 8143). *First Author: Lauren Christine Harshman, Dana-Farber Cancer Institute, Boston, MA*

Background: As of 2018, there is no standard adjuvant systemic therapy that increases overall survival (OS) over surgery alone for patients with non-metastatic RCC. Nivolumab (nivo), an antibody against PD-1, improves overall survival in metastatic RCC and is well tolerated. Mouse solid tumor models have revealed an OS benefit to a short course of PD-1 blockade when given neoadjuvantly compared to adjuvantly. Two ongoing phase 2 studies of perioperative nivo in M0 RCC patients are showing preliminary feasibility and safety with no surgical delays (NCT02575222; NCT02595918). The PROSPER RCC trial will examine if administering perioperative nivo with radical or partial nephrectomy can increase cures, time to recurrence and survival in patients with high risk localized and locally advanced RCC. **Methods:** This global, unlinded, phase 3 National Clinical Trials Network study is accruing patients with clinical stage ≥T2 or node positive M0 RCC of any histology. Tumor biopsy prior to randomization is mandatory to ensure RCC and will also permit unparalleled correlative science. The investigational arm will receive two doses of nivo prior to surgery followed by adjuvant nivo for 9 months (q2 wks x 3 mo followed by q4 wks x 6 mo). The control arm will receive standard of care surgical resection followed by observation. Randomization will be stratified by clinical T stage, node positivity, and histology. With 766 patients, there is 84.2% power to detect a 14% absolute benefit in recurrence-free survival (RFS) at 5 years assuming the ASSURE historical control of ~56% to 70% (HR = 0.70). The study is also powered to evaluate a significant increase in overall survival (HR 0.67). Safety, feasibility, and quality of life endpoints critical to adjuvant therapy considerations will be evaluated. PROSPER RCC exemplifies team science with a wealth of embedded correlative work aimed at investigating the impact of the baseline immune milieu, the changes induced by neoadjuvant anti-PD-1 priming, and how both correlate with clinical outcomes. Clinical trial information: NCT03055013.

TPS4598 Poster Session (Board #418a), Sat, 8:00 AM-11:30 AM

A phase 3, randomized, open-label study of nivolumab combined with cabozantinib vs sunitinib in patients with previously untreated advanced or metastatic renal cell carcinoma (RCC; CheckMate 9ER). *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: Over the past decade, treatment options for advanced RCC have evolved to include multiple agents targeting the vascular endothelial growth factor (VEGF) pathway. In addition, the recent innovation of treating cancer with immunotherapy has further expanded the therapeutic armamentarium. Biomarker studies suggest that promotion of an immune suppressive tumor microenvironment can contribute to anti-VEGF therapy resistance and point to a rationale for combining anti-VEGF therapy with immunotherapy. Cabozantinib, a tyrosine kinase inhibitor with targets including VEGF receptor, MET and the TAM receptor family has shown immunomodulatory properties suggestive of synergistic effects with immune checkpoint inhibitors. Indeed, in a recent phase 1 study, combination of the programmed death-1 (PD-1) inhibitor nivolumab with cabozantinib showed encouraging antitumor activity in pretreated patients with metastatic RCC and other advanced genitourinary tumors (Nadal et al. ASCO GU 2018). This phase 3 study will assess nivolumab plus cabozantinib vs sunitinib in previously untreated patients with advanced or metastatic RCC (NCT03141177). **Methods:** Key inclusion criteria: Measurable disease with a clear-cell component, no prior systemic therapy for RCC, evaluable tumor biopsy, and age ≥18 years. Key exclusion criteria: Active CNS metastases and autoimmune disease. Patients will be randomized 1:1 to either nivolumab plus cabozantinib or sunitinib. Treatment will continue until disease progression or unacceptable toxicity (maximum nivolumab treatment of 2 years). Stratification factors: International Metastatic RCC Database Consortium (IMDC) risk score, PD-1 ligand 1 (PD-L1) tumor expression, and geographic region. Primary endpoint: Progression-free survival by blinded independent central review (BICR) in all randomized patients; secondary endpoints: Overall survival and objective response rate by BICR in all randomized patients, and safety/tolerability in all treated patients. Enrollment began August 2017 with a target of 580 randomized patients. Clinical trial information: NCT03141177.

TPS4599 Poster Session (Board #418b), Sat, 8:00 AM-11:30 AM

KEYNOTE-564: A phase 3, randomized, double blind, trial of pembrolizumab in the adjuvant treatment of renal cell carcinoma. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

Background: The typical management for renal cell carcinoma (RCC) is nephrectomy. Despite this, patients with intermediate- to high-risk advanced disease can experience relapse with metastatic, usually incurable, disease. Adjuvant therapies are needed for patients at risk for recurrence after nephrectomy. Upregulation of the programmed death 1 (PD-1) pathway is associated with poor prognosis in RCC, and drugs to target the PD-1 pathway have shown efficacy and reasonable safety in metastatic RCC. Therefore, the PD-1 pathway may represent a novel target to prevent disease recurrence. The randomized, double-blind, placebo-controlled phase 3 KEYNOTE-564 trial (NCT03142334) is designed to evaluate the efficacy and safety of pembrolizumab in the adjuvant treatment of RCC after nephrectomy. **Methods:** Key inclusion criteria include age ≥18 years, histologically confirmed clear cell RCC of intermediate-high risk (pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0 M0), high risk (pT4, any grade, N0 M0; or pT any stage, any grade, N+ M0), or M1 NED; no prior systemic therapy for advanced RCC; negative surgical margins; Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; and tumor sample available for biomarker analyses. Patients will be randomly assigned 1:1 to receive pembrolizumab 200 mg or placebo every 3 weeks by intravenous infusion. Treatment will continue until disease recurrence, treatment discontinuation, or the completion of 17 cycles. Imaging will be performed every 12 weeks. The primary end point is disease-free survival (DFS) per investigator assessment. The secondary end point is overall survival (OS). Additional secondary analyses include safety and tolerability, pharmacokinetic parameters, antidrug antibodies, and DFS and OS per PD-L1 expression status. Biomarkers that may be associated with response will be evaluated as an exploratory objective. Recruitment will continue until ~950 patients are enrolled. Clinical trial information: NCT03142334.

TPS4600 **Poster Session (Board #419a), Sat, 8:00 AM-11:30 AM**

Optimized management of nivolumab (NIVO) and ipilimumab (IPI) in advanced renal cell carcinoma (OMNIVORE): A response-based phase II study. *First Author: Xiao X. Wei, Dana-Farber Cancer Institute, Boston, MA*

Background: CheckMate 025 established NIVO as a standard of care (SOC) option for advanced clear cell RCC (ccRCC) after prior antiangiogenic therapy. The combination of IPI plus NIVO is anticipated to become a new SOC option for intermediate/poor risk patients (pts) with treatment-naïve advanced ccRCC based on CheckMate 214. Outstanding questions include optimal treatment duration in responders, ability of IPI to convert NIVO non-responders to responders, activity of these agents in non-clear cell RCC (nccRCC), and discovery of predictive biomarkers. **Methods:** This phase II, open-label, non-randomized trial enrolls treatment-naïve or previously treated pts with advanced ccRCC or nccRCC (NCT03203473). Pts previously treated with immune checkpoint inhibitor(s) are excluded. All pts start NIVO alone and subsequent management is based on RECIST response within the first 6 months of NIVO. Pts with confirmed partial response (PR) or complete response (CR) discontinue NIVO and are observed. At progression, NIVO is reinitiated, and if further progression, 2 doses of IPI are added to NIVO (Arm A). Pts with stable disease (SD) or progressive disease (PD) on initial NIVO will receive 2 doses of IPI with NIVO continuation until PD (Arm B). NIVO monotherapy dose is 240mg Q2W, and 3mg/kg Q3W when given with IPI. IPI dose is 1mg/kg Q3W. The co-primary endpoints are proportion of pts with durable CR/PR at 1-year (yr) after NIVO discontinuation (Arm A) and proportion of pts with SD or PD on NIVO alone who convert to PR/CR at 1-yr after adding IPI to NIVO (Arm B). Enrollment of 17 pts is planned for Arm A to achieve 90% power to assess a true 1-yr PR/CR rate of $\geq$35% vs a null PR/CR rate of 10%. Enrollment of 41 pts is planned for Arm B to achieve 90% power to assess a true 1-yr conversion rate of 20% vs a null conversion rate of 5%. Fresh tumor biopsy is required at baseline and optional at progression time points. Correlative studies are tightly integrated including circulating immune cells, cytokines/chemokines, circulating tumor cells, cfDNA, tumor immunohistochemistry, bulk genomic profiling, and bulk and single-cell transcriptomic analysis. As of February 2018, 18 of planned 58 patients have been accrued. Clinical trial information: NCT03203473.

TPS4601 **Poster Session (Board #419b), Sat, 8:00 AM-11:30 AM**

CANTATA: A randomized phase 2 study of CB-839 in combination with cabozantinib vs. placebo with cabozantinib in patients with advanced/metastatic renal cell carcinoma. *First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Glutamine utilization is a metabolic pathway upregulated in renal cell carcinoma (RCC) and important for RCC tumor cell proliferation and survival. CB-839 is a first-in-class, potent, oral inhibitor of the mitochondrial enzyme glutaminase (GLS) that controls a critical step in tumor cell utilization of glutamine. In preclinical RCC models, CB-839 demonstrated synergistic anti-tumor activity when combined with cabozantinib, a VEGFR/MET inhibitor. A phase 1 study cohort of CB-839 plus cabozantinib as 2L+ therapy showed encouraging safety and efficacy results, with 40% overall response rate (ORR; RECIST v1.1) and 100% disease control rate in patients with clear cell advanced/metastatic RCC (mRCC). These findings prompted the initiation of a randomized phase 2 study comparing CB-839 plus cabozantinib vs. placebo plus cabozantinib in patients with clear cell mRCC. **Methods:** This international, randomized, double-blind, placebo-controlled, multi-center study (NCT03428217) will enroll ~300 patients with clear cell mRCC. Eligible patients will have received 1-2 prior lines of systemic therapy for mRCC including $\geq$1 anti-angiogenic therapy or the combination of nivolumab + ipilimumab. Other eligibility criteria include KPS $\geq$70%, measurable disease (RECIST v1.1), and no prior cabozantinib (or other MET inhibitor). Patients will be randomized 1:1 to receive CB-839 (800 mg twice daily per oral [PO] route) or placebo in combination with cabozantinib (60 mg daily PO) in 28-day cycles until disease progression or unacceptable toxicity. Patients will be stratified by prior PD-1/PD-L1 inhibitor therapy (Y/N) and IMDC prognostic risk group (favorable vs intermediate vs poor). The primary endpoint is progression-free survival (PFS; RECIST v1.1) by blinded independent radiology review; secondary endpoints are investigator-assessed PFS and overall survival. Safety, disease responses per RECIST, and quality of life will also be assessed. This important study will contribute to understanding the efficacy and safety profile of CB-839, a first-in-class metabolic inhibitor, in combination with cabozantinib in patients with mRCC. Clinical trial information: NCT03428217.

TPS4602 **Poster Session (Board #420a), Sat, 8:00 AM-11:30 AM**

NIVES study: A phase II trial of nivolumab (NIVO) plus stereotactic body radiotherapy (SBRT) in II and III line of patients (pts) with metastatic renal cell carcinoma (mRCC). *First Author: Cristina Masini, Medical Oncology Unit, Clinical Cancer Center, AUSL-IRCCS Reggio Emilia, Reggio Emilia, Italy*

Background: Despite recent advances in drug therapy, pts with mRCC have about a 10% 5-year survival rate. Several preclinical studies have documented an increase in peripheral antitumour immunity following radiation, a phenomenon known as the abscopal effect. NIVO is an anti-programmed cell death-1 (PD-1) monoclonal antibody that blocks tumour growth in different ways by targeting certain cells. It might work even better when combined with SBRT. The irradiated tumour cell death can enhance antitumor immunity by inducing antigen expression on tumour cells and activating lymphocytes. The aim of the study is to evaluate whether the antitumour immunity of NIVO can be enhanced by SBRT. **Methods:** This is an ongoing phase II, single arm, multicentre study in pts with mRCC with progression disease after $\leq$ 2 prior anti-angiogenic therapies and with 2 or more measurable non-brain metastatic sites, at least one of which potentially suitable for treatment with SBRT. All pts will receive hypofractionated radiation at a lesion at a dose and schedule of 10 Gy/3 fractions respectively after 7 days from the first infusion of NIVO. NIVO will be given as flat dose of 240 mg in intravenous infusion beginning on day 1 every 14 days for 6 months, then switch to 480 mg q4-weekly in responding (CR, PR, SD) pts until PD or unacceptable toxicity. The primary objective is to evaluate the activity of this combination in terms of Objective Response Rate (ORR), the best response recorded on the ITT population according to RECIST v1.1. Our hypothesis is that treatment with NIVO plus SBRT compared to NIVO monotherapy can increase the ORR from 25% to 40%. Secondary endpoints are progression free survival (PFS), overall survival (OS), ORR of irradiated and non-irradiated metastases, duration of response and safety profile. An Exploratory Project also identifies molecular basis of synergistic effect of SBRT and immunotherapy, potential mechanisms of resistance to checkpoint inhibitors. Twenty of the planned 68 pts were enrolled from July 2017 to January 2018. Study duration will be 12 months for the accrual and 36 months for the follow-up. Clinical trial information: EudraCT Num 2016-003032-20.

TPS4603 **Poster Session (Board #420b), Sat, 8:00 AM-11:30 AM**

CABOPRE: Phase II study of cabozantinib prior to cytoreductive nephrectomy (CN) in locally advanced and/or metastatic renal cell carcinoma (mRCC). *First Author: Guillermo de Velasco, Department of Medical Oncology, University Hospital 12 de Octubre, i+12, Madrid, Spain., Madrid, Spain*

Background: Cabozantinib is a small molecule tyrosine kinase inhibitor (TKI) of VEGFR2, MET and AXL that has shown a statistically significant improvement for mRCC patients in all three endpoints of clinical efficacy (objective response rate [ORR], progression free survival [PFS], and overall survival [OS]) in a phase III randomized trial compared to everolimus, as well as a significant clinical benefit in PFS and ORR over sunitinib as first-line therapy in patients with IMDC intermediate- or poor-risk. Although no robust evidence is available, CN remains as the standard of care in patients who will be treated with VEGF TKI. CABOPRE is a multicenter, non-randomized, uncontrolled phase II trial that evaluates the efficacy and safety of cabozantinib as perioperative therapy in patients with advanced RCC who are candidates for CN. **Methods:** Eligible patients are aged $\geq$ 18 years, mRCC with a component of clear cell, suitable for CN with acceptable risk for surgery, PS 0-1, no prior systemic therapy. Cabozantinib 60mg PO QD is administered for 12 weeks before CN (cabozantinib is stopped at least 72 hours before CN). A 14-day treatment break is required after surgery and then cabozantinib is continued until progression disease or toxicity. The primary endpoint is ORR by RECIST 1.1 at 12 weeks after initiation of therapy. Secondary endpoints include PFS at 12 months and OS. Based on Simon two-stage minimax design (p0 = 0.25, p1 = 0.45, alpha = 0.05, power = 90%) up to 50 patients will be recruited consecutively. Tumor biopsies and peripheral blood will be collected to assess changes in tumor microenvironment at 3 different time points: 1) at baseline, prior to initiation of cabozantinib, 2) before cytoreductive nephrectomy 3) at disease progression. Biomarkers study will include, but not limited to the expression of c-MET and AXL in exosomes derived from tumor cells.

TPS4604 Poster Session (Board #421a), Sat, 8:00 AM-11:30 AM

A phase 2, single-arm trial of neoadjuvant axitinb plus avelumab in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). *First Author: Axel Bex, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Surgery is the standard treatment for non-metastatic RCC. Despite curative intent, pts with a high risk of relapse have a 5-year metastasis-free survival rate of only 30 % and prevention of recurrence is an unmet need. In a phase 1b study (JAVELIN Renal 100), the axitinib + avelumab response rates (RR) and safety profile were promising with objective RR of 60 % and toxicity profiles as seen with VEGFR-treatment. The combination is currently being tested in a phase III trial against sunitinib in untreated metastatic RCC. We initiated a neoadjuvant study of axitinib + avelumab in pts with high-risk of relapse (NCT03341845). **Methods:** The study is designed as a open label, single arm, phase 2 trial with a Simon's two-stage design evaluating neoadjuvant axitinib + avelumab followed by complete surgical resection in 40 pts with high-risk non-metastatic clear-cell (cc) RCC. Key inclusion criteria are planned radical or partial nephrectomy with curative intent; biopsy proven ccRCC; clinical high risk defined as cT1b-cT2a grade (G) 4, cT2b G3, cT3a G 3-4, cT3b-cT4 any G cN0 cM0, or cT any cN1 cM0; World Health Organization (WHO) performance status of 0-1, and completely resectable primary tumours. Key exclusion criteria are metastatic disease, corticosteroid or immunosuppressive systemic treatment, active autoimmune disease, prior systemic treatment for RCC including immunotherapy, biologic therapy, investigational therapy or hormonal therapy. Pts receive axitinib 5 mg BID escalated to 10 mg BID if tolerated and avelumab 10 mg/kg iv Q2W for 6 cycles following H1 blockers and acetaminophen every 2 weeks . Pts with a tumour increase from baseline at CT after the first 6 weeks or no change after dose escalation will be taken off trial and undergo surgery. All others will complete 3 months followed by resection. Primary endpoint (ept): Partial RR (RECIST 1.1) following neoadjuvant therapy. Secondary epts: DFS, OS, rate of recurrence, safety, and tolerability. Exploratory epts include investigation of effects on neoangiogenesis, immune infiltrates and MDSC components to support a rationale for the combined use of axitinib and avelumab. Clinical trial information: NCT03341845.

TPS4605 Poster Session (Board #421b), Sat, 8:00 AM-11:30 AM

Vorolanib (CM082), everolimus, and the combination in patients with pretreated metastatic renal cell carcinoma (CONCEPT study): A randomized, phase 2/3, double-blind, multi-center trial. *First Author: Jun Guo, Peking University Cancer Hospital and Institute, Beijing, China*

Background: VEGF and mTOR pathways play key role in the development of renal cell carcinoma (RCC), the combination of agents targeting both VEGF- and mTOR-mediated pathways have been investigated with distinct results. Vorolanib (CM082) is a potent and selective inhibitor of VEGFR and PDGFR. Previous phase 1 study (NCT02577458) found that the combination of vorolanib 200 mg plus everolimus 5mg was associated with manageable toxicity consistent with individual agents and no new safety signals, antitumor activities was also seen in 35.7% patients with RCC patients who progressed on at least one VEGFR TKI therapy. Based on these findings, we conducted the CONCEPT study, a randomized, phase 2/3, double-bind, multicenter trial to assess vorolanib, everolimus, or their combination as second-line treatment in Chinese patients with metastatic RCC. **Methods:** Patients with cytologically or histologically confirmed RCC who had disease progression after one prior VEGFR TKI were eligible for participation in the study. They will be randomized by 1:1:1 ratio to receive matching placebo plus vorolanib or everolimus, or the combination. Randomization was stratified according to the MSKCC risk scores. The sample size was specified assuming a hazard ratio (HR) of 0.60, equating to an expected 6.5 months for everolimus and 10.5 months for vorolanib with or without everolimus. To provide 80% power at a two-sided 5% significance level, and an estimated 20% dropout rate, a total of 390 patients are required. This study is registered as NCT03095040. Progression: This study in conducted in 35 centers in China, so far 32 centers have been activated. Recruitment was started since March 10, 2017, and a total of 101 patients were randomized currently. Clinical trial information: NCT03095040.

5000 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized phase III trial between adjuvant docetaxel and surveillance after radical radiotherapy for intermediate and high risk prostate cancer: Results of SPCG-13 trial. *First Author: Pirkko-Liisa Irmeli Kellokumpu-Lehtinen, Department of Oncology, Tampere University Hospital, Tampere, Finland*

Background: Docetaxel combined with androgen deprivation therapy (ADT) has improved survival in advanced prostate cancer (PCa). This randomized trial evaluates if six courses of docetaxel improves biochemical disease free survival (BDFS) after radical radiotherapy (RT) for intermediate or high risk PCa. **Methods:** : A total of 376 patients were randomised in this multinational phase III study, to receive either 6 cycles of adjuvant docetaxel 75mg/m^2 every 3 weeks without continuous prednisone (Arm A, n = 188) or surveillance (Arm B, n = 188) after RT (NTC006653848). Neoadjuvant/adjuvant ADT was mandatory for all patients. Primary end-point was a rising PSA $\geq$ 2 ng/ml above the nadir PSA value. Intermediate or high risk prostate cancer was defined as T2 with Gleason score (GS) 4+3, PSA $>$ 10; T2, GS 8-10 any PSA; or any T3. Patients were followed for 5 years with PSA every 3 months for two years and thereafter every 6 month. Study power was 89% to detect a difference between groups and the sample size calculation accounted for T2/T3 distribution (12%/15% difference in BDFS was assumed for T2/T3 patients). **Results:** All six cycles were completed in 147 (78.2%) of patients in arm A. Mean age was 66.2 years in Arm A and 66.4 years in ARM B; 75.0 % had T3 disease, 46.3% had GS 8-10. Median follow up was 59.4 months (range 1 to 111 months, one without follow-up). The primary endpoint was reached in 30.7% of patients; 31.0% in Arm A and 30.3% in Arm B. In a Kaplan-Meier analysis there showed no difference between the BDFS curves (p = 0.631) between treatment groups. Febrile neutropenia occurred in 16.1 % of docetaxel patients. No deaths were related to docetaxel treatment. There were 43 deaths during the trial (20 in Arm A and 23 in Arm B) of which 9 and 7 due to PrCa. In a Cox multivariate analysis, GS (p = 0.001) was significant predictor of PSA progression. Hazard Ratio for Arm A (docetaxel) vs Arm B (surveillance) was 1.14 (95% CI 0.79 to 1.64, p = 0.495). **Conclusions:** Adjuvant docetaxel without prednisone did not improve BDFS after radical radiotherapy with ADT for intermediate or high risk prostate cancer. Clinical trial information: NTC006653848.

5001 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Accuracy of ^{68}Ga-PSMA11 PET/CT on recurrent prostate cancer: Preliminary results from a phase 2/3 prospective trial. *First Author: Wolfgang Fendler, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, Munich, CA*

Background: ^{68}Ga-PSMA11 PET/CT provides improved localization of biochemically recurrent prostate cancer. For approval and reimbursement, accuracy needs to be established in a prospective study employing independent lesion validation. **Methods:** In this phase 2/3 prospective trial (NCT02940262), patients with biochemically recurrent prostate cancer after primary prostatectomy (n = 205) or radiation therapy (n = 45) underwent ^{68}Ga-PSMA11 PET/CT. Presence of prostate cancer was recorded on a patient and region base. Regions were prostate bed, pelvis, extra-pelvic, and bone. Lesions were validated in 51% of PET/CT-positive patients by histopathology (n = 33), imaging (n = 62) and/or PSA after targeted radiation therapy (n = 9 patients). PSA response after ^{68}Ga-PSMA11 PET/CT guided focal salvage therapy (surgery/radiotherapy) was recorded in 23 of 25 patients (8% drop out). Endpoints were positive predictive value (PPV), detection rate and outcome. **Results:** PPV validated by histopathology was 85% on a patient base (primary endpoint). PPV as determined by any type of validation was 89% on a patient and 91% on a region base. ^{68}Ga-PSMA11 PET/CT localized recurrent prostate cancer in 197 of 250 (79%) patients; stratified by PSA: 41% for $<$ 0.5 ng/ml (n = 54), 66% for 0.5 to $<$ 1.0 ng/ml (n = 38), 86% for 1.0 to $<$ 2.0 ng/ml (n = 36), 96% for 2.0 to $<$ 5.0 ng/ml (n = 55), and 99% for $\geq$5.0 ng/ml (n = 67). Lesion location was in 35% prostate bed, 61% pelvis, 35% extra-pelvic, and 31% bone. Following focal salvage therapy alone, 18 (78%) patients had a PSA drop of 50% or more, 7 (30%) patients had biochemical complete response (PSA undetectable). **Conclusions:** Using an independent reference standard, we establish high ^{68}Ga-PSMA11 PET/CT PPV for localization of recurrent prostate cancer. PET/CT guided salvage therapy resulted in high biochemical response rates. Pooled multicenter findings will be submitted for a New Drug Application. Clinical trial information: NCT02940262.

5002 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

A randomized study of finite abiraterone acetate (AA) plus leuprolide (LHRHa) versus LHRHa in biochemically recurrent non metastatic hormone naïve prostate cancer (M0HNPC). *First Author: Eleni Efstathiou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Intermittent Androgen Deprivation (ADT) is an acceptable treatment option in M0HNPC with no significant survival difference and improved quality of life versus (vs) continuous. AA improves survival in metastatic HNPC. We hypothesize that AA added to intermittent ADT will improve outcome without delaying testosterone (T) recovery. **Methods:** Patients (Pts) with PSA recurrent, after definitive local treatment, M0HNPC were randomized 1:1 to 8 month AA(1g/qd)+ prednisone (5mg /qd)+LHRHa vs LHRHa. Pts were eligible to cross over upon progression We primarily studied difference in PSA free survival. Secondary endpoints included time to T recovery, safety and associations with clinical/tumor characteristics. Sample size had 93% power to detect 1 year post treatment PSA free survival difference of 20 %. Stratification factors were radical prostatectomy (RPS) vs radiation (EBRT), PSA $\geq$ vs $<$ 10, time to recurrence $\geq$ vs $<$ 3yrs. Rising PSA of 0.2 confirmed by subsequent $>$ 0.2 required after RPS and nadir PSA +2 for prior EBRT. **Results:** 197 of 200 randomized pts were treated (99 AA+LHRHa /98 LHRHa). Median age was 65 (range 42- 85), Performance Status 0, PSA 1 (0.3-33.3 ng/ml), T 346 (160-946 ng/dL). 186 (94%) had undergone RPS. 128 (65 %) had PSA relapse by Jan/18. Pts on 8 month AA+LHRHa had median PSA free survival 28.3 months (range 24.2—35.4) vs 21.1 (19.1-27.2) for LHRHa pts. (HR 0.62; 95 % Confidence Interval 0.44-0.88; p 0.007). Median time to T recovery for AA+LHRHa was 13.1 ms vs 12.9 for LHRHa. AA+LHRHa treatment outcome was favorable regardless of pre-treatment PSA, Gleason Score, pathology, time to relapse from treatment, definitive treatment type, including if RPS +EBRT (57%). No Grade 4 adverse events (AE) or new safety concerns reported. Grade 3 AEs: arterial hypertension 6 (5 AA+LHRHa arm), liver function test elevation 4 (AA+LHRHa arm). Most common AEs were Grade 1 hot flashes (71%) and fatigue (51%) with no difference between arms. **Conclusions:** Findings support that 8 month treatment with Abiraterone Acetate plus LHRHa in M0HNPC improves PSA free survival compared to LHRHa without delay in testosterone recovery or significant safety concerns. Clinical trial information: NCT01786265.

5003 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Olaparib combined with abiraterone in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): A randomized phase II trial. *First Author: Noel Clarke, The Christie and Salford Royal NHS Foundation Trusts, Manchester, United Kingdom*

Background: mCRPC pts with a homologous recombination repair mutation (HRRm) previously showed improved response to the PARP inhibitor olaparib (Lynparza) as monotherapy vs pts without a HRRm (Mateo J *et al*, *NEJM* 2015). We report data from a Phase II, placebo-controlled trial of olaparib combined with the anti-hormonal therapy abiraterone in post-chemotherapy mCRPC pts whose tumors did not need to have a HRRm (NCT01972217). **Methods:** mCRPC pts were randomized (1:1) post-docetaxel to olaparib 300 mg bid (tablets; combination) or placebo (comparator) plus abiraterone (1000 mg od) and treated until disease progression. Primary endpoint was investigator-assessed radiologic progression-free survival (rPFS; RECIST 1.1, PCWG-2). HRRm status was assessed using optional tumor (n = 68), whole-blood and plasma samples. **Results:** 142 pts (median age: 69 yrs) were randomized and treated (both arms, n = 71). Overall, a statistically significant increase in rPFS was seen with the combination vs comparator (Table; *P*= 0.03). A rPFS benefit in the combination arm was suggested irrespective of HRRm status. Median overall survival was 23.3 vs 20.9 mths in the combination vs comparator arms, respectively (HR 0.89, 95% CI 0.581.35). 54% vs 28% of pts, respectively, had grade $\geq$3 AEs; 34% vs 18% reported serious AEs, including more cardiovascular AEs with the combination. 30% vs 10% of pts, respectively, discontinued treatment due to an AE. Median time to deterioration in quality of life (QoL; FACT-P) was 5.7 vs 6.0 mths, respectively (HR 0.97, 95% CI 0.681.40). **Conclusions:** This is the first trial to show clinical benefit for mCRPC pts treated with a PARP inhibitor combined with abiraterone, regardless of HRRm status. Safety data were less favorable for the combination, but no detriment to QoL was seen. Our study indicates synergy between olaparib and abiraterone. Clinical trial information: NCT01972217.

rPFS by HRRm status.

Pt group	Median rPFS,* mths (combination vs comparator)	HR (95% CI)
Overall, n = 142	13.8 vs 8.2	0.65 (0.44–0.97)
HRRm, n = 21	17.8 vs 6.5	0.74 (0.26–2.12)
HRRwt,† n = 35	15.0 vs 9.7	0.52 (0.24–1.15)
HRRm unknown, n = 86	13.1 vs 6.4	0.67 (0.40–1.13)

*Kaplan-Meier method; †tumor test result required. wt, wild-type.

5004 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

The PROPHECY trial: Multicenter prospective trial of circulating tumor cell (CTC) AR-V7 detection in men with mCRPC receiving abiraterone (A) or enzalutamide (E). *First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC*

Background: It is unclear if CTC AR-V7 detection is a valid predictive biomarker of clinical efficacy in men with mCRPC receiving A/E or just an indicator of aggressive disease and high tumor burden. **Methods:** We conducted a multicenter prospective study of circulating biomarkers in men with high-risk mCRPC (PROPHECY, NCT02269982) starting A/E. The primary endpoint was association of baseline AR-V7 with radiographic/clinical progression free survival (PFS), using the Johns Hopkins modified-AdnaTest CTC AR-V7 mRNA assay and the Epic Sciences CTC nuclear AR-V7 protein assay. Overall survival (OS) and PSA decline were key secondary endpoints. **Results:** We enrolled 118 men with mCRPC starting A/E; 52% had ≥5 Cellsearch CTCs, 36% had prior A/E. On study therapy was A (n = 56), E (n = 59) or both A/E (n = 3). AR-V7 detection by the JHU AR-V7 assay and the Epic AR-V7 assay were independently associated with worse PFS and OS after adjusting for CTC count and established clinical factors (see below table). Concordance between the two AR-V7 assays was 82%. Epic AR-V7 (+) men had more CTC phenotypic heterogeneity: 63% had Shannon Index > 1.5 vs 14% of AR-V7 (-) men; most CTCs in Epic AR-V7 (+) men were AR-V7 (-). We found genetic alterations of aggressive mCRPC in AR-V7 (+) and AR-V7 (-) men including gain of AR, MYCN, and MYC and loss of PTEN, TP53, and DNA repair enzymes in CTCs and ctDNA. **Conclusions:** We validate AR-V7 detection as an independent CTC-adjusted negative predictive biomarker of short PFS and OS with A/E treatment in men with mCRPC, identify CTC heterogeneity of AR-V7 expression, and highlight the importance of non-AR-V7 drivers of aggressive disease. Clinical trial information: NCT02269982.

Outcome	AR-V7 (JHU n = 116) (+) n = 28 (24%) / (-) n = 88 (66%)	AR-V7 (Epic n = 105) (+) n = 11 (10%) / (-) n = 94 (90%)
Median PFS (mo)	3.1 / 7.3	3.1 / 6.0
p-value	0.0003	0.007
HR* (95% CI)	2.4 (1.6-3.8)	2.4 (1.3-4.6)
HR^(95% CI)	2.4 (1.4-3.9)	2.2 (1.0-4.9)
Median OS (mo)	11.5 / 25.5	8.4 / 25.5
HR*(95% CI)	3.9 (2.1- 7.3)	4.5 (2.1-9.8)
HR^ (95% CI	4.6 (2.3-9.2)	3.6 (1.5-8.6)
≥ 50% confirmed PSA decline	11% / 28%	0% / 26%
Odds Ratio (95% CI)	0.31 (0.09-1.12)	Not estimable

*univariate, ^adjusted for Cellsearch CTC enumeration, PSA, Alk Phos, Hgb

LBA5005 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Overall survival between African-American (AA) and Caucasian (C) men with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Susan Halabi, Duke University Medical Center, Durham, NC*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

5006 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Results of PROSPECT: A randomized phase 3 trial of PROSTVAC-V/F (PRO) in men with asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer. *First Author: James L. Gulley, Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: PRO is a PSA-targeted, poxvirus-based cancer vaccine using a heterologous prime-boost regimen comprising a recombinant vaccinia vector prime followed by 6 booster doses with the recombinant fowlpox vector. PROSPECT was designed as a confirmatory trial of a prior randomized phase 2 trial (RandPh2) that showed 8.5 months prolongation of median OS (25.1 m PRO vs 16.6 m Placebo (Pbo)) (Kantoff, JCO 2010; 28:1099) **Methods:** Double-blind randomization to one of the following 3 arms: PRO+Pbo (V), PRO+GM-CSF (VG), or Pbo+Pbo (P). Stratified per PSA < or ≥ 50 ng/mL and LDH < or ≥ 200 U/L. Primary Endpoint: OS. Secondary endpoints: Alive without event at 6 months (AWE-6) and Safety. **Results:** Between Dec 2011 and Jan 2015, 1297 pts were randomized in 15 countries. Demographics: mean age: 71 (SD: 8.25), ECOG PS0/1-2: 74%/26%, mean PSA: 74.5 (SD:209). Site of metastasis: bone 74.7, lymph node 15.7, visceral 8.4%. The 3rd interim analysis was held in Sep 2017, after reaching 80% of the expected deaths, and the DMC recommended closure of the study on grounds of futility. The K-M OS curves showed a substantial overlap between the 3 arms and the planned statistical analysis showed statistically non-significant differences. Median OS was 34.8, 33.9 and 34.7 months for V, VG and P arms respectively. Two comparisons were prespecified: V vs P and VG vs P, and the HR were 1.02 (p = 0.40) and 1.03 (p = 0.66) respectively. No benefit was seen in the secondary endpoint AWE6. Although 91% of patients experienced AEs of any grade, and 65% experienced injection site reactions, only 5.8% lead to premature discontinuation of treatment. **Conclusions:** PROSPECT failed to confirm an OS benefit observed in a prior RandPh2. Of interest, OS observed in all arms was approximately one year longer than anticipated based upon historical controls, likely related to improved standard of care since study enrollment began in 2011. Clinical trial information: NCT01322490.

5007 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

KEYNOTE-199: Pembrolizumab (pembro) for docetaxel-refractory metastatic castration-resistant prostate cancer (mCRPC). *First Author: Johann S. De Bono, Royal Marsden Hospital, London, United Kingdom*

Background: Efficacy of PD-1 inhibition has not been demonstrated in large-scale mCRPC trials. Pembro showed preliminary antitumor activity in PD-L1+ mCRPC in KEYNOTE-028 (n = 23). Here, we present results from cohorts 1-3 (n = 258) of the phase 2 KEYNOTE-199 study of pembro monotherapy in docetaxel-refractory mCRPC (NCT02787005). **Methods:** Cohorts 1 (C1) and 2 (C2) enrolled patients (pts) with RECIST-measurable PD-L1+ and PD-L1– disease, respectively. C3 enrolled pts with nonmeasurable, bone-predominant disease. All pts had ECOG PS 0-2 and received ≥1 novel endocrine therapy (eg, abiraterone, enzalutamide) and 1-2 prior chemotherapies including docetaxel. Pts received pembro 200 mg Q3W until PD or intolerable toxicity. Response was assessed Q9W in yr 1, then Q12W. Primary end point was ORR per RECIST v1.1 by central review in C1 and C2, separately and combined. Key secondary end points included DCR (CR + PR + SD) per PCWG3-modifed RECIST and safety in all 3 cohorts. **Results:** 131 pts enrolled in C1, 67 in C2, and 60 in C3. Median follow-up as of Oct 13, 2017, was 8.1 mo, 7.9 mo, and 11.8 mo, respectively. Antitumor activity was observed in all cohorts (Table). Across cohorts, DCR lasting ≥6 mo was 11%. In C1 and C2, 9% of pts had a ≥30% decrease in target lesions; 48% had target lesion changes between –30% and +20%. The response rate was numerically higher in pts with somatic *BRCA1/2* or *ATM* mutations (12%). Drug-related grade 3-5 AE rates were 13% in C1, 12% in C2, and 17% in C3. **Conclusions:** Pembro shows antitumor activity and disease control with acceptable safety in pts with docetaxel-refractory mCRPC, regardless of PD-L1 status, in both RECIST-measurable and nonmeasurable disease. These data support further evaluation of pembro in mCRPC, including in pts wth homologous recombination defects. Clinical trial information: NCT02787005.

	C1	C2	C3	C1+C2	C1+C2+C3
RECIST v1.1					
ORR, % (95% CI	5 (2-11)	3 (< 1-10)	NA	5 (2-8)	NA
DCR, % (95% CI)	22 (15-30)	24 (14-36)	37 (25-50)	23 (17-29)	26 (21-32)
DCR ≥6 mo, % (95% CI)	9 (5-16)	6 (2-15)	22 (12-34)	8 (5-13)	11 (8-16)
PCWG3-modified RECIST					
ORR, % (95% CI)	5 (2-11)	3 (< 1-10)	NA	5 (2-8)	NA
DCR, % (95% CI)	27 (20-36)	42 (30-54)	57 (43-69)	32 (26-39)	38 (32-44)
DCR ≥6 mo, % (95% CI)	11 (6-17)	9 (3-18)	30 (19-43)	10 (6-15)	15 (11-20)

5008 Oral Abstract Session, Mon, 3:00 PM-6:00 PM

A randomized phase 2 study investigating 3 dosing regimens of radium-223 dichloride (Ra-223) in bone metastatic castration-resistant prostate cancer (mCRPC). *First Author: Cora N. Sternberg, San Camillo-Forlanini Hospital, Rome, Italy*

Background: Ra-223, standard dose (SD) 55 kBq/kg q4w for 6 cycles improved overall survival (OS) and delayed time to symptomatic skeletal events (SSEs) in patients (pts) with mCRPC and bone metastases in the ALSYMPCA study (Parker C, N Engl J Med. 2013;369(3):213-23). The current study investigated different Ra-223 treatment regimens in a similar patient population. **Methods:** Pts with bone mCRPC were randomized 1:1:1 to Ra-223 SD or Ra-223 high dose (HD) 88 kBq/kg q4w for up to 6 cycles, or to Ra-223 SD extended (EXT) q4w for up to 12 cycles. The primary objective was to compare SSE-free survival (SSE-FS) between HD and SD, and EXT and SD. Hypothesis testing was performed at a 2-sided alpha level of 0.20 with no adjustment for multiplicity. **Results:** 391 pts were randomized; baseline characteristics were well balanced. No statistically significant differences in SSE-FS were observed between Ra-223 SD and HD [median 12.3 vs 12.9 months, hazard ratio (HR) 1.06, 80% CI 0.88–1.27, p = 0.70] or Ra-223 SD and EXT [median 13.2 vs 10.8 months, HR 1.26, 80% CI 0.94–1.69, p = 0.31]. Median OS was 15.8, 16.0 and 14.4 months in the SD, HD and EXT arms, respectively. A total of 370 pts received Ra-223 with a median number of doses of 6 in each arm. The most frequent treatment emergent adverse events (TEAEs) were fatigue, anemia and nausea. Grade ≥3 TEAEs were noted in 34%, 48% and 53% of pts in the SD, HD and EXT arms, respectively. The most frequent grade ≥3 TEAEs overall were anemia (13%), bone pain (5%), thrombocytopenia (4%) and hypertension (4%). TEAEs leading to permanent discontinuation occurred in 9%, 16% and 17% of pts in the SD, HD and EXT arms, respectively. **Conclusions:** No statistically significant differences in SSE-FS were noted between Ra-223 SD and HD or Ra-223 SD and EXT. However, HD and EXT arms had a higher incidence of grade ≥3 TEAEs than the SD arm. The study supports the currently approved dose and schedule of Ra-223. Clinical trial information: NCT02023697.

LBA5009 Poster Discussion Session; Displayed in Poster Session (Board #236), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Abi Race: A prospective, multicenter study of black (B) and white (W) patients (pts) with metastatic castrate resistant prostate cancer (mCRPC) treated with abiraterone acetate and prednisone (AAP). *First Author: Daniel J. George, Duke University, Durham, NC*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On-site at the Meeting, this abstract will be printed in the Saturday edition of *ASCO Daily News*.

5010 Poster Discussion Session; Displayed in Poster Session (Board #237), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Health-related quality of life (HRQoL) deterioration and pain progression in men with non-metastatic castration-resistant prostate cancer (M0 CRPC): Results from the PROSPER study. *First Author: Gerhardt Attard, The Institute of Cancer Research and the Royal Marsden, Surrey, United Kingdom*

Background: The Phase 3 PROSPER trial (NCT02003924) showed a statistically significant improvement in metastasis-free survival (MFS) with enzalutamide (ENZA; n = 933) vs. placebo (PBO; n = 468) in asymptomatic men with M0 CRPC and prostate-specific antigen doubling time ≤10 months. We report the results of the HRQoL and pain evaluations. **Methods:** Functional Assessment of Cancer Therapy–Prostate (FACT-P) and Brief Pain Inventory, Short Form, were used to assess HRQoL and pain at baseline (BL) and every 16 weeks during treatment. Pain progression was defined as ≥2 points in pain severity items and mean scores increase from BL; HRQoL improvement/deterioration as an increase/decrease from BL using pre-established thresholds for clinically meaningful difference. Time to first confirmed (at two consecutive visits) and unconfirmed HRQoL deterioration/pain progression were assessed using Kaplan-Meier estimates and Cox proportional hazards models under censoring not at random assumption. **Results:** BL characteristics and scores were similar between arms with low pain (median 0) and high HRQoL (median FACT-P total score, 121). Decrease in attrition rate was greater in PBO vs. ENZA mainly due to disease progression (53% vs. 68% at week 49, respectively). Most patients reported no change or improvement in HRQoL. Proportion of patients with pain progression at week 49 was similar between ENZA (11–20%) and PBO (14–21%). Lower risk of pain progression was observed with ENZA vs. PBO in the confirmed analysis (hazard ratio [HR] 0.78–0.93; $p > 0.05$). Nominal statistically significant lower risk of deterioration was observed with ENZA for FACT-P total, FACT Advanced Prostate Symptom Index, prostate cancer subscale (PCS), and emotional well-being (EWB) in the confirmed (HR 0.75, 0.77, 0.77, 0.69, respectively; $p < 0.05$) and for PCS and EWB in the unconfirmed (HR 0.82, 0.80, respectively; $p < 0.05$) analyses. **Conclusions:** In PROSPER, ENZA significantly delayed MFS vs. PBO without worsening HRQoL and significantly reduced the risk of clinically meaningful HRQoL deterioration in several FACT-P domains. Pain progression was similarly low in both arms. Clinical trial information: NCT02003924.

5011 Poster Discussion Session; Displayed in Poster Session (Board #238), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Self-management in prostate cancer survivors: A randomized controlled trial. *First Author: Ted A. Skolarus, Department of Urology, Dow Division of Health Services Research, University of Michigan, Ann Arbor, MI*

Background: The purpose of this randomized trial was to compare a personally-tailored symptom management intervention consisting of 4 automated telephone assessments and tailored education for improving symptom self-management among prostate cancer survivors to usual care (1 non-tailored newsletter about symptom management). We hypothesized improved symptom self-management and prostate cancer quality of life following the intervention. **Methods:** A total of 556 prostate cancer survivors experiencing symptom burden were recruited from April 2015 to February 2017 across 4 sites. Participants were randomized to intervention (n = 278) and usual care (n = 278) groups as reported in our protocol. Our primary outcome was symptom burden assessed via patient report 5 months after enrollment using the EPIC-26 instrument. Secondary outcomes included psychosocial outcomes and domain-specific changes according to intervention participants' primary symptom area (urinary, bowel, sexual, general). We used multivariable regression analysis to evaluate intervention impact on outcomes. **Results:** The mean age of prostate cancer survivors was 66.7 years and the majority was treated with radiation therapy (56.7% vs. 46.2% surgery). The 5 month primary outcome assessment was completed by 89% of participants. There were no baseline differences across groups. At 5 months, we observed differences between groups in urinary domains (irritative - 61.8 control vs. 63.4 intervention, adjusted mean difference (aMD) 2.6, p = 0.07; obstructive - 74.5 control vs. 77.4 intervention, aMD 2.6, p = 0.07) with no significant differences in other outcomes. Intervention participants choosing urinary (crude mean difference (cMD) irritative 3.0; p = 0.09, obstructive 6.1; $p < 0.01$), bowel (cMD 9.1; p = 0.08), and sexual (cMD 5.6; $p < 0.01$) domains as their primary focus area reported improvements at 5 months. Participants reported high satisfaction with the intervention. **Conclusions:** A personally-tailored, automated telephone symptom management intervention for prostate cancer survivors was feasible and led to differences in urinary and sexual health symptoms in this randomized trial. Self-management of treatment-related side effects appears warranted. Clinical trial information: NCT01900561.

5012 Poster Discussion Session; Displayed in Poster Session (Board #239), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phenotypic and genomic characterization of CTCs as a biomarker for prediction of Veliparib therapy benefit in mCRPC. *First Author: Ryan Dittamore, Epic Sciences, Inc., San Diego, CA*

Background: Response to PARPi in mCRPC patients (pts) particularly those with DNA damage response mutations (DDRm) was observed in the TOPARP trials (utilizing Olaparib) which enrolled heavily pre-treated, high CTC pts. However, the NCI 9012 study, randomizing 1st line mCRPC pts to Abiraterone (A) or A + Veliparib (V), did not demonstrate an advantage for V in any pre-specified subgroup, with DDRm pts having better outcomes on both arms. Here we explore the use of CTCs to ascertain phenotypic Genomic Instability (pGI) as a proposed selection biomarker for PARPi. **Methods:** 212 blood samples from 84 pts (n = 39 A & n = 42 A+V, 3 uneval) prior to and during therapy were processed utilizing the Epic Sciences CTC platform. 32 pts had a concomitant fresh biopsy sequenced by MI-ONCOSEQ. CTC pGI was determined using previously described algorithms (Scher et al. ASCO 2016) which predicts genomic instability with morphological features and protein expression. A subset of CTCs (n = 466) underwent single cell sequencing for genomic scarring/DDRm and results were compared to tissue DDRm. CTC biomarkers were correlated with pt outcomes. **Results:** 80.2% (65/81) of baseline (BL) blood samples had enumerable CTCs. 48% (39/81) of these had ≥ 1 CTCs with pGI detected (pGI+). pGI+ pts had improved PSA response in the A+V arm, 83% (20/24) compared to 33% (5/15) in A ($p = 0.002$). Higher BL CTC counts were detected in tissue DDRm vs. DDR wild type (wt) pts (med 3.8 CTC/mL vs. 2.7 CTC/mL). pGI+ CTCs were detected in 42% (5/12) DDRm pts and 35% (7/20) DDRwt pts. Discordant results between CTC genomic scarring and tissue DDRm were observed. 3 pts with tissue DDRm only had CTCs with low genomic scarring. Conversely, 3 DDRwt pts had CTCs with high genomic scarring. pGI+ CTCs decreased in pGI+ pts from baseline to on-therapy with A+ V, 82% (9/11) pts (mean of 40 pGI+ CTC/mL) had reductions to < 1 pGI CTC/mL , whereas on A, only 20% (1/5) pts. (mean of 6 pGI+ CTC/mL) had a reduction to < 1 pGI CTC/mL (p = 0.036). **Conclusions:** A CTC biomarker, pGI, is correlated to differential PSA responses associated with A + V. Single cell CTC sequencing highlights the heterogeneity of genomic scarring in patients with and without DDRm and may be more sensitive than tissue based markers. Clinical trial information: NCT01576172.

5013 Poster Discussion Session; Displayed in Poster Session (Board #240), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Genomic profiling of primary prostate tumors from patients who develop metastatic castration-resistant prostate cancer (mCRPC). *First Author: Joaquin Mateo, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: mCRPC is enriched for genomic aberrations in *TP53*, *RB1*, *AR*, *PTEN* and DNA damage repair (DDR) compared to localized prostate cancer. Here we pursued NGS of 470 primary prostate tumors from patients who all later developed mCRPC to evaluate this enrichment in this poor prognosis population. We also compared 49 pairs of same patient primary tumor and mCRPC biopsies. **Methods:** Libraries for targeted DNA NGS were built using a customized amplicon-based panel (Generead v2 DNAseq, Qiagen) and read in a MiSeq (Illumina). Copy number aberrations (CNA) were assessed using a previously described bioinformatics pipeline (Seed, CCR 2017) for 98 genes. We compared gene aberration frequencies with previously reported cohorts. **Results:** A total of 470 treatment naïve primary prostate biopsies were sequenced and passed QC filters for mutation and CNA calling. Frequencies for TP53 (27%) and RB1 (5%) aberrations were higher than previously reported for localized prostate cancer (TCGA, $p<0.01$ each) but lower than for mCRPC (SU2C/PCF, *TP53* p = 0.001, *RB1* p = 0.07). Conversely DDR gene defects were more common: *BRCA2* 5% (p = 0.004); *CDK12* 5% (including 7 cases with two mutations; p = 0.06); *ATM* 4% (p = 0.2), and *PALB2*, *BRCA1*, RAD50, *FANCA* 1% each. Overall, 2% of primary tumors had detectable mutations in MMR genes. PTEN genomic loss was detected in 12% of primary tumors; 5% had activating mutations of *PIK3CA* or *AKT*. Other genes recurrently mutated were SPOP (7%) and CTNNB1 (3%). Surprisingly, in 5 cases (1%) AR mutations at low allele frequencies were detectable prior to ADT. Among the 49 patient matched sample pairs, mutations detectable only in mCRPC were identified in *AR* (n = 4), *TP53* (4), *RB1* (3) and *CTNNB1* (1). All 9 truncating mutations in *BRCA2*, *ATM*, *CDK12*, *PALB2* were shared between treatment naïve and mCRPC samples. **Conclusions:** *TP53* and *RB1* aberrations are more common in poor prognosis primary prostate cancer than in localized, more curable, disease (TCGA) but lower than in mCRPC (SU2C/PCF). Aberrations detected only at mCRPC in patient-matched samples support the evolution of these mutations under treatment selection pressures. Poorer prognosis prostate cancers are enriched for *BRCA2* aberrations.

5014 Poster Discussion Session; Displayed in Poster Session (Board #241), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

The complete genomic landscape of metastatic prostate cancer pinpoints clinically targetable subgroups. *First Author: Lisanne Francisca van Dessel, Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University, Rotterdam, Netherlands*

Background: Recent genome analysis efforts have shown that genomic alterations obtained from primary and metastatic prostate cancer (mPCa) vary widely, stressing the need to obtain comprehensive genomic data from metastatic tissue. Understanding the complete genomic atlas of mPCa will increase our understanding of cancer progression and improve management of these patients. **Methods:** Fresh-frozen tissue biopsies of 153 patients with mPCa were analyzed by whole-genome sequencing (WGS) to a minimum depth base coverage of 90x for tumor samples and 30x for peripheral blood (reference). Biopsy sites included bone, lymph node and viscera. Sequencing data were analyzed to call tumor specific single nucleotide variants (SNV), small insertions and deletions (InDels), copy number alterations (CNA) and chromosomal rearrangements and their incidence was compared to results reported for primary disease (Fraser et al. Nature 2017). **Results:** Median tumor cell content of the biopsied lesions was 60% (95% CI: 56-64%). Median SNV burden was 2.6 SNVs per million base pairs (Mbp; 95% CI: 2.44-2.88) compared to 0.53 SNVs per Mbp in primary disease. High SNV and InDel load correlated with microsatellite instability (MSI) mutational signatures (8/153 tumors). Furthermore, we identified a distinct subgroup harboring signature 3 mutations likely to be associated with *BRCA* deficiency (26/153 tumors; Alexandrov et al. Nature 2013). Median number of interchromosomal rearrangements was 58 (95% CI: 49-67) compared to 19 in primary disease. We found a total of 69 and 62 alterations, including SNVs and CNAs, in the genes *AR* and *TP53*, respectively, both important drivers in mPCa. We will present additional data on novel and recurrent genomic alterations and mutational signatures. **Conclusions:** WGS of metastatic tissue from patients with mPCa shows a clear evolution of aberrations compared to primary disease. Increased frequency of alterations in specific driver genes confirms their role in dissemination and/or therapy failure. Using whole-genome sequencing, we were able to stratify patients into clinically relevant groups (MSI, *BRCA*ness, *PI3K* and *RB*) advancing towards improved treatment management of patients with mPCa.

5015 Poster Discussion Session; Displayed in Poster Session (Board #242), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase 2 randomized cross-over trial of abiraterone + prednisone (ABI+P) vs enzalutamide (ENZ) for patients (pts) with metastatic castration resistant prostate cancer (mCPRC): Results for 2nd-line therapy. *First Author: Daniel Khalaf, British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, Canada*

Background: ABI+P and ENZ have similar efficacy for 1st-line treatment of mCRPC but cross-resistance confounds treatment with the alternate agent at progression. The optimal sequencing has not been prospectively investigated and predictive biomarkers are needed. **Methods:** A multi-centre trial of ABI+P followed by ENZ at PSA progression (arm A) vs ENZ followed by ABI+P (arm B). Primary endpoints were PSA decline > 50% (PSA50) on 2nd-line therapy and time to 2nd PSA progression (TT2P) (from start of 1st-line). Deep-targeted sequencing of serial samples of circulating tumour DNA (ctDNA) was performed. **Results:** 202 pts (101/ arm) were accrued with median follow-up 22.3 months (m). 65 pts from arm A and 71 from arm B crossed-over to 2nd-line treatment and 30 pts (15/arm) stopped treatment without cross-over. Baseline characteristics at time of 2nd-line therapy were balanced: median age 75 (range 50-93), PSA 14.5 (6.6-62.1), alkaline phosphatase > upper limit of normal (ULN) in 39% of pts and bone/liver metastasis (mets) in 89%/9%. ECOG PS was 0-1 in 89% vs 76% of pts for arm A vs arm B (p = 0.044) and LDH was > ULN in 25% vs 8% (p = 0.013). PSA50 for 2nd-line therapy for arm A vs arm B was 34% vs 4% ($p<0.001$) and median time to PSA progression on 2nd-line therapy (TTPP) was 2.7 m vs 1.3 m (HR 0.38, 95% CI 0.26-0.56). For the intention-to-treat population, TT2P was 13.6 vs 11.9 m (HR 0.75, 95% CI 0.53-1.06). Median overall survival (OS) was not reached vs 24.3 m (HR 0.82, 95% CI 0.53-1.27). On multivariable analysis, factors associated with 2nd-line TTPP were: bone mets (HR 2.22, 95% CI 1.08-4.54), liver mets (HR 3.18, 95% CI 1.21-8.41) and treatment arm A vs B (HR 0.27, 95% CI 0.17-0.40). At progression, AR gene copy number increased in 14% of evaluable pts (7/49) and AR L702H/T878A(S) mutations were present in 8% of pts. ctDNA fraction ≥2% at baseline was associated with worse TT2P (HR 2.04, 95% CI 1.43 - 2.90) and OS (HR 4.07, 95% CI 2.40-6.91). **Conclusions:** The sequence of ABI+P followed by ENZ was associated with superior PSA50 and TTPP on 2nd-line therapy. AR alterations associated with ABI+P and ENZ resistance were detectable in ctDNA. Clinical trial information: NCT02125357.

5016 Poster Discussion Session; Displayed in Poster Session (Board #243), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase 2, randomized, 3-arm study of abiraterone acetate and prednisone (AAP), AAP plus degarelix (AAP+D), and degarelix (D) alone for patients (pts) with biochemically-recurrent prostate cancer (PC) following radical prostatectomy (RP). *First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Androgen deprivation therapy (ADT) with GnRH analogs does not entirely suppress androgen signaling. AAP + ADT decreases blood and intratumoral testosterone (T) levels by ≥1 log, and in pre-RP trials resulted in greater pathologic responses relative to ADT alone. Trial designs that can rapidly assess therapies (txs) are critical given the long natural history of PC and resources required for phase 3 trials. Using a novel endpoint (endpt) (undetectable PSA [PSA0] with T recovery [rec]), we hypothesized that AAP+D given in the rising PSA state post-RP, a low volume but potentially lethal setting, could eliminate all disease, a prerequisite to cure. **Methods:** Post RP ± salvage radiotherapy pts with a rising PSA ≥1.0 ng/ml, doubling time ≤9 months (mo), no metastases (met) on CT/bone scan, and T ≥150 ng/dl were eligible [NCT01751451]. Prior ADT ≤8 mo was allowed. Pts were randomized (1:1:1) to AA 1000 mg + P 5 mg QD (Grp 1), AAP + monthly D (Grp 2), or monthly D (Grp 3) for 8 mo, followed by cessation of txs. The primary (1^0) endpt was PSA0 with T > 150 at 18 mo and secondary, PSA0 at 8 mo. **Results:** 120 pts were treated; 113 were evaluable for the 1^0 endpt; 7 had PSA0 at 18mo without T rec. No difference was seen in PSA0 at 8 mo with AAP vs AAP+D (p > 0.99), or AAP vs D (p = 0.11) (Table). Overall, 11.5% of pts achieved the 1^0 endpt with no difference between groups (Grp 1 vs Grp 3; Grp 2 vs Grp 3 [p = 0.43; p = 0.75]). T rec was shortest in Grp 1 relative to Grp 3 (p < 0.001). Clinical trial information: NCT01751451. **Conclusions:** Although no difference between tx grps was identified by the 1^0 endpt (PSA0 + T rec), these results set a benchmark for future trials that 10-15% of pts can achieve this outcome. Given the survival benefit of AAP + ADT in non-castrate met PC, a longer duration of androgen suppression may yield greater benefit. In addition to novel systemic txs, use of PET directed imaging to identify and target micro-mets with focal txs may enhance the likelihood of eliminating disease in this setting.

Cohort	PSA0 at 8mo	Median time to T rec (wks)	PSA0 + T > 150 at 18mo
Grp 1: AAP	31/37 (84%)	36	2/37 (5%)
Grp 2: AAP+D	32/37 (86%)	57	6/37 (16%)
Grp 3: D	26/39 (67%)	54	5/39 (13%)

5017 Poster Discussion Session; Displayed in Poster Session (Board #244), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Prostate radiotherapy in newly-diagnosed metastatic hormone-sensitive prostate cancer: A single-institution experience. *First Author: Scott Carlyle Morgan, Division of Radiation Oncology, University of Ottawa, Ottawa, ON, Canada*

Background: In patients presenting with metastatic prostate cancer (mPCa), the role of local therapy is undefined. Recent registry analyses have suggested, however, that external beam radiotherapy (RT) directed at the prostate may improve overall survival (OS). We reviewed the experience of primary tumor-directed RT in this setting at our center. **Methods:** The study population consisted of men with newly-diagnosed mPCa referred to a comprehensive cancer center between 2005 and 2015 and treated initially with androgen deprivation therapy. Patients were eligible for inclusion if they received 1) prostate RT with biologically effective dose at least that of a course of 40 Gy in 15 fractions or 2) no prostate RT. The association between receipt of prostate RT and OS was studied. OS was estimated using the Kaplan-Meier method while univariate and multivariate Cox regression were used to identify factors associated with OS. **Results:** A total of 304 cases were eligible. Prostate RT was received in 105 cases. Median age at diagnosis was 75 years (IQR, 67-82 years). Median follow-up was 72.2 months. On univariate analysis, prostate RT was associated with improved OS (HR 0.62, 95% CI 0.46-0.84, p = 0.002). 2-year and 5-year OS was 74.7% and 41.8% respectively in those receiving prostate RT and 56.9% and 27.6% respectively in those not receiving RT. Median OS in those receiving RT was 48.3 months versus 29.2 months in those not receiving RT. In a multivariate Cox model taking account of age at diagnosis, year of diagnosis, presenting PSA, T stage, N stage, and M1 subdivision, RT remained associated with improved survival (HR 0.64, 95% CI 0.43-0.96, p = 0.033). **Conclusions:** This cohort represents the largest single-center experience of primary tumor-directed RT in mPCa reported to date. In this population, receipt of prostate RT was associated with improved OS. The observed 19-month absolute difference in median OS is clinically significant. This analysis could not account for performance status, volume of metastatic disease, comorbidities, receipt of systemic therapies, and other potential confounders. Only large-scale RCTs will be able to definitively assess the value of prostate RT in this setting.

5018 Poster Discussion Session; Displayed in Poster Session (Board #245), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Timing of androgen deprivation therapy for prostate cancer patients after radiation: Planned combined analysis of two randomized phase 3 trials. *First Author: Andrew Loblaw, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: The TOAD (TROG 03.06; NCT00110162) phase 3 randomized trial showed that immediate androgen deprivation therapy (IADT) improved overall survival (OS) and time to clinical progression compared with delayed ADT (DADT) in progressive or relapsed prostate cancer patients after radical radiotherapy (RT) or prostatectomy + RT. ELAAT (NCT00439751) was a similarly designed trial but failed to reach its accrual goal. The two investigative teams planned a combined analysis before ELAAT was activated. **Methods:** The PSA failures from TOAD and 78/79 patients accrued to ELAAT were combined (1 patient was excluded due to castrate resistant prostate cancer (CRPC)). Participants for both trials were randomized 1:1 to IADT or DADT. The primary endpoint was all-cause mortality by intention-to-treat. Secondary endpoints were cancer-specific mortality (CSM), local progression, distant progression, CRPC, and prostate cancer complications (PCC). **Results:** 261 patients from TOAD and 78 patients from ELAAT were followed a median of 5.0y. TOAD patients were younger (mean age 70.5 vs 73.8y) and more had a relapse-free interval < 2y from RT (30% vs 10%). In the DADT arms, 63% received ADT a median of 1.58y for TOAD; 38% received ADT a median 1.65y for ELAAT. For patients receiving ADT, the mean pre-ADT PSAs were 3.52 and 30.2 ng/ml in the IADT and DADT arms of TOAD and 3.98 and 18.1 ng/ml in ELAAT. There were 60 deaths, 40 and 20 respectively. Overall, for IADT and DADT arms the proportions of deaths in each trial were 15%, 11%, 19% and 26%, 27% and 24%. All-cause mortality (HR 0.75, 95% CI 0.40, 1.41; p = 0.37) and CSM (HR 0.57, 95% CI 0.22, 1.49) were not statistically different between IADT and DADT. Time to local progression (survival time ratio 1.97, 95% CI 1.28, 3.04; p = 0.002) and distant progression (survival time ratio 1.28, 95% CI 1.04, 1.58; p = 0.02) was higher while PCC (3.7 v 7.5%, p = 0.06) was lower with IADT. CRPC outcomes will be presented at conference. **Conclusions:** No difference in OS was detected between IADT and DADT in the combined analysis. A possible explanation is that ELAAT accrued older patients with lower risk of CSM and had a smaller difference in PSA between the IADT and DADT arms.

5019 Poster Discussion Session; Displayed in Poster Session (Board #246), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

KEYNOTE-046: ADXS-PSA plus pembrolizumab (pembro) in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Mark N. Stein, Columbia University Medical Center, New York, NY*

Background: ADXS–PSA, an attenuated *Listeria monocytogenes*-based immunotherapy that targets prostate-specific antigen (PSA), is designed to generate antigen-specific T cell effectors that kill tumor cells. Published data has shown synergy of ADXS Lm-LLO-TAA treatment with a PD-1 blocking antibody in an animal model. **Methods:** This phase 1/2 trial studied pts with progressive mCRPC, ≥18 yrs who received ≤2 prior chemo-/targeted-/immunotherapies or ≤1 prior chemotherapy in a metastatic setting. Part A (PA; n = 14) pts received ADXS-PSA doses $1x10^9$; $5 x10^9$ and $1x10^{10}$ colony forming units (CFU) IV every 3 wks and Part B (PB; n = 37) pts received $1x10^9$ CFU + 200 mg pembro IV every 3 wks with a 4^{th} pembro dose 3 wks later, for up to 2 yrs or until progression/toxicity. The 1° endpoint was safety/tolerability. Anti-tumor activity and effect on PSA level were evaluated. Preliminary results are presented. **Results:** At entry, PA and PB pts were similar in age (~70 yrs), Gleason score (~8.3) and prior abirateroneuse. PB pts had higher median BL PSA (40.6 v 20.8 ng/ml), and more prior enzalutamide (53 v 26%) and chemotherapy (49 v 36%) use v PA. 46 pts (94%) experienced treatment-related AEs (TRAE) with 16 pts having grade 3-4 events: fatigue, hypotension, hypertension, anemia. TRAEs ≥10% of any grade were cytokine release symptoms including chills, fever, nausea and hypotension. TRAE incidence was similar between groups and all resolved with supportive care. Accrual is complete but pts remain on trial. Overall, 2 PA (14%) v 16 PB pts (43%) had a decreased PSA post-BL. Of these, 8 PB (22%) v 0 PA pts achieved a PSA reduction ≥50% from BL; which was confirmed in 3 PB pts (38%). At the time of analysis, tumor measurements were available for 5 PA and 23 PB pts. One PA pt (20%) and 10 PB pts (43%) had SD (RECIST 1.1). Four PB pts (40%) with SD also had a decreased PSA post-BL; a confirmed response was seen in 2 of these pts. 9 PA and 14 PB pts had non-measurable disease at BL; 33% (3/9) and 79% (11/14) had disease stabilization (non-CR/non-PD). **Conclusions:** In this population of heavily pretreated mCRPC pts ADXS-PSA + pembro had a manageable safety profile and showed promising activity compared to monotherapy. These preliminary data warrant further study. Clinical trial information: NCT02325557.

5020 Poster Discussion Session; Displayed in Poster Session (Board #247), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Microsatellite instability in prostate cancer and response to immune checkpoint blockade. *First Author: Wassim Abida, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Immune checkpoint blockade has shown clinical benefit in mismatch repair deficient (dMMR) cancers, leading to accelerated FDA approval of pembrolizumab, a PD1-targeting agent, for the treatment of dMMR or microsatellite instability-high (MSI-H) advanced solid tumors. However, the frequency of MSI-H prostate cancer (PCa), as well as response to PD1/PDL1 agents in this disease subset, remain poorly defined. **Methods:** 839 PCa patients underwent targeted next-generation sequencing (NGS) of tumor and matched normal samples on an institutional protocol for the characterization of somatic mutations, copy number alterations and germline mutations (with specific consent). MSIsensor analysis, a computational method for detecting MSI, was performed. Tumor mutation burden (TMB) was calculated, with additional analysis for mutational signatures and immunohistochemical (IHC) staining of MMR proteins in selected cases. **Results:** 20/839 PCa patients (2.4%) were found to have MSI-H/dMMR tumors, defined as an MSIsensor score of ≥ 3 and TMB of ≥ 10, confirmed by IHC and mutational signature analysis. Of 13/20 MSI-H patients who consented to germline analysis, 3/13 (23%) had a germline MMR gene mutation. 3/5 MSI-H patients who underwent profiling of ≥ 2 matched tumors demonstrated MSI in the later tumor. In total, 10 patients with MSI-H tumors received a PD1/PDL1 targeting agent. 2/10 had radiographic PR with PSA decline of $> 80\%$. 3/10 are early in their treatment with PSA decline of $> 60\%$. 1/10 had stable disease for 6 months then progressed. 3/10 had no response. 1/10 was inevaluable. **Conclusions:** Tumor profiling for MSI status can be considered for patients with advanced PCa. MSI can develop as a later somatic event, arguing for profiling of a recent tumor when possible. Germline profiling should be recommended for patients with MSI-H PCa. While early in this dataset, responses to PD1/PDL1 therapy may occur in ~50% of patients with MSI-H/dMMR PCa. Longer follow up and additional prospective studies will be necessary to confirm responses in this patient population.

5021 Poster Session (Board #248), Sat, 1:15 PM-4:45 PM

Immunotherapy utilizing the combined use of NK and ADCC mediating agents with PARP inhibition. *First Author: Kathleen Fenerty, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) prevent single-stranded DNA repair. PARPi has antitumor activity in patients with known double-stranded DNA repair deficiencies (germline BRCA mutations). Olaparib is FDA approved for BRCA mutant ovarian and breast carcinoma. Emerging clinical data**NCT02484404. JCO, Karzai et al.* suggests a benefit of combining olaparib with checkpoint inhibition in prostate cancer patients. Here, we interrogated the immunomodulatory potential of olaparib *in-vitro,* focusing on prostate carcinoma. We hypothesized that olaparib increases immune cell killing of tumor cells independent of BRCA status or checkpoint modulation. **Methods:** BRCA mutant and BRCA wildtype prostate carcinoma cell lines were pretreated with olaparib and then exposed to human healthy donor natural killer (NK) cells with or without the antibody-dependent cellular cytotoxicity (ADCC)-mediating monoclonal antibodies (mAb) avelumab (anti-PD-L1) or cetuximab (anti-EGFR). Tumor cell lysis was monitored. Anti-CD16 antibody was used to confirm NK-induced ADCC. Flow cytometry was performed on tumor cells treated with olaparib to evaluate phenotypic changes of NK ligands and death receptors. **Results:** NK-mediated killing was significantly increased in both BRCA WT and mutant prostate cell lines. NK killing was further increased using ADCC-mediating mAbs in both WT and mutant cell lines. The enhanced ADCC was blocked using anti-CD16 mAb. Notably, the expression levels of PD-L1 and EGFR did not change with olaparib treatment. On tumor cells, olaparib exposure upregulated NK ligands and death ligands. Additional tumor cell lines (lung, breast) were also assessed. **Conclusions:** We show here for the first time that a) olaparib increased tumor cell sensitivity to NK-mediated killing and ADCC in both BRCA wild-type and BRCA deficient prostate carcinoma cells, independent of PD-L1 or EGFR modulation; b) olaparib treatment enhanced NK killing in 6/6 cell lines; and c) mechanistically, treatment with olaparib upregulated NK ligands MICA/B, CD112, and death receptors Fas and Trail-R. These studies support the combined use of NK and ADCC mediating agents with PARPi in BRCA mutant and WT prostate carcinoma.

5022 Poster Session (Board #249), Sat, 1:15 PM-4:45 PM

Radium-223 re-treatment in an international, open-label, phase 1/2 study in patients with castration-resistant prostate cancer and bone metastases: 2-year follow-up. *First Author: A. Oliver Sartor, Tulane Cancer Center, New Orleans, LA*

Background: Radium-223 (Ra-223) treatment (tx) is indicated for patients (pts) with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases (mets) (6 $\times$ 55 kBq/kg IV injections [inj]; 1 inj q4wk). Early results of an international, open-label, phase 1/2 study (NCT01934790) showed that re-treating pts with Ra-223 was well tolerated with favorable effects on disease progression. Here we report safety and efficacy findings from a 2-year follow-up. **Methods:** Pts with CRPC and bone mets who completed 6 initial Ra-223 inj with no disease progression in bone and later progressed were eligible for Ra-223 re-tx (6 additional Ra-223 inj), provided that hematologic parameters were adequate. No concomitant cytotoxic chemotherapy was allowed; other concomitant agents for prostate cancer (including abiraterone and enzalutamide) were allowed at investigator discretion. The primary objective was safety. Exploratory objectives were time to radiographic bone progression, radiographic progression-free survival (rPFS), overall survival (OS), time to first symptomatic skeletal event (SSE), and SSE-free survival, all calculated from re-tx start. Pts will be followed for safety up to 7 years after last Ra-223 dose; an active 2-year follow-up evaluated exploratory objectives. Safety results from the active follow-up period and updated efficacy are reported. **Results:** 44 pts were re-treated with Ra-223; 29 (66%) completed all 6 inj (median number inj = 6). 34 (77%) of 44 pts entered active follow-up, during which no new safety concerns were noted. There were no serious drug-related adverse events. 26 (59%) of 44 pts had an rPFS event (radiographic progression or death); median rPFS was 12.0 months. Only 5 (11%) of 44 pts had radiographic bone progression; median time to radiographic bone progression was not reached. Median OS was 24.4 months. Median time to first SSE and SSE-free survival were 16.7 and 12.8 months, respectively. **Conclusions:** Re-treating with Ra-223 was well tolerated in this select pt population, led to minimal hematologic toxicity, and provided continued disease control in bone at 2-year follow-up. Clinical trial information: NCT01934790.

5023 Poster Session (Board #250), Sat, 1:15 PM-4:45 PM

Longer term preplanned efficacy and safety analysis of abiraterone acetate + prednisone (AA + P) in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC) from the phase 3 LATITUDE trial. *First Author: Karim Fizazi, Gustave Roussy, University of Paris Sud, Villejuif, France*

Background: The LATITUDE study in pts with NDx-HR mCNPC found significant improvements in OS, rPFS, and all secondary end points, including pt-reported outcomes when combining AA + P with androgen deprivation therapy (ADT) vs placebos (PBOs) + ADT, which led to unblinding of the study at first interim analysis. **Methods:** 1199 NDx-HR mCNPC pts were randomized 1:1 to AA (1 g QD) + P (5 mg QD) + ADT or PBOs + ADT. Co-primary end points were OS and rPFS. A stratified proportional hazards model assessed longer term follow-up on OS, secondary end points, and adverse events (AEs), including those associated with mineralocorticoid excess, from the preplanned second interim analysis, when approximately 65% (≈554) of expected deaths were observed. **Results:** With a median follow-up of 41 mo (range, 0.1-54.0), 205 (34%) pts in the AA + P arm and 70 (12%) in the PBOs arm (of whom 57 [81%] had crossed over to AA + P) remained on treatment. Updated OS continued to favor the AA + P arm (HR [95% CI] 0.638 [0.538-0.758]; $p < 0.0001$) as did secondary end points (Table). Serious AEs occurred in 27% of pts on AA + P and 20% of pts on PBOs. Grade 3/4 AEs included (AA + P vs PBOs; %): hypertension (21 vs 10), hepatotoxicity (8 vs 3), hypokalemia (12 vs 2), fluid retention (1 vs 1), and cardiac disorders (4 vs 1). 328 pts (54%) from the PBOs arm received a life-prolonging therapy. **Conclusions:** This long-term analysis continues to demonstrate the OS benefit of adding AA + P to ADT in NDx-HR mCNPC pts, with a 36% reduction in the risk of death, although most pts remaining on PBOs treatment had crossed over to AA + P. The secondary end points also continued to favor the AA + P arm, underscoring AA + P as a standard of care for pts with NDx-HR mCNPC. Clinical trial information: NCT01715285.

	AA + P + ADT (n = 597)	PBOs + ADT (n = 602)	HR (95% CI)	p Value
Primary end point, median mo				
OS	NR	36.7	0.638 (0.538-0.758)	< 0.0001
Secondary end points, median time to, mo				
Pain progression	47.4	17.9	0.723 (0.608-0.860)	0.0002
Skeletal-related event	NR	NR	0.739 (0.579-0.943)	0.0148
Chemotherapy initiation	NR	47.3	0.471 (0.378-0.586)	< 0.0001
Subsequent PC therapy	NR	21.2	0.428 (0.361-0.507)	< 0.0001

NR, not reached.

5024 Poster Session (Board #251), Sat, 1:15 PM-4:45 PM

Radium-223: Disease response and fracture assessment by whole body diffusion-weighted MRI (WB-DWMRI) in metastatic castration resistant prostate cancer (mCRPC). *First Author: Chris C. Parker, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom*

Background: Ra-223 improves overall survival in patients with mCRPC. Imaging criteria to assess response in bone are lacking but could inform treatment strategies. **Methods:** We did a prospective phase II study to evaluate potential response biomarkers to Ra-223. Patients with chemotherapy-naïve, bone mCRPC were randomised (1:1) to receive Ra-223 at 55 or 88 kBq/kg for 6 cycles, at 4-week intervals. WB-DWMRI was done at baseline, at cycles 2 and 4, and 1 month post-treatment. MRI response was defined as a 30% increase in the mean of the mean Apparent Diffusion Coefficient (ADC) using up to 5 target lesions. PSA response was defined per PCWG2 criteria. Circulating tumour cells (CTC) response was defined as decrease from ≥5 cells/7.5ml to < 5/7.5ml. **Results:** 27 evaluable patients received a median of 6 cycles of Ra-223. Overall MRI response was seen in 56% (15/27), PSA response in 11% (3/27) and CTC response in 55% (5/9) evaluable patients. There was an association between the greatest percentage increase in ADC and greatest percentage decline in PSA during treatment, rho = -0.59; p = 0.001. Responders on MRI received higher administered activity per cycle of Ra-223 than non-responders (median 5840kBq versus 4820kBq; rank sum test p = 0.04). Discordant ADC response, with both response (ADC ≥30% increase) and non-response (ADC < 30% increase) in different bone metastases, was seen in 44% (12/27) of patients. New bone metastases were seen during the treatment period in 67% (18/27), including 60% (9/15) who had an overall response by MRI. Four patients developed 11 new fractures in uninvolved bone during the treatment period. **Conclusions:** WB-DWMRI demonstrates marked inter- and intra-patient heterogeneity of response to Ra-223, and a dose-response relationship. Both new bone metastases, and fractures in uninvolved bone, are common during treatment. Future research should aim to test the role of Ra-223 dose-escalation, of intermittent treatment and of combination therapy with bone health agents. Clinical trial information: ISRCTN17805587.

5025 Poster Session (Board #252), Sat, 1:15 PM-4:45 PM

Cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC): Real-life use, effectiveness, safety, and quality of life (QoL) in the FUJI cohort. *First Author: Stephane Oudard, Hopital Europeen Georges Pompidou, Paris, France*

Background: Cabazitaxel (CAB) was marketed in March 2012 in France, based on overall survival (OS) benefit in mCRPC in 2nd-line (2L) post-docetaxel (DOC). FUJI is a post-authorisation study of the real-life performance of CAB. **Methods:** FUJI is a multicenter (n = 42) cohort study describing OS, safety, QoL (using FACT-P) and pain (using BPI-SF) in mCRPC CAB initiators in real-life, included from Sept 2013 to Aug 2015 in a retrospective cohort (follow-up (FU) 18 mths), and from March 2016 to March 2017 in a prospective cohort (FU 6 mths). **Results:** The retrospective cohort included 401 pts (median age 70) with CAB in 2L (18%), 3L (39%), 4L (23%), or > 4L (20%). Treatments before CAB included DOC (100%), abiraterone acetate (ABI 77%), enzalutamide (ENZ 33%). Median CAB use was 3.4 mths. Median OS was 11.9 mths [95%CI, 10.1-12.9]. In multivariate analyses, factors associated with a shorter OS were: grade ≥ 3 adverse event (AE) (HR = 2.05 [1.53-2.73]), visceral metastases (HR = 1.98 [1.40-2.80]), polymedication > 5 drugs (HR = 1.74 [1.23-2.45]), > 5 bone metastases (HR = 1.74 [1.20-2.53]), disease progression during DOC (HR = 1.69 [1.13-2.53]) or within 3 mths of last DOC cycle (HR = 1.51 [1.07-2.14]), ≥3 drugs such as DOC, ABI, ENZ before CAB (HR = 1.39 [1.00-1.92]), and PSA ≥ 135 ng/ml (HR = 1.36 [1.01-1.82]). Factors associated with better OS were ≥ 10-yr cancer history before CAB (HR = 0.66 [0.46-0.96]), ≥ 6 mths from last DOC dose to CAB initiation (HR = 0.71, [0.52-0.97]). Grade ≥ 3 AEs occurred in 55%, mainly anaemia (27%), neutropenia (15%), febrile neutropenia (8%), renal failure (7%), septicaemia/septic shock (5%). The prospective cohort included 61 pts (median age 72) previously treated with DOC (98%), ABI (61%) and ENZ (61%). 49 pts were evaluable for QoL and 44 for pain. QoL improved in 41%, was maintained in 29%, and deteriorated in 38%. 25% had pain decrease ≥ 1 level, 50% were stable and 25% increase ≥ 1 level. **Conclusions:** Real-life median OS in FUJI was lower than in TROPIC (11.9 *vs.* 15.1 mths), but very few FUJI pts would have satisfied TROPIC inclusion criteria. There were no new safety issues. Improved/stable QoL and pain were reported by 70% and 75% of pts treated by CAB, respectively.

5026 Poster Session (Board #253), Sat, 1:15 PM-4:45 PM

Survival outcomes from a cumulative analysis from worldwide observational studies on sequential use of new agents (NAs) in metastatic castration-resistant prostate cancer (mCRPC) (CASTOR study). *First Author: Orazio Caffo, Santa Chiara Hospital, Trento, Italy*

Background: After the introduction in the daily clinical practice of cabazitaxel (CABA) and new hormone agents (NHAs), abiraterone acetate (AA) and enzalutamide (ENZ), several small retrospective reports described their activity when sequentially used as second- and third-line after docetaxel (DOC) failure. Data from survival plots suggested that after DOC, CABA-based sequences led to a better overall survival (OS) than sequences based on NHAs only. The present work is based on individual-data analysis from some of the published reports on sequential use of at least two NAs after DOC. **Methods:** All authors of the published papers meeting the study criteria were prompted to provide individual data of the pts evaluated in their work. We calculated the overall survival (OS) from the second-line start by sequence strategy. For the OS analysis we considered three different types of NAs sequences after DOC: one new hormone agent (AA or ENZ) followed by CABA (NHA→CABA); CABA followed by AA or ENZ (CABA→NHA); one NHA followed by the other NHA (NHA→NHA). **Results:** We collected data from 1,099 pts. Cumulative OS did not differ significantly among the three different strategies (median cumulative OS ranging 21.0-22.1 mos, p = 0.957). Pts treated with NHA second-line had a statistically significant longer PFS although marginal in clinical terms (6.1 vs 5.6 mos, p < 0.0001), while in third-line CABA led to a statistically significant prolongation of OS (from the third-line start) compared to NHAs: 12.2 vs 9.1 mos (p = 0.039). These results were confirmed after adjustment by age and visceral mets presence. Interestingly, in the case of a NHA-based second-line pts with a longer PFS (> 6 mos) were more frequently treated with a NHA in third-line: in this setting of pts the sequence NHA→ NHA led to a cumulative OS worse than NHA → CABA: 24.8 vs 30.0 (p = 0.022). **Conclusions:** Recognizing the limits of a retrospective analysis, this report is the largest on sequencing use of NAs after DOC and provides some useful suggestions for the therapeutic strategy in DOC pre-treated mCRPC pts.

5027 Poster Session (Board #254), Sat, 1:15 PM-4:45 PM

Relationship between sipuleucel-T (sip-T) cytolytic T lymphocyte (CTL) activity and overall survival (OS) in patients (pts) with metastatic castration resistant prostate cancer (mCRPC). *First Author: Charles G. Drake, Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY*

Background: Sip-T, an autologous cellular immunotherapy approved in the US for pts with asymptomatic/minimally symptomatic mCRPC, is produced by culturing peripheral blood mononuclear cells with the immunogen PA2024 (prostatic acid phosphatase [PAP] conjugated to granulocyte macrophage colony-stimulating factor). A biomarker that can identify mCRPC pts who are likely to respond well to sip-T may inform therapeutic decisions. PA2024 and PAP cellular and humoral immune responses induced by sip-T correlate with prolonged OS (Sheikh, CCI 2013;62:137). Robust CTL activity post sip-T treatment has been reported (Drake, ASCO 2017). We investigated the relationship between sip-T lytic activity (using CD107a expression, a cell surface surrogate marker) and OS in mCRPC pts. **Methods:** PA2024- and PAP-specific CD8+ T (CTL) cells expressing CD107a were identified via flow cytometry at baseline (BL, prior to sip-T infusion), and at 6 and 26 weeks (wks) post-sip-T in pts who were treated in 2 clinical trials (STRIDE: NCT01981122, n = 12 and STAMP: NCT01487863, n = 10), and 3 healthy volunteers (control). **Results:** CTL activity was significantly (p < 0.0001) increased in response to PA2024 and PAP at wks 6 and 26 post-sip-T vs BL. A strong correlation between PAP and PA2024-specific CTL activity was seen at wk 26 (Pearson's R = 0.8973, p < 0.0001), but not at BL or wk 6. At wk 26, there were positive correlations between both PAP-specific CTL activity (R = 0.5187, p = 0.0134) and PA2024-specific CTL activity (R = 0.6735, p = 0.0006) and OS. Median OS for pts with PAP- or PA2024-specific CD107a expression above or below the median CTL activity at 26 wks was 37.1 and 25.2 months, respectively. **Conclusions:** These analyses demonstrate that sip-T induces a robust PAP-specific CTL activity, indicative of tumor lytic activity, which is positively correlated with prolonged OS in mCRPC pts. This finding is a significant addition to the elucidation of the mechanism of sip-T induced immune responses and OS benefit. Clinical trial information: STRIDE: NCT01981122, STAMP: NCT01487863.

5028 Poster Session (Board #255), Sat, 1:15 PM-4:45 PM

Subsequent treatment after abiraterone acetate + prednisone (AA + P) in patients (pts) with newly diagnosed high-risk metastatic castration-naïve prostate cancer (NDx-HR mCNPC): Detailed analyses from the phase 3 LATITUDE trial. *First Author: Kim N. Chi, BC Cancer Agency - Vancouver Centre, Vancouver, BC, Canada*

Background: Pts with NDx-HR mCNPC quickly progress to castration-resistant disease when using androgen deprivation therapy (ADT) alone. The LATITUDE study found significant improvement in OS and rPFS when AA + P was added to ADT. Pts receiving placebo (PBO) could cross over after unblinding at the first interim analysis. We present details on subsequent therapies pts received after unblinding at this second preplanned analysis. **Methods:** NDx-HR mCNPC pts were randomized 1: 1 to AA (1 g QD) + P (5 mg QD) + ADT or PBOs + ADT. Secondary end points, median time to subsequent prostate cancer (PC) therapy and chemotherapy (chemo), and a post hoc exploratory end point, time to life-prolonging therapy, were analyzed by stratified proportional hazards model. **Results:** 1199 pts were enrolled (ITT). At median follow-up of 41.4 mo, median treatment exposure was 25.8 vs 14.4 mo (AA + P vs PBOs, respectively), and treatment was ongoing for 34% and 12% of pts receiving AA + P and PBOs, respectively. 60 PBOs pts crossed over to AA + P, with a median AA + P exposure of 2 mo (57/60 still on AA + P). The most common reason for discontinuation was progressive disease (AA + P, 40%; PBOs, 64%). Pts receiving subsequent and life-prolonging therapies (Table) were 37% and 26% on AA + P, and 58% and 45% on PBOs, respectively. Compared with PBOs, AA + P delayed time to subsequent PC therapy (HR [95% CI] 0.428 [0.361-0.507]), life-extending PC therapy (HR [95% CI] 0.398 [0.326-0.486]), and chemo (HR [95% CI] 0.471 [0.378-0.586]). Median duration of first life-prolonging therapy was 3.7 mo for AA + P (n = 155) and 5.7 mo for PBOs (n = 268). **Conclusions:** Adding AA + P to ADT delays the need for subsequent PC therapy vs ADT for pts with NDx-HR mCNPC. Time to subsequent therapy, life-prolonging therapy, and chemo strongly favored AA + P, even though most pts receiving PBOs remaining on treatment had crossed over to AA + P or other life-prolonging subsequent therapy. Clinical trial information: NCT01715285.

Life-prolonging therapy	AA + P (n = 597)	PBOs (n = 602)
Any, n (%)	155 (26)	268 (45)
Docetaxel	127 (21)	207 (34)
Enzalutamide	47 (8)	89 (15)
Radium-223	23 (4)	39 (6)
Cabazitaxel	17 (3)	42 (7)
AA + P	12 (2)	76 (13)

5029 Poster Session (Board #256), Sat, 1:15 PM-4:45 PM

Genomic and phenotypic evidence for prostate cancer osteomimicry in circulating tumor cells from men with metastatic castration resistant prostate cancer (mCRPC) treated with radium-223. *First Author: Andrew J. Armstrong, Duke Cancer Institute, Duke University, Durham, NC*

Background: Radium-223 is a targeted alpha-therapy that improves survival in men with mCRPC. The biologic basis for radium-223 efficacy is not completely understood. We hypothesized that PC osteomimicry, a form of epithelial plasticity leading to an osteoblastic phenotype, may contribute to the intralesional deposition of radium-223 and subsequent irradiation of the tumor microenvironment. **Methods:** We conducted a pharmacodynamic study (NCT02204943) of radium-223 in men with bone metastatic CRPC to investigate genomic and phenotypic alterations in circulating tumor cells (CTCs), ctDNA, and metastases. Prior to and 3 & 6 months after radium, we collected liquid and metastatic biopsies including CTCs for phenotypic characterization and CTC/ctDNA genomic analysis. The primary objective was to describe the prevalence of CTC bone alkaline phosphatase (BAP) over time. We measured radium-223 decay products in tumor and surrounding normal bone during treatment. **Results:** We enrolled 20 men with heavily pre-treated symptomatic bone predominant mCRPC and treated with radium-223 over a median of 6 doses; 55% had elevated serum BAP. PFS was 5.5 mo; OS was 13.3 mo; 13% had unfavorable ($\geq$5) to favorable ($<$ 5) Cellsearch CTC conversion; 5% had $\geq$30% PSA decline. We found evidence of persistent BAP+CTCs in the majority of men over time during radium-223 therapy despite serum BAP normalization in 53% of men. We identified genomic gain of key osteomimicry regions in CTC DNA, including gains of BAP, osteopontin, and OB-cadherin. We observed greater gamma emission from radium-223 from tumor biopsies than adjacent normal bone. CTC DNA and matched ctDNA studies suggested persistence of aggressive genomic alterations such as AR, FOXA1, and MYC/N-MYC gain and PTEN, GRHL2, FGFR2, and BRCA1 loss. We established several prostate CTC cultures exhibiting evidence of epithelial plasticity and BAP expression. **Conclusions:** Osteomimicry may contribute to the uptake of Radium-223 within bone metastases and may thereby enhance the therapeutic benefit of radium-223. We found genomic and phenotypic evidence of osteomimicry in CTCs from men with mCRPC. Clinical trial information: NCT02204943.

5030 Poster Session (Board #257), Sat, 1:15 PM-4:45 PM

Genomic characterization of ductal adenocarcinoma of the prostate. *First Author: Michael Thomas Schweizer, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Ductal prostate cancer (dPC) is a rare prostate cancer variant associated with poor outcomes. Prior small case series have documented that dPCs may be enriched for alterations in DNA damage repair (DDR) pathway genes and activation of WNT- and PI3K-pathways. To expand these findings, we formed a multicenter collaboration with the goal to provide a comprehensive overview of the spectrum of mutations associated with dPC. **Methods:** We assembled three case series across multiple institutions in the United States and Canada. All patients carried a diagnosis of dPC, and histopathologic classification was confirmed by an expert genitourinary pathologist at each respective institution. All tumor tissue was sequenced on a targeted next-generation sequencing (NGS) assay, UW-OncoPlex, according to previously published methods. Tumor samples were acquired from men with dPC treated at the University of Washington/Seattle Cancer Care Alliance (N = 21), Johns Hopkins Hospital (N = 21) and University of Calgary (N = 8). Only pathogenic/likely pathogenic mutations are reported. **Results:** Tumors from 50 patients with known dPC were sequenced. Overall, 26 (52%) individuals had at least one alteration in a DDR gene, including 7 (14%) with a mismatch repair (MMR) gene mutation. Twenty (40%) cases had mutations predicted to result in PI3k-pathway activation, 15 (30%) patients had mutations that were predicted to result in activation of the WNT-signaling pathway (N = 11 inactivating *APC* mutations; N = 4 activating *CTNNB1* mutations), and 12 (24%) had mutations in genes involved in MAPK-signaling. Other frequently altered genes included: *FOXA1* (N = 17, 34%), *TP53* (N = 9, 18%) and *SPOP* (N = 6, 12%). Alterations in *AR* were relatively infrequent (N = 4, 8%). **Conclusions:** This study confirmed that dPCs are enriched for actionable mutations. Over 50% of cases demonstrated at least one alteration in a DDR pathway gene, including a high percentage of cases with MMR deficiency. Patients with dPC should be offered NGS to guide standard of care treatment (e.g. anti-PD1 therapy, platinum-based chemotherapy) or to triage toward an appropriate clinical trial (e.g. PARP inhibitor trials).

5031 Poster Session (Board #258), Sat, 1:15 PM-4:45 PM

Combination of niclosamide to target androgen receptor variant 7 (AR-V7) and abiraterone to target androgen synthesis for the treatment of castration-resistant prostate cancer (CRPC): Initial results from a phase Ib/II trial. *First Author: Chong-xian Pan, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: The androgen receptor (AR) variant AR-V7 lacks the ligand binding domain, constitutively activates the AR pathway, and confers resistance to Abiraterone (Abi) and enzalutamide (Enza). We discovered that the anti-helminthic drug niclosamide targets AR-V7 and sensitizes resistant CRPC to Enza and Abi. We hypothesize that niclosamide/PDMX1001 potentiates the efficacy of Abi against CRPC. **Methods:** Eligible patients (pts) have progressive CRPC with serum testosterone $<$ 50 ng/dl. No prior Abi was allowed. In the Phase Ib cohort, pts received Abi 1000 mg PO qd, prednisone 5 mg PO bid, with intrapatient dose-escalation of niclosamide/PDMX1001 from 400 mg PO bid to 1600 mg PO tid. Trough niclosamide/PDMX1001 levels were measured. The Phase II cohort will enroll 27 patients with detectable AR-V7 in the peripheral blood. Co-primary endpoints include toxicity and response as determined by the Prostate Cancer Working Group 2 criteria. **Results:** Of 6 pts (age 74-83) in the Phase Ib cohort, five pts tolerated a niclosamide/PDMX1001 dose of 1,600 mg po tid without dose limiting toxicity; per protocol, this is the recommended Phase II dose. Niclosamide/PDMX1001 trough level was 0.305-0.648 μM in the three pts analyzed thus far, higher than the target level of 0.1μM required for anti-cancer activity. Of 6 pts, two pts achieved undetectable PSA ($<$ 0.01 ng/ml) for over 16 cycles and are still going on, compared to historical control 0/30 pts treated with Abi alone; two with partial PSA response ($\geq$50% decrease). Of the remaining two pts, one was prematurely taken off from the study after one cycle because of rising PSA, and the other had PSA decrease of 17.1%, but biopsy of the only enlarged lymph node showed all necrotic tissue. No dose-limiting toxicity was observed. The Phase II cohort will now enroll. Molecular correlative studies will be presented. **Conclusions:** The combination of niclosamide/PDMX1001, Abi and prednisone is well tolerated with promising safety and efficacy data. Targeted serum trough levels of niclosamide are clinically achievable. Clinical trial information: NCT02807805.

5032 Poster Session (Board #259), Sat, 1:15 PM-4:45 PM

Association of metastasis-free survival (MFS) and overall survival (OS) in nonmetastatic castration-resistant prostate cancer (nmCRPC). *First Author: Matthew Raymond Smith, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: Intermediate clinical end points are needed for prostate cancer to inform clinical decisions and facilitate drug development. The international Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group reported that MFS is a strong surrogate of OS in hormone-sensitive localized prostate cancer. We sought to determine the relationship between MFS and OS in patients with nmCRPC. **Methods:** Data from the phase 3 SPARTAN trial in men with high-risk nmCRPC were used to undertake a landmark analysis for MFS. A Cox proportional hazard regression model, adjusted for covariates, evaluated the relationship of OS and development of metastases. The correlation of MFS and OS was assessed by Spearman's and Fleischer's correlation statistics. **Results:** As of May 2017, 1207 patients with nmCRPC had a median time to metastasis of 40.5 months. A landmark analysis showed that patients who developed metastases at 6, 9, and 12 months had significantly shorter median OS compared with those patients without metastasis (Table); after adjusting for baseline covariates, the development of metastases remained associated with OS. A significant positive correlation was observed between MFS and OS (Spearman's correlation coefficient: 0.62; $p < 0.0001$). The more robust, parametric Fleischer's statistical model confirmed the positive correlation (correlation coefficient: 0.69), with ≈50% of variability in OS explained by MFS. **Conclusions:** MFS has a significant association with OS and is predictive of OS in high-risk nmCRPC. This analysis demonstrates that MFS is a meaningful and valid intermediate clinical end point for OS. Clinical trial information: NCT01946204.

Landmark time	6 mo	9 mo	12 mo
Patients with metastases, n	105	175	230
Median OS, mo			
Metastases	NR	33.3	33.3
No metastasis	NR	NR	NR
HR (95% CI)	4.55 (2.94-7.04)	5.39 (3.61-8.06)	6.95 (4.59-10.53)
p Value	< 0.0001	< 0.0001	< 0.0001

NR, not reached.

5033 Poster Session (Board #260), Sat, 1:15 PM-4:45 PM

Relationship of time to metastasis (TTM) and site of metastases in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): Results from the phase 3 SPARTAN trial. *First Author: Matthew Raymond Smith, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: SPARTAN, a randomized placebo (PBO)-controlled phase 3 study, evaluated the effect of apalutamide (APA), an orally administered next-generation androgen receptor inhibitor, in men with nmCRPC and a rapidly rising PSA. In SPARTAN, APA was associated with a 73% relative risk reduction of distant metastasis. We assessed the relationship between TTM and site of metastases after androgen deprivation therapy (ADT) plus APA or PBO. **Methods:** 1207 pts with nmCRPC and PSA doubling time (PSADT) ≤ 10 months were randomized 2:1 to APA (240 mg QD) or PBO, with concurrent ADT (both arms). TTM, defined as time from randomization to first evidence of blinded central review–confirmed radiographically detectable distant metastasis, was assessed by site of metastases, nodal (M1 nodes + soft tissue) vs bone (bone ± M1 nodes) vs visceral (visceral, regardless of other sites). Kaplan-Meier methods were used to analyze TTM. A stratified proportional hazards model with treatment group as a factor, stratified by PSADT, bone-sparing agent use, and loco-regional disease, was used to estimate HR and 95% CI. **Results:** Of those pts with metastases (APA vs PBO, respectively), 30% (52/175) and 40% (76/191) developed nodal metastases, while 57% (100/175) and 52% (100/191) developed bone metastases, and 13% (23/175) and 8% (15/191) developed visceral metastases. The HRs (APA vs PBO; 95% CI) for TTM for the intent-to-treat population were 0.19 (0.13-0.27) and 0.31 (0.23-0.41) for nodal and bone metastases, respectively ($p < 0.0001$). **Conclusions:** Treatment with APA markedly decreased the risk of metastases, regardless of the site of metastasis. The consistency of these results provides further evidence for the clinical benefit of APA in nmCRPC. Clinical trial information: NCT01946204.

5034 Poster Session (Board #261), Sat, 1:15 PM-4:45 PM

Predicting disease progression in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): An analysis from the phase 3 SPARTAN trial. *First Author: Eric Jay Small, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA*

Background: Men with nmCRPC and prostate-specific antigen doubling time (PSADT) of ≤ 10 mo are at high risk for metastatic disease and associated death. Apalutamide (APA), a next-generation androgen receptor inhibitor, extended metastasis-free survival (MFS) by median > 2 years in men with nmCRPC (HR [95% CI] 0.28 [0.23-0.35]; $p < 0.0001$) in SPARTAN. A multivariate analysis (MVA) was undertaken to identify independent predictors of MFS in this pt population. **Methods:** A nonstratified proportional hazards model assessed predictors of clinical end points and examined the following covariates: treatment, PSADT, use of bone-sparing agents, N0 vs N1 at study entry, Eastern Cooperative Oncology Group performance status (ECOG PS), prior therapies, Gleason score, age, and baseline PSA. **Results:** 1207 pts were randomized (806, APA; 401, PBO), and the overall population was evaluated. The following covariates emerged as independent predictors of longer MFS for the combined arms: APA treatment, PSADT > 6 mo, N0 disease, Gleason score at diagnosis ≤ 7, and baseline PSA ≤ 7.8 ng/mL (Table). A relationship between shorter PSADT and faster time to metastasis or death was observed. **Conclusions:** APA treatment, PSADT, nodal disease, Gleason score, and baseline PSA were independent predictors of MFS in pts with nmCRPC from SPARTAN. The treatment effect of APA remained highly significant after adjusting for covariates, with a similar magnitude of risk reduction for MFS in the MVA to that of the original primary analysis. Furthermore, there is a continuous relationship between PSADT and time to metastasis or death. Clinical trial information: NCT01946204.

Covariate	HR (95% CI)	p Value
Treatment, APA vs PBO	0.26 (0.21-0.32)	< 0.0001
Baseline PSA, ≤ 7.8 ng/mL vs > 7.8 ng/mL	0.59 (0.47-0.73)	< 0.0001
PSADT, > 6 mo vs ≤ 6 mo	0.65 (0.51-0.84)	0.0007
Loco-regional disease, N0 vs N1	0.68 (0.52-0.89)	0.0055
Gleason score at diagnosis, ≤ 7 vs ≥ 8	0.75 (0.61-0.92)	0.0063
Age per 10 years	0.88 (0.77-1.01)	0.0784
ECOG PS at baseline, 0 vs 1	0.84 (0.66-1.07)	0.154
Use of bone-sparing agent, yes vs no	0.78 (0.55-1.12)	0.174
Prior hormonal therapies; n, ≥ 2 vs 1	0.90 (0.69-1.16)	0.406

5035 Poster Session (Board #262), Sat, 1:15 PM-4:45 PM

Testing the impact of adjuvant radiotherapy (aRT) after radical prostatectomy (RP) on overall mortality (OM) in prostate cancer patients with pathologically node positive disease: A nationwide analysis. *First Author: Firas Abdollah, Vattikuti Urology Institute, Detroit, MI*

Background: Using institutional data, we have previously identified subgroups of patients with pN1 prostate cancer, who can benefit from aRT plus adjuvant hormonal therapy (aHT) after RP. Our objective is to assess the generalizability of our previous findings using nationwide database. **Methods:** We identified 4276 patients with pN1 disease, who were treated with RP followed by aHT ± aRT, between 2004 and 2013, within the National Cancer DataBase. We stratified patients into five risk groups using pathological data, and based on previously established criteria - Group 1: men with 1-2 positive nodes and Gleason score (GS) < = 6; Group 2: men with 1-2 positive nodes, GS = 7, and stage < = pT3a with negative surgical margins; Group 3: men with 1-2 positive nodes, GS = 7, and stage > = pT3b or positive surgical margins; Group 4: men with 3-4 positive nodes; and Group 5: men with > 4 positive nodes. Univariable and multivariable analyses tested the relationship between aRT status and OM in each group. **Results:** Median (interquartile range) age, # of nodes removed, and # of positive nodes were 62 yrs (56-67), 9 nodes (5-15), and 1 node (1-2), respectively. Mean and median follow-up were 53.6, and 49.4 months, respectively. The percentage of men included in Groups 1 to 5 was respectively 0.6%, 14.6%, 60.1%, 14.2%, and 10.4%. On univariable analysis, aRT improved outcomes in Group 3 and Group 4 only. Specifically, in patients treated without aRT vs with aRT, the 5-year OM was 15.2% vs 11.4% ($p = .01$) in Group3, and 24.7% vs 14.1% ($p < .001$) in Group 4. In multivariable analysis adjusting to age and comorbidity, aRT decrease OM risk in Group 3 (hazard ratio [HR]: 0.78, $p = .01$), and Group 4 (HR: 0.37, $p < .001$), but not in the other groups. **Conclusions:** We validated our previously published results, and demonstrate that certain sub-groups of patients with pathologically proven node positive prostate cancer can benefit from maximizing local control by adding aRT to RP. Our new findings generalize our results to a nationwide setting, and shows that the beneficial impact of aRT is evident also for OM, which is the most significant endpoint in cancer treatment.

5036 Poster Session (Board #263), Sat, 1:15 PM-4:45 PM

Correlates of response to anti-PD-1 immune checkpoint blockade (ICB) in mismatch repair proficient (MMRp) and deficient (MMRd) patients (pts) with metastatic castration resistant prostate cancer (mCRPC). *First Author: Minke Smits, Department of Medical Oncology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands*

Background: Predictive biomarkers are needed to improve the proportion of pts with mCRPC that may benefit from anti-PD-1/PD-L1 ICB. A comprehensive characterization of both genomic alterations as the immunological landscape during ICB may prove fundamental. **Methods:** We investigated correlates of response and progression in pts with mCRPC treated with anti-PD-1 ICB. Pts were selected by PD-L1 $>$ 1% and/or MMRd. Optional pre-treatment and post-progression biopsies were collected for whole-genome sequencing and multiplex IHC. 8-color flow cytometry was performed on frozen mononuclear cells at baseline and on treatment (Tx) using 6 immune-panels. MMR status was evaluated in exosome subsets using nested amplification PCR. Response was evaluated per PCWG3 criteria and Tx was continued until radiological progression with lack of clinical benefit or due to ICB-toxicity. **Results:** At present 13 CRPC pts started Tx with median follow-up of 5.3 months. 10/13 pts had PD-L1 expression $>$ 1%, 6/13 pts were MMRd. Tx is ongoing in 4/13 pts. In evaluable pts with MMRp and MMRd, range of mutational burden (TMB) was 2-8 and 25-74 mutations per megabase, respectively (resp); objective responses were only seen in MMRd pts; PSA $>$ 50% declines were seen in 75% and 13%, resp; median progression-free survival was 3.7 vs 7.8 months, resp ($p = 0.007$). No relationship was seen between PD-L1, TMB and CD3+tumour infiltrating lymphocytes (TILs); TILs were increased in MMRd vs MMRp pts ($p = 0.06$). During Tx, significant changes were seen in circulating T cell populations, including CD4+PD-1+, CD4+CD28+PD-1+, CD8+PD-1+, CD4+ICOS+and CD8+ICOS+ subsets, with on Tx CD4+PD-1+ cells differing between responders and non-responders ($p = 0.03$). Additional results on genomic and immune correlates will be presented in more detail. **Conclusions:** Deep and durable responses to anti-PD-1 ICB were seen in pts with mCRPC, particular those with MMRd. Circulating T cell subsets are associated with response to ICB. An integrative biomarker suite to predict for responsive mCRPC pts to anti-PD-1 ICB is key and these and other correlates should be further investigated.

5038 Poster Session (Board #265), Sat, 1:15 PM-4:45 PM

A transcriptome analysis of castration resistant prostate cancer metastases in a prospective cohort study reveals high expression of AKT pathway genes predictive of long term response to abiraterone acetate/prednisone. *First Author: Manish Kohli, Mayo Clinic, Rochester, MN*

Background: To determine transcriptome based markers associated with long-term response to abiraterone acetate/prednisone (AA/P) in metastatic castration-resistant prostate cancer (mCRPC). **Methods:** RNAsequencing (RNA-seq) of metastatic biopsies were performed in a prospective cohort study of treatment naïve mCRPC patients initiating AA/P (visit1) and repeated after 12 weeks on treatment (visit2). Patients (pts) were followed for time to treatment change (TTTC), defined as time from enrollment until change of AA/P treatment due to progressive disease. The lower and upper quartiles of TTTC for the whole cohort defined short term and long term responders. Previously we published the primary analysis revealing Wnt pathway activation as markers of primary resistance to AA/P (*Annals of Oncology;*2017; PMID29069303). As a secondary study goal gene-set variation analysis (GSVA) of 113 prostate cancer related gene sets was performed with post treatment visit2 RNA-seq data to identify associations with long from short-term responders. RNA-seq based candidates identified as associated with long term response were also evaluated in visit1 biopsies. **Results:** 83/90 enrolled pts had a visit2 biopsy of which 58 biopsy specimens had good quality RNA for analysis. 18/58 had short (median 3.6 months; range 1.4-4.5) and 11/58 patients and long- (median 29 months; range 23.5-41.7) term responses. In the metastases of Visit2 biopsies, long-term responders had lowered expression of steroid-biosynthesis genes (e.g., *CYP7B1, CYP39A1, AKR1D1*) (p-value $<$ 0.005) and higher expression of genes upregulated by AKT activation (e.g. *GOT1, PPP4C, KRT8*) (p-value $<$ 0.02). Similar elevated expression of AKT activation was observed at Visit1 (p-value $<$ 0.04) in long-term responders. The AKT activation signature was also negatively correlated with the steroid biosynthesis signature (Spearman correlation of -0.61, p-value $<$ 2e-7). **Conclusions:** AA/P was more effective in pts with high pre-treatment AKT pathway gene expression signatures suggesting that AKT activation can be used as a predictive biomarker for AA/P. Clinical trial information: NCT# 01953640.

5039 Poster Session (Board #266), Sat, 1:15 PM-4:45 PM

DNA repair mutations and treatment-emergent small cell neuroendocrine prostate cancer (t-SCNC) as hallmarks of distinct subgroups of metastatic castration resistant prostate cancer (mCRPC): Data from the West Coast Prostate Cancer Dream Team. *First Author: Rahul Raj Aggarwal, UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Genomic alterations in DNA repair genes are present in approximately 20-30% of patients with mCRPC. t-SCNC may be increasing in prevalence and is associated with adverse clinical outcomes. Potential overlap between these two subsets of mCRPC was assessed. **Methods:** Eligible patients (pts) underwent a metastatic tumor core needle biopsy at one of 5 centers. Tumor tissue was sent for consensus pathology call (JH, GT, LT) and targeted next-generation DNA sequencing. Chi-square test was used to compare the frequency of genomic alterations in select DNA repair genes (*BRCA1*, *BRCA2*, *ATM*, *CDK12, RAD51*, *PALB2*, *FANCA*, *CHEK2, MLH1*, *MSH2*, *MLH3*, and *MSH6*) between tumors with versus those without small cell histology. Frozen tissue from the same metastatic tumor underwent RNA sequencing (RNA-seq). Pts were prospectively followed for overall survival (OS). **Results:** 119 consecutive biopsies with sufficient tumor to permit histologic assessment and targeted NGS were included, including 14 biopsies (13%) with t-SCNC. In the overall cohort, DNA repair mutations were present in 41 biopsies (34%). By histologic subtype, mutations were present in 40/105 (38%) of adenocarcinoma tumors vs. only 1 of 14 (7%) biopsies with t-SCNC histology ($p = 0.047$). In contrast, *TP53* and/or *RB1* loss were enriched in the t-SCNC cohort (83% vs. 34%, $p = 0.0015$). Unsupervised hierarchical analysis of the transcriptome identified small cell-enriched cluster of biopsies ($N = 12$) that were mutually exclusive of DNA repair mutations and enriched for E2F transcriptional targets on RNA-seq. The presence of t-SCNC histologic differentiation was associated with worse OS from date of mCRPC (median OS 44.5 vs. 36.6 months; log-rank $p = 0.027$); the presence of DNA repair mutations was not ($p = 0.734$). **Conclusions:** Tumors harboring DNA repair pathway mutations or t-SCNC differentiation may represent distinct disease subsets of mCRPC with differing clinical outcomes. Added together, the two subsets account for approximately 40% of mCRPC pts. Independent prospective validation of these findings is warranted. Clinical trial information: NCT02432001.

5040 Poster Session (Board #267), Sat, 1:15 PM-4:45 PM

Lutetium-177 PSMA617 theranostics in metastatic castrate-resistant prostate cancer (mCRPC): Interim results of a phase II trial. *First Author: Shahneen Kaur Sandhu, Department of Medical Oncology, Peter MacCallum Cancer Centre, Australia, Melbourne, Australia*

Background: Lutetium-177 (^{177}Lu)-PSMA617 (LuPSMA) is a radiolabelled small molecule that binds with high affinity to prostate specific membrane antigen (PSMA) enabling tumor-targeted delivery of beta-radiation. We previously reported favourable activity and toxicity in 30 patients with mCRPC and now report updated safety and efficacy results including an additional 20 patient expansion cohort. **Methods:** In this phase II trial, 50 patients with PSMA-avid mCRPC who had progressed after conventional therapies received up to 4 cycles of LuPSMA every 6 weeks. The primary endpoints were 50% PSA response rate (PCWG2) and toxicity (CTCAE v4.3). Other endpoints were objective response rate (ORR), quality of life (EORTC QLQ-C30, BPI), PSA progression free survival (PFS) and overall survival (OS). **Results:** 50 patients (median age 71, range: 50-87) were eligible for treatment. 90% had progressed after abiraterone and/or enzalutamide, and 88% progressed after chemotherapy (84% post docetaxel and 48% following docetaxel and cabazitaxel). A median of 4 (range: 1-4) cycles and mean radioactivity of 7.5 GBq/cycle was administered. At this interim analysis (cut-off: 19 Jan 2018), the primary endpoint of PSA decline $\geq$ 50% was achieved in 31 of 50 patients (62%, 95% CI 47-75%), including 22 patients (44%, 95% CI 30-59%) with a PSA decline $\geq$ 80%. Common toxicities included dry mouth (68%), fatigue (38%), nausea (48%) and pain flare (10%). These were all Grade 1-2, self-limiting or manageable. G3-4 hematological toxicities attributed as possibly related to LuPSMA included thrombocytopenia (10%), anemia (10%), and neutropenia (6%). Median PSA PFS was 7.0 months (95% CI 5.7-8.8) and median OS was 12.0 months (95% CI 10.0-18.7). **Conclusions:** This LuPSMA Phase II trial suggests high response rates and low toxicity in men with mCRPC who progressed after multiple conventional therapies. These compelling results have justified a randomized trial comparing LuPSMA to carbazitaxel (NCT03392428). Updated QOL, ORR, PSA-PFS and OS data will be presented. Clinical trial information: 12615000912583.

5041 Poster Session (Board #268), Sat, 1:15 PM-4:45 PM

Sipuleucel-T (sip-T) overall survival (OS) and clinical outcomes by baseline (BL) prostate-specific antigen (PSA) quartiles in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): PROCEED registry. *First Author: A. Oliver Sartor, Tulane Medical School, New Orleans, LA*

Background: Sip-T is an autologous cellular immunotherapy for asymptomatic/minimally symptomatic mCRPC. IMPACT analyses suggested that OS was longer in treated and control pts with low baseline PSA, and OS benefit was greatest for sip-T vs control in the pts with the lowest PSA (Schellhammer Urol 2013). We analyzed the prognostic value of BL PSA in PROCEED (NCT01306890), a phase 4 registry study in mCRPC pts. **Methods:** Eligible mCRPC pts were scheduled to receive 3 sip-T infusions at ~2-weekly intervals. Objectives included cerebrovascular event risk (primary) and OS (secondary). Follow-up was every 3 months after sip-T for 3 years minimum or until death or withdrawal. This is a *post-hoc* analysis (see Table for tests) of outcomes by PSA quartile. **Results:** 1976 pts were enrolled between 2011–2017: median age 72 yrs; 87% Caucasians, 12% African Americans; 51% had a Gleason score ≥8; prior therapies 78% (local) & 99% (hormonal). 1255 pts died. Median (range) BL PSA was 15 (0–7497) ng/mL. All outcomes in Table were significantly worse in the 2nd, 3rd & 4th PSA quartiles vs the 1st (lowest PSA) quartile. Clinical trial information: NCT01306890. **Conclusions:** OS & time to first ACI are longer in sip-T treated pts in the lowest BL PSA quartile vs sip-T treated pts with higher PSA. Survival of nearly 5 years was seen in the lowest PSA quartile. Although PROCEED did not have a comparator arm, the trend for longer OS is concordant with that seen in IMPACT.

	BL PSA ng/mL			
	≤5.27 N = 472	>5.27–≤15.08 N = 471	>15.08–≤46 N = 472	>46 N = 471
	Median time to event (months; 95% CI)[a]			
	Hazard ratio (95% confidence interval) vs 1st quartile[†]			
OS	48 (44–51)	33 (31–36) 1.6 (1.3–1.9)[†]	27 (24–30) 2.0 (1.7–2.4)[†]	18 (16–21) 3.0 (2.6–3.6)[†]
Time to 1st ACI	10 (9–12)	8 (7–9) 1.4 (1.2–1.6)[†]	7 (6–8) 1.5 (1.3–1.8)[†]	6 (6–7) 1.7 (1.5–2.0)[†]
Time to death due to disease progression[b]	57 (49–not estimable)	37 (34–42) 1.7 (1.4–2.1)[†]	34 (29–39) 2.0 (1.7–2.5)[†]	24 (21–27) 3.1 (2.5–3.7)[†]

[a]Kaplan Meier; [b]clinical or PSA progression
ACI, anticancer intervention (abiraterone, enzalutamide, radium-223, docetaxel, cabazitaxel)
[†]$p < 0.001$ (Cox regression model)

5042 Poster Session (Board #269), Sat, 1:15 PM-4:45 PM

Cancer-related morbidity at the end of life in men with prostate cancer. *First Author: Divya Yerramilli, Harvard Radiation Oncology, Boston, MA*

Background: Limited data exist regarding disease-related complications (DRCs), such as bone fractures and urinary obstruction (UO), near end of life of men who die with prostate cancer. We aimed to describe the burden of DRCs in these patients. **Methods:** As part of the Cancer Research-UK funded Clustered randomised trial of PSA testing for prostate cancer, we examined a cohort of 2603 men who died within 10 years of diagnosis. We collected clinical factors and DRCs. We used univariate analysis to examine association between diagnostic risk-group (low/intermediate, high, and metastatic, as defined by NCCN) and Kaplan-Meier analyses to compare median times to each DRC. We also explored a subgroup of men with metastatic disease who became castrate-resistant. **Results:** Men with higher risk disease at time of enrolment had higher frequency of DRCs and shorter time to each DRC (Table 1). 19% of high risk men developed cord compression, 16% had pathologic fracture, and 10% had renal failure. High risk men had bone metastases (BM) 2.9 months from diagnosis (IQR 1.7-4.9) versus men with low/int. risk disease (4.2 mos, 2.8-6.3), $p < 0.001$. Men with castrate resistance had higher odds of developing BM (OR 1.97, 95% CI (1.53-2.55), $p < 0.001$) and UO (OR 2.10, 95% CI (1.47-3.02), $p < 0.001$). **Conclusions:** In the largest contemporary cohort prostate cancer patients, we found that a significant proportion of men experience cancer-related morbidity prior to death. Men with localized disease at diagnosis can have long intervals until development of DRCs. Furthermore, men who become castrate resistance are particularly vulnerable to DRCs.

Frequency & time to event at 10 years.

	Low/Int Risk (n = 490)	High Risk (n = 616)	T4,N1, or M1 (n = 1005)	
Proportion of Event %				
Median Time to 1st Event, Years (IQR)				
Any Bone Metastases	7.2 4.2 (2.8-6.3)	28.1 2.9 (1.7-4.9)	40.9 1.3 (0.6-2.4)	< 0.001 < 0.001
Pathological Fracture	1.4 6.6 (4.8-7.5)	6.2 4.7 (2.0-5.9)	16.3 1.4 (0.7-3.0)	< 0.001 < 0.001
Spinal Cord Compression	2.1 4.5 (3.4-5.9)	5.2 2.9 (1.3-4.8)	18.8 1.3 (0.8-2.4)	< 0.001 < 0.001
Ureteric Obstruction	2.5 2.7 (2.4-6.5)	10.6 3.6 (2.1-5.6)	15.5 1.6 (0.7-3.1)	< 0.001 < 0.001
Renal Failure Due to Ureteric Obstruction	0.6 4.3 (2.4-7.1)	6.5 3.5 (1.5-5.5)	10.3 1.3 (0.6-2.3)	< 0.001 < 0.001

5043 Poster Session (Board #270), Sat, 1:15 PM-4:45 PM

Association between health-related quality of life (HRQoL) and clinical outcomes in non-metastatic castration-resistant prostate cancer (M0 CRPC): Results from the PROSPER study. *First Author: Gerhardt Attard, The Institute of Cancer Research and the Royal Marsden, Surrey, United Kingdom*

Background: We used the PROSPER trial (NCT02003924) to assess (a) the relationship between time to HRQoL deterioration and prostate-specific antigen (PSA) response and (b) the association between HRQoL and metastasis-free survival (MFS). **Methods:** In PROSPER, 1401 men with M0 CRPC at high risk of metastasis were randomized 2:1 to enzalutamide (ENZA) or placebo. HRQoL was assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) at baseline (BL) and every 16 weeks during treatment. Association between time to first HRQoL clinically meaningful deterioration and PSA response (defined as a ≥50% decline from BL) was explored with stratified Cox regression analyses, and between longitudinal HRQoL changes and MFS with joint models including HRQoL as longitudinal covariate, after adjusting for treatment and relevant clinical/demographic variables. **Results:** Overall, 723 of 1401 (52%) patients were confirmed PSA responders, significantly less likely to deteriorate on all FACT-P scores than non-responders (hazard ratio [HR] 0.56–0.82), except on physical well-being (PWB) [HR 0.90; p = 0.244]. When treatment is included in the model, stronger effects were observed, explained by 98% of PSA responders receiving ENZA. Most FACT-P scores were prognostic for MFS (7 of 10 scores). Every 10-point increase in FACT-P total score (i.e. improvement) was associated with a 6% decreased risk of metastasis (HR [95% confidence interval] 0.94 [0.88, 1.00]). Every 3-point increase in PWB, emotional well-being, or prostate cancer subscale was associated with a 14% (0.86 [0.81, 0.92]), 12% (0.88 [0.78, 0.99]), and 9% (0.91 [0.86, 0.96]) decreased risk of metastasis, respectively. **Conclusions:** The research indicates a ≥50% reduction in PSA from BL would result in reduced risk of HRQoL deterioration, also showing a relationship between changes from BL in HRQoL and metastases. Thus, patient-reported outcomes are not only useful in describing patient experience in clinical trials, but may complement traditional clinical practice methods to monitor disease progression. Clinical trial information: NCT02003924.

5044 Poster Session (Board #271), Sat, 1:15 PM-4:45 PM

Transcriptional and post-transcriptional regulation of ribonucleotide reductase (RRM2) control its oncogenic role in prostate cancer progression. *First Author: Ying Zhang Mazzu, Memorial Sloan Kettering Cancer Center, New York*

Background: The role of DNA repair pathways has been recognized in prostate cancer (PC) progression. Ribonucleotide reductase (RNR) is essential for DNA synthesis and repair. The subunit of RNR complex, RRM2, can regulate tumor initiation, progression and drug resistance in multiple cancer types. There is limited knowledge of RRM2 function in PC. **Methods:** The clinical cohort was analyzed for the correlation of RRM2 and clinical outcomes. RNA-seq and protein array were applied for the mechanism studies. ChIP and reporter assays were used for transcriptional study. **Results:** High level of RRM2 was associated with lethal disease, independent from Gleason grade (odds ratio:3.54; 95% CI, 1.76-7.4) in a cohort of men in the Physicians' Health Study and the Health Professionals' Follow-up Study (n = 404). Transcriptomic analysis revealed that multiple oncogenic transcription factor networks were inhibited by inhibition of RRM2, while p53 signaling was strongly activated. Phosphoproteomic analysis showed inhibition of RRM2 could repress multiple oncogenic signals including SFK, STAT, and Akt/mTOR signaling. Intriguingly, inhibition of RRM2 by siRRM2 and the inhibitor (COH29) could specially target gene profiling of poor-prognosis subtypes (PCS1 and PAM50) in PC. In an *in vivo* PC xenograft model, COH29 strongly inhibited tumor growth. Amplification of RRM2 is rarely observed in PC, thus, transcription and post transcription may largely contribute to overexpression of RRM2. A bioinformatics strategy was developed to search the putative RRM2-targeting transcription factors (TFs). Among 13 TFs candidates, FoxM1 and E2F1 were validated to target the RRM2 promoter. Additionally, we found that methylation-induced silencing of miR-193b could release the inhibition control of FoxM1 and RRM2 in PC cells. DNMTs inhibitor (5-Aza) restored miR-193b expression, leading to the upregulation of RRM2 and FoxM1 in PC cells. **Conclusions:** We reveal the function of RRM2 in PC and unravel the mechanism of dysregulation of RRM2 in PC. Our findings suggest that RRM2 may serve as a key regulator of PC growth and a possible therapeutic target for PC therapy.

5045 Poster Session (Board #272), Sat, 1:15 PM-4:45 PM

c15-160: Enzalutamide (ENZA) plus CC-115 in men with metastatic castration-resistant prostate cancer (mCRPC): A phase 1b Prostate Cancer Clinical Trials Consortium study. *First Author: Dana E. Rathkopf, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Studies in PTEN-deficient prostate cancer (PC) models have shown additive anti-tumor activity when ENZA is combined with PI3K pathway inhibition due to modulation of reciprocal feedback loops. In addition, interplay between AR and DNA-PK regulates hormone-dependent DNA repair and PC progression. This phase Ib trial aims to optimize therapy for mCRPC with the combination of ENZA and the dual mTOR/DNA-PK inhibitor CC-115. **Methods:** This was a phase Ib multicenter trial (NCT02833883) for first-line mCRPC patients. Treatment was fixed dose ENZA (160 mg PO QD) with escalating doses of CC-115 (5 mg and 10 mg PO BID) using a 3 x 3 design. The primary endpoints were safety, PK and the recommended phase 2 dose (RP2D) of the combination. Secondary endpoints were PSA response, time on study and exploratory correlates using tumor biopsies, CTCs and ctDNA. **Results:** 16 patients were treated: 9 in dose escalation and 7 in dose expansion, for a total of 13 patients treated at the RP2D of CC-115 10 mg PO BID. There were no drug-drug interactions. Median time on study was 26 (18-74+) weeks (wks), and 9 patients remain on active treatment. All evaluable patients had a $>$ 50% PSA response, and 60% of patients achieved a $\geq$90% decline. The most common AEs were low grade fatigue (31%) and diarrhea (25%). At the RP2D, 8/13 (62%) patients developed rash: grade 3 (n = 6), grade 2 (n = 1) and grade 1 (n = 1) prompting dose reduction. 12 patients had baseline tissue analysis by IHC and/or NGS: 6 men had PTEN inactivation and 3 had DNA damage response and repair (DDR) alterations. Median time on study for those with PTEN deletions was 25 wks (7-57+), and was 29 wks (28-41+) for those with DDR alterations. Data on ctDNA and CTC biomarkers is pending. **Conclusions:** The combination of ENZA and CC-115 is safe and active in mCRPC, as demonstrated by all evaluable patients achieving a $>$ 50% PSA decline and 60% achieving a $\geq$90% PSA decline. Due to a higher than expected incidence of rash, the protocol was amended to continue with CC-115 at 7.5 mg PO BID for the phase 2 expansion. Funding: Celgene and Gateway for Cancer Research. Clinical trial information: NCT02833883.

5046 Poster Session (Board #273), Sat, 1:15 PM-4:45 PM

Patterns of PSA versus clinically progressive disease in the E3805 CHAARTED trial. *First Author: Alan Haruo Bryce, Mayo Clinic, Phoenix, AZ*

Background: Recent data has highlighted the high frequency with which metastatic prostate cancer can progress either radiographically or symptomatically without a rise in PSA, so called PSA-Clinical discordance. Recognizing this clinical phenomenon is important to implementing appropriate criteria for disease monitoring during treatment. **Methods:** 790 men were accrued from 7/28/06 to 11/21/2012 and randomized to ADT or ADT + Docetaxel at 75mg/m2 every 3 weeks for 6 cycles. Patients were prospectively stratified into high volume (HV) vs. low volume (LV) disease. Clinical PD was defined as increasing symptomatic bone metastases, progression per RECIST criteria, or clinical deterioration due to cancer per investigator's opinion. PSA PD was defined as an increase in PSA of more than 50% above the on-treatment nadir, with two consecutive increases at least 2 weeks apart. Concurrent PSA PD and Clinical PD is defined as both events occurring within 1 month. **Results:** As of the data cutoff of 4/30/2016 403 men with HV disease and 157 with LV disease had progressed. In HV disease, the most common progression pattern was PSA PD followed by clinical PD in both the ADT + D and ADT arms (39.5 vs 43.2%). Clinical PD without PSA progression occurred in 29.5% and 31.0% of patients. In LV disease, the dominant pattern of progression was Clinical PD without PSA PD, occurring in 44.8% and 34.4% of patients. PSA PD followed by clinical PD occurred in 28.4% and 37.8% of patients. Table 1: Disease progression pattern by treatment arm and disease volume Clinical trial information: NCT00309985. **Conclusions:** Clinical progression of disease in the absence of a PSA rise is frequent in patients treated for metastatic castration sensitive prostate cancer. The results highlight the need to incorporate imaging into treatment monitoring rather than relying on PSA alone to trigger imaging.

	High volume		Low volume	
Disease progression pattern	**ADT+D**	**ADT alone**	**ADT+D**	**ADT alone**
Concurrent PSA PD and clinical PD	11 (5.8%)	18 (8.5%)	3 (4.5%)	1 (1.1%)
PSA PD first and then clinical PD	75 (39.5%)	92 (43.2%)	19 (28.4%)	34 (37.8%)
PSA PD only	48 (25.3%)	37 (17.4%)	15 (22.4%)	24 (26.7%)
Clinical PD only	56 (29.5%)	66 (31.0%)	30 (44.8%)	31 (34.4%)
Total	190	213	67	90

5047 Poster Session (Board #274), Sat, 1:15 PM-4:45 PM

Pembrolizumab (Pembro) plus enzalutamide (Enz) in metastatic castration resistant prostate cancer (mCRPC): Extended follow up. *First Author: Julie Nicole Graff, VA Portland Health Care System, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: Anti-PD1 treatment with Pembro is a promising treatment strategy in many solid tumors. Here, we report clinical outcomes of adding Pembro to men with mCRPC progressing on Enz. **Methods:** We enrolled 28 patients with mCRPC who had not previously had chemotherapy for mCRPC or checkpoint inhibitors. Pembro was given 200 mg IV every 3 weeks for 4 doses, which could be repeated for the patients who had stable or responsive disease. The primary endpoint was prostate specific antigen (PSA) response (PSA decline of $\geq$ 50%). Secondary endpoints were radiographic objective response (RECIST 1.1), PSA progression free survival, time to subsequent treatment, and time to death from any cause. Baseline tumor biopsies were done if there was a metastatic deposit amenable to biopsy. We are presenting updated clinical outcomes and evaluation of samples for presence of Program Death-Ligand 1 (PD-L1), microsatellite instability (MSI) and DNA repair defects. **Results:** Five of 28 patients (18%) had a PSA decline of $\geq$ 50%. Three of 12 patients (25%) with measurable disease at baseline achieved an objective response on radiographs. Of the responders (R), one passed away from an unrelated cause without PSA recurrence after 14.2 mos, and one relapsed after 10 mos and did not respond to a second course of Pembro. The other 3 continue to be in response (range 21.9-33.8 mos). For the entire cohort, the median follow up was 22.7 mos, and the median PSA-PFS time was 3.8 mos (95% CI: 2.8 – 9.9 mos). Time to subsequent treatment was 8.2 mos (95% CI: 5.1 – 12.8 mos). Median overall survival was 22.2 mos (95% CI: 14.7 – 28 .4 mos). Median radiographic PFS was 10.8 mos (5-22 mos). There were 8 immune related adverse events in 7 unique patients (hypothyroid 3, hyperthyroid 1, myositis 2, colitis 2). Seventeen patients had baseline biopsies of a metastatic deposit: 3 R, 14 non-responders (NR). Of the 3 R who had baseline biopsies, one had MSI and DNA repair defects. The other 2 had neither. Of the NR who had sequencing, 4 had a DNA repair defects, and none had MSI. None of the biopsies showed tumoral PD-L1 expression (Qualtek, 22C3). **Conclusions:** Pembro has activity in mCRPC when added to Enz. Responses were deep and durable in a subset of patients. Clinical trial information: NCT02312557.

5048 Poster Session (Board #275), Sat, 1:15 PM-4:45 PM

Association of genomic alterations (GAs) in circulating tumor DNA (ctDNA) with progression on abiraterone acetate (AA) or enzalutamide (enza) in advanced prostate cancer. *First Author: Andrew W Hahn, University of Utah Hunstman Cancer Institute, Salt Lake City, UT*

Background: Two androgen axis inhibitors, enza and AA plus prednisone, are approved for the treatment of advanced prostate cancer (aPC). Although initial responses are common with these agents, almost all men experience disease progression. Due to advances in next-generation sequencing (NGS) of ctDNA, it is feasible to assess the tumor genomic landscape in these men at different time points in their treatment. Here, we aim to identify GAs in ctDNA that contribute to resistance to AA and/or enza, which may guide development of novel therapies targeting these GAs. **Methods:** Men with aPC who underwent NGS of ctDNA using G360 (Guardant Health, Inc., Redwood City, CA) from the Huntsman Cancer Institute, University of Utah, and Tulane University were included. Non-matched men were classified as pre-AA/enza, post-AA/enza, and others were excluded. Post-AA/enza was defined as disease progression on AA or enza as one's most recent treatment at the time of testing. G360 is a 73 gene panel that provides complete sequencing of selected exons in order to maximize detection of known somatic mutations, as well as, copy number amplifications across 18 genes and selected fusions in 6 genes. Two-sided Fisher exact tests and t-tests were used to assess the frequency and number of alterations pre- or post-AA/enza, respectively. *P* values of less than .05 were considered statistically significant. **Results:** Of 354 men with advanced prostate cancer and ctDNA NGS available, 128 were pre AA/enza and 84 were post AA/enza. Compared with pre-AA/enza profiles, post-AA/enza studies showed higher mean number of GAs (5.01 vs. 3.03, p=0.02). GAs were significantly higher in *AR* (54.8% vs. 25.8%, p$<$0.0001), *TP53* (51.2% vs. 32.0%, p=0.006), *PIK3CA* (20.2% vs. 9.4%, p=0.04), and *CCNE1* (10.7% vs. 3.1%, p=0.04). Patients with liver metastases had significantly more GAs than those without (11.7 vs. 3.5, p$<$0.0001). **Conclusions:** In these hypothesis-generating data, men who progress on AA or enza have more alterations in *AR*, *TP53*, *PIK3CA*, and CCNE1 and increased number of GAs. These alterations may contribute to treatment resistance and be targets of interest for further drug development.

5049 Poster Session (Board #276), Sat, 1:15 PM-4:45 PM

Bone targeted therapy and skeletal related events in the era of modern therapies for castration resistant prostate cancer with bone metastases. *First Author: Li Zhang, DFCI at St. Elizabeth Medical Center, Boston, MA*

Background: Bone metastases in castration resistant prostate cancer (CRPC) is associated with serious morbidity and costs. The optimal timing of initiation and duration of bone targeted therapy (BTT) Zoledronic acid and Denosumab is unknown in the current era with four classes of therapy for CRPC prolonging overall survival (OS). We sought to define the practice patterns of BTT use and outcomes (skeletal related events - SRE and OS) in a high-volume center in the modern era of metastatic CRPC management. **Methods:** A retrospective cohort of patients (pts) who have received Abiraterone and/or Enzalutamide for CRPC from 2007 to 2017 was identified based on a single-institution's clinical database. The database and electronic medical record review was used for data collection, including pts' characteristics and pattern of BTT uses. Kaplan Meier method and Cox proportional hazards model assessed association of BTT use with time to first SRE and OS, respectively. **Results:** 197 pts were identified, and 79(40%) had $\geq$ 4 bone metastases (BM) and median follow-up was 4.7 (95%CI: 4.2-5.9) years. More pts with $\geq$ 4 BM received BTT with first line therapy (49% vs 32% - p-int $<$ 0.01). Pts with $\geq$ 4 BM, receiving BTT with first line therapy for CRPC had a 19% reduced risk of developing SRE - HR 0.81 (95%CI: 0.45-1.45). Pts with $<$ 4 BM did not have a lower HR when starting BTT with first line CRPC therapy. No OS difference was noted in pts who received BTT with first line therapy or not, regardless of the volume of bone metastases. **Conclusions:** Our cohort suggested that in the modern era, with more effective and greater number of CRPC therapies, pts with $\geq$ 4 BM still benefit from starting BTT with first line CRPC therapy.

5050 Poster Session (Board #277), Sat, 1:15 PM-4:45 PM

Phase II safety and tolerability study of Radium-223 (R223) in combination with enzalutamide (ENZA) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): CTRIAL-IE (ICORG) 13-21. *First Author: Raymond S. McDermott, Adelaide and Meath Hospital, Dublin, Ireland*

Background: R223 and ENZA are standard of care agents in the treatment of patients (pts) with mCRPC. The combination of R223 and ENZA is of interest due to differing modes of action and non-overlapping toxicity profiles, leading to the potential for synergy. **Methods:** This phase II, open-label, multicentre single arm study (NCT02225704) enrolled pts with mCRPC to bone with or without visceral/lymph node involvement who had progressed on androgen deprivation therapy. Prior docetaxel chemotherapy for hormone sensitive prostate cancer was allowed. Pts received 6 cycles of R223 (55 kBq/kg IV Q4W) in combination with ENZA (160mg/day), followed by ENZA alone until disease progression (PD), unacceptable toxicity or consent withdrawal. The primary endpoint was safety for the 6 months of combination therapy which is reported here. **Results:** From July 2015 to July 2017, 45 pts were enrolled in Ireland. 42 pts (93.3%) received all 6 cycles of combination therapy. A total of 13 pts (28.9 %) had grade (gr) 3/4 adverse events (AEs). The most frequent gr 3/4 AEs (Table) were neutropenia (n = 3, 6.6%) and fatigue (n = 3, 6.6%) followed by nausea, lower respiratory tract infection (LRTI), lymphocytopaenia, leukopaenia, hyperkalaemia, hypokalaemia, back pain, headache, urticaria, syncope and hypertension (all n = 1, 2.2%). 2 pts (4.4%) discontinued treatment due to AEs, gr 3 LRTI (n = 1) and gr 2 nausea and pain (n = 1). One pt discontinued due to symptomatic PD. There were no therapy-related deaths. **Conclusions:** R223 in combination with ENZA is well tolerated with acceptable early safety and toxicity profiles consistent with those seen when they are used as single agents and allowing for concomitant administration. Evaluation of secondary endpoints including skeletal related events with longer follow up is ongoing. Clinical trial information: NCT02225704.

	R223 + ENZA (n = 45)				
AE	**Gr 1**	**Gr 2**	**Gr 3**	**Gr 4**	**n (%)**
Fatigue	14	8	3		25 (55.5)
Nausea	14	6	1		21 (46.6)
Back pain	6	3	1		10 (22.2)
Neutropenia	1	5	2	1	9 (20)
Headache	4	1	1		6 (13.3)
Lymphocytopaenia	1	3	1		5 (11.1)
Leukopaenia	2	2	1		5 (11.1)
Hypertension		4	1		5 (11.1)
LRTI		3	1		4 (8.8)
Urticaria			1		1 (2.2)
Syncope			1		1 (2.2)
Hypokalaemia			1		1 (2.2)
Hyperkalaemia			1		1 (2.2)

5051 Poster Session (Board #278), Sat, 1:15 PM-4:45 PM

Efficacy and tolerability of first-line abiraterone + prednisone (ABI) versus enzalutamide (ENZ) for metastatic castration-resistant prostate cancer (mCRPC) in men $\geq$ 80 years: A retrospective cohort study. *First Author: Daniel Khalaf, British Columbia Cancer Agency - Vancouver Centre, Vancouver, BC, Canada*

Background: ABI and ENZ are first-line treatment options for mCRPC with comparable efficacy. In men $\geq$ 75 years, ABI and ENZ are associated with higher rates of adverse events. For very elderly patients (pts), the efficacy and tolerability of ABI and ENZ have not been directly compared. **Methods:** Retrospective analysis in pts $\geq$ 80 years of age who received ABI or ENZ for first-line treatment of mCRPC between July 2009 and September 2016 at the BC Cancer Agency. Medical records were reviewed for clinical characteristics and outcomes including PSA response rate (PSA50) (decrease of $\geq$50% from baseline), time to first progression (TTP) (PSA, radiographic or clinical progression) and overall survival (OS). **Results:** There were 106 pts in the ABI cohort and 104 in the ENZ cohort. Baseline characteristics were well balanced including median age 85 years (IQR 83-88); median Charlson Comorbidity Index (CCI) 7 (IQR 7-8); hemoglobin (HB) $<$ 130 in 75%; ECOG PS 0-1 in 60%; serum alkaline phosphatase (ALP)/LDH $>$ upper limit of normal (ULN) in 32%/35% and bone/lung/liver metastasis in 86%/10%/6%. Time from start of androgen deprivation therapy to castration-resistance (TTCR) was $<$ 12 months (m) in 16% vs 29% for ABI vs ENZ (p = 0.031). PSA50 was 43.4 % for ABI vs 77.9 % for ENZ ($p < 0.001$, X^2) and median TTP was 4.7 m vs 8.0 m (HR 1.52, 95% CI 1.12-2.08). On multivariable analysis, factors associated with TTP were: treatment arm ABI vs ENZ (HR 1.76, 95% CI 1.27-2.45), ALP $>$ ULN (HR 1.89, 95% CI 1.34-2.68), HB $<$ 130 (HR 1.61, 95% CI 1.13-2.30), CCI $>$ 7 (HR 1.57, 95% CI 1.13-2.19) and TTCR $>$ 12 months (HR 1.73, 95% CI 1.18-2.55). At least one dose reduction due to toxicity was required for 7.5% of pts for ABI vs 29.8% for ENZ ($P<0.001$, X^2). For pts in the ENZ cohort who had a dose reduction, the median TTP was 11.8 m vs 6.2 m for those without (HR 0.65, 95% CI 0.40-1.08). Median OS was 13.2 m for ABI vs 18.7 m for ENZ (HR 1.20, 95% CI 0.89-1.63). **Conclusions:** In this very elderly cohort, the PSA50 and TTP were superior for the ENZ cohort compared to the ABI cohort despite more dose reductions in the ENZ cohort. The retrospective nature of the analysis is a limitation of this study.

5052 Poster Session (Board #279), Sat, 1:15 PM-4:45 PM

Evolution of the genomic landscape of circulating tumor DNA (ctDNA) in advanced prostate cancer (aPC) over treatment and time. *First Author: David D. Stenehjem, University of Minnesota College of Pharmacy, Duluth, MN*

Background: While men with aPC respond to initial treatment, most will progress and require sequential therapies. Due to advances in next-generation sequencing (NGS), it is feasible to assess the tumor genomic landscape via blood or tumor tissue at different time points in treatment. Much debate exists over the concordance of tissue (tDNA) and ctDNA NGS. Some hypothesize that the genomic landscape of aPC evolves with treatment and time; however, there is a paucity of experimental data to support these statements. In this exploratory analysis, we compare the genomic landscape of aPC as detected by commercially available tDNA and ctDNA NGS platforms at different points during the course of disease. **Methods:** Men with aPC from the Huntsman Cancer Institute, University of Utah with matched tDNA NGS using FoundationOne (Foundation Medicine, Cambridge, MA) and ctDNA NGS using G360 (Guardant Health, Inc., Redwood City, CA) were included. Clinical data was collected retrospectively. Exonic regions from 69 genes covered by both platforms were included for analysis. Paired *t*-tests were used to assess number of genomic alterations (GAs) between testing platforms and were confirmed with nonparametric testing. Number of alterations was assessed by time and number of treatments between tDNA and ctDNA testing by multivariate nonparametric trend tests. **Results:** 101 men with aPC who had matched tissue and ctDNA NGS were included. In men with no new treatments and $\leq$ 1 year between tests, a similar number of GAs were detected in both tests (2.0 vs. 2.2, p=0.78). In contrast, men with $\geq$ 1 new treatment between tests had significantly more GAs after treatment (5.0 vs. 2.4, p=0.005). Total number of GAs was correlated with number of new treatments between testing (p=0.003) and not time between testing (p=0.76). **Conclusions:** In these hypothesis-generating data, the genomic landscape of aPC evolves with subsequent therapies. These data suggest that, in addition to baseline tumor genomic profiling, a contemporary tumor genomic profile at the time of disease progression may optimize guidance towards subsequent therapy selection.

5053 Poster Session (Board #280), Sat, 1:15 PM-4:45 PM

Unique patterns of the selection and change in circulating tumor cell (CTC) phenotypes and genotypes by drug class in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Biomarkers to predict outcomes for individual patients (pts) on standard of care Rx is an unmet medical need in the treatment of mCRPC. Using baseline (BL) blood draws, we previously reported a phenotypic CTC heterogeneity algorithm that predicted for differential survival times on ARSi vs. taxanes. We have also observed that certain gene alterations as well as genomic instability are linked to different CTC phenotypic subtypes. We sought to associate CTC phenotypes to response, and to characterize phenotypic and genotypic changes to populations of CTCs associated from selection pressures by specific drug classes. **Methods:** 456 blood samples (228 matched BL and on-therapy) from 184 unique mCRPC pts were collected and processed utilizing the Epic Sciences CTC platform. CTCs were enumerated and characterized for phenotype (n = 11,722) including CTC subtypes, from pts who received ARSi therapy (n = 131), taxanes (n = 57) or a platinum containing regimen (n = 40). 985 CTCs of various phenotypic subtypes were single cell sequenced for DNA copy number variation. **Results:** CTCs were detected in 88.6% (202/228) BL and in 76.3% (174/228) on therapy samples, med = 3.5mL (0 to 490) and median = 2.7mL (0 to 992) respectively. Changes in CTC phenotypic features were observed unique to specific therapy classes, including changes to nuclear size, shape and texture. Persistent CTC phenotypes in pts treated with ARSi and taxane, but not platinum, were enriched with cells having AR over-expression and genomic instability ($p < 0.001$) while those in pts treated with ARSi but not taxane, were enriched with PTEN, RB1 and TP53 loss (all $p < 0.001$). Models to predict resistance to the therapies based on specific CTC prevalence in early on-therapy draws will be presented. **Conclusions:** We observed broad CTC phenotypic and genotypic heterogeneity prior to Rx, and patterns of clonal selection specific to different standard of care drug classes. Models utilizing these insights have potential to predict resistance if observed pre-therapy or during therapy to enable a change in therapy prior to clinical manifestation. Further development of these models is ongoing.

5054 Poster Session (Board #281), Sat, 1:15 PM-4:45 PM

Clonal concordance and genomic heterogeneity in single CTC copy number alterations vs. paired IMPACT metastatic tissue sequencing from mCRPC patient samples. *First Author: Howard I. Scher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: High CTC phenotypic heterogeneity is associated with non-response to ARSi but not taxane chemotherapy assessed using a non-invasive rapid blood test. The MSK-IMPACT™ NGS assay is FDA approved for tumor tissue profiling to guide treatment selection. The frequency of directly actionable alterations in prostate cancer (PC) is ~35%. Recognizing many cancers harbor intra, inter and intracellular heterogeneity, we sought to evaluate concordance of sequencing single CTCs vs. paired biopsy analyzed by MSK-IMPACT, to assess CTC clonality in circulation vs. tumor, the relationship to CTC phenotypic heterogeneity and response. **Methods:** Metastatic tumor biopsies collected from 50 mCRPC patients (lymph nodes n = 26, bone n = 9, visceral n = 10 and other soft tissue n = 5) prior to new treatment were sequenced by MSK-IMPACT. Time matched blood samples (n = 50) were collected for CTC analysis (Epic Sciences). CTCs (n = 644, range 2-27, med = 13) underwent single cell low pass whole genome sequencing for copy number variation (CNV). Intra-patient CTC clonality was estimated based on similarity of DNA copy number segments. Phenotypic CTC heterogeneity was estimated by previously developed algorithms and compared to genomic clonal heterogeneity. **Results:** Large chromosomal CNV were detected in CTCs from 47/50 (94%) patients, 34/50 (67%) had multiple subclones with distinguishable CNV. Overall, a median of 3 distinct clones/pt (range 1-6) were observed across the cohort, with the number of clones not associated with the number of CTCs detected. Genomic clones observed in tissue were confirmed in CTCs from 32/50 (64%) pts, while 16/50 (32%) pts were discordant in CTCs, 2 pts were unevaluable. > 4 genomic clones were found in 13/50 pts, 12 of which had high phenotypic heterogeneity scores (top 50%). **Conclusions:** Single CTC sequencing is often concordant to metastatic tissue, but unique CTC clones highlight the prevalence of sub-clonal disease in mCRPC patients under-sampled by tissue biopsy. High genomic heterogeneity can be predicted by phenotypic CTC heterogeneity and may be useful to find patients unlikely to respond to targeted therapy.

5055 Poster Session (Board #282), Sat, 1:15 PM-4:45 PM

Clinical outcomes with cumulative tumor suppressor gene (TSG) alterations in castration sensitive (CSPC) and resistant (CRPC) prostate cancer. *First Author: Anis Hamid, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Alterations (alt) in *TP53*, *PTEN* and *RB1* TSGs have been identified in some prostate cancers. Preclinical data suggest that co-operative loss of 2 or more TSGs drives development of more aggressive disease. **Methods:** We identified men who underwent targeted exome sequencing (DFCI PROFILE) of CSPC (localized [L] and M1 presentation) and CRPC tissue samples. Biomarker(BM)-positive(+) was defined as copy number loss or deleterious mutation of ≥1 TSG (*TP53*, *PTEN* or *RB1*). For pts presenting with L-CSPC, Kaplan-Meier method estimated time from biopsy to PSA relapse/metastasis/death (EFS), CRPC, and death (OS). Cox model assessed association of BM status and outcomes, adjusted for age, stage and Gleason score in multivariate analyses (MVA). Time from ADT start for M1-CSPC to CRPC and death was also estimated. For M1-CRPC, duration on 1st line CRPC therapy and time from CRPC to death was estimated, adjusting for age, volume and location of metastasis in MVA. Association of cumulative BM+ hits (0 vs 1 vs 2 vs 3) and outcomes was assessed. **Results:** For BM+ frequencies see table. L-CSPC with BM+ had a shorter EFS (median 2.6 years, HR 1.95, 95% CI 1.22-3.13) and time to CRPC (HR 3.36, 95% CI 1.01-11.16). MVA confirmed association with EFS (HR 1.84, p = 0.029). More gene hits lead to greater risk of relapse (MVA; 1 vs 0 hit: HR 1.75, p = 0.05; 2/3 vs 0: HR 2.74, p = 0.04). None of the 43 M1-CSPC pts who were BM-neg had died with median follow-up of 3.3 yrs; BM+ 4-year OS was 64%. Only 4 (8%) of the CRPC cohort (n = 48) were BM-neg and with a median follow-up 4.1 years, only 1 had died (5.2 yrs). Cumulative TSG loss was associated with shorter duration on 1st line therapy in MVA (3 vs 0/1 hit: HR 2.86, p = 0.013). **Conclusions:** Deleterious *TP53*, *PTEN* and *RB1* variants are associated with increased risk of relapse (M0) and death (M1) in CSPC and shorter duration on 1st line therapy in CRPC. BM-neg in CRPC is rare but may represent a subset of pts with very good prognosis. Poorer outcomes are seen with cumulative gene hits across cohorts.

Cohort	N	Median follow-up (yrs)	1 or more TSG-alt	2 or more TSG-alt
L-CSPC	205	3.1	39%	8%
M1-CSPC	43	3.3	63%	18%
M1-CRPC	48	4.1	92%	63%

5056 Poster Session (Board #283), Sat, 1:15 PM-4:45 PM

Clinical outcomes following androgen receptor axis therapies (ARAT) among men with prostate cancer (PCa) having major cardiovascular diseases (CVDs) or extreme polypharmacy (EPP): A population based study. *First Author: Grace L. Lu-Yao, Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA*

Background: The safety of ARAT (Abiraterone acetate (AA) and Enzalutamide (ENZ)) among men with existing CVDs or EPP (≥10 concurrent medications) is unknown since patients with these conditions are often excluded from the clinical trials. This study was undertaken to fill these knowledge gaps. **Methods:** This population-based study identified PCa patients from the linked Surveillance, Epidemiology and End Result-Medicare files diagnosed during 1/1/1991-12/31/2013. The primary endpoint was 6-month overall mortality after drug initiation. CVDs include acute myocardial infarction (AMI), atrial fibrillation (AFIB), congestive heart failure (CHF), stroke, and ischemic heart disease (IHD). Cox proportional hazard models were used to assess the risk of 6-month mortality. **Results:** Our study included 3,116 patients treated with AA only or AA as first ARAT and 1,162 patients treated with ENZ only or ENZ as first ARAT. The characteristics of the patients treated with AA and ENZ were similar. The majority of patients (67%) treated with ARAT had existing CVDs and the prevalence of EPP before drug initiation was high (46% for AA and 44% for ENZ). Six-month mortality was elevated among men with existing CVDs treated with ARAT (Table 1). EPP with ARAT was associated with an increase in 6-month mortality (AA: HR 3.22, 95% CI 2.16-4.81; ENZ: HR 1.63, 95% 1.03-2.58). To our knowledge, this is the largest population-based study to provide outcomes data among patients with existing CVDs or EPP, who were under-represented in the pivotal trials. The elevated 6-month mortality of men with CVDs or EPP treated with ARAT suggested that these patients represent a vulnerable patient population. Further studies are needed to determine the clinical benefits and risks of ARAT in men with advanced PCa and existing CVDs or EPP.

Hazard ratios for 6-month mortality among men with cvds conclusions.

	AMI/no CVD	CHF/no CVD	AFIB/no CVD	Stroke/no CVD	IHD/no CVD
AA	1.89 (1.27-2.80)	1.54 (1.20-1.97)	1.61 (1.22-2.12)	1.61 (1.18-2.20)	1.14 (1.13-1.77)
ENZ	1.46 (0.73-2.92)	1.20 (0.79-1.81)	1.80 (1.14-2.82)	1.50 (0.90-2.50)	1.40 (0.99-1.99)

5057 Poster Session (Board #284), Sat, 1:15 PM-4:45 PM

Safety data from a phase II randomized trial of radium-223 dichloride (Ra-223) plus enzalutamide (Enza) vs. Enza alone in men with metastatic castration refractory prostate cancer (mCRPC). *First Author: Benjamin Louis Maughan, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Ra-233, a bone targeting alpha radiopharmaceutical, and Enza, are approved for mCRPC. Per SWOG0421, the subset of men with mCRPC with the highest bone metabolism marker levels had improved survival with concomitant decrease in these markers on treatment (Rx) with atrasentan, a bone targeting agent (Lara P et al, JNCI, 2014). Our hypothesis was that Rx with Ra-223+ Enza will be safe and feasible, and decrease bone metabolism markers compared to Enza alone. **Methods:** In this phase 2 trial (NCT02199197), men with progressive CRPC on continuous androgen deprivation therapy were included. Ra-223 was administered at standard dose of 55 kBq/kg IV Q4 weeks x 6, and Enza at 160 mg orally daily until disease progression or unacceptable toxicities. Primary objectives: 1) Safety and feasibility of combining Ra-223+Enza, 2) changes in the bone metabolism markers with Rx. Secondary objectives included time to progression, skeletal events, percent change in opioid use. The pre-specified primary safety endpoint was the proportion of patients treated with the combination who experienced grade 3+ cytopenias relative to historic controls (21%) from the phase 3 ALSYMPCA trial using an exact binomial test with a one-sided 0.05 significance level. All adverse events between arms were compared using Fisher's Exact Test. **Results:** Safety data are presented. 49 patients were accrued between 2014-2017. 35 men received Rx with Ra-223+Enza and 14 men with Enza alone. The primary safety endpoint occurred in 3 patients in the combination arm (incidence 8.6%, n = 35 patients), and in 0 patients in the Enza only arm (n=14). These were similar to historic data (ALSYMPCA trial) of monotherapy with Ra-223 (P = 1.00), and not different between arms (P=0.55). Serious adverse events (SAEs), "regardless" of attribution were similar in both arms (P=0.66). **Conclusions:** Combining Ra-223+Enza is safe and feasible in men with progressive mCRPC with no difference observed in SAEs regardless of attribution between two arms. Specifically, there was no incidence of skeletal related events in either arm. Safety data will be elaborated during the meeting. Clinical trial information: NCT02199197.

5058 Poster Session (Board #285), Sat, 1:15 PM-4:45 PM

Six-month patient-reported outcome (PRO) results from AQUARiUS, a prospective, observational, multicenter phase 4 study in patients (Pts) with metastatic castration-resistant prostate cancer (mCRPC) receiving abiraterone acetate + prednisone (AAP) or enzalutamide (ENZ). *First Author: Antoine Thiery Vuillemin, Medical Oncology Unit, CHU Minjoz, Besançon, France*

Background: AQUARiUS is an ongoing study of PROs and medical resource use in chemotherapy-naïve pts with mCRPC newly initiated on AAP or ENZ in a real-world setting. Initial 3-month (mo) subset analyses suggested favorable outcomes for AAP vs ENZ in cognition and fatigue. We report 6-mo results. **Methods:** AQUARiUS prospectively collects PROs on quality of life, cognition, fatigue, and pain using EORTC QLQ-C30, FACT-Cog, BFI-SF, and BPI-SF questionnaires, over 12 mos. PROs were collected at baseline (BL) and during visits based on real-world practice schedules. Incidence of clinically meaningful worsening (CMW) and change from BL scores were determined, adjusting for BL characteristics. **Results:** All 211 pts were analyzed (AAP, n = 105; ENZ, n = 106). BL characteristics were well balanced (no significant differences). A significantly lower proportion of pts on AAP vs ENZ experienced CMW for cognition and fatigue during the first 6 mos of treatment (TABLE). Clinical trial information: NCT02813408. PRO scales with consistent significant differences ($p < 0.05$ for ≥ 3 consecutive time points) in change from BL scores were "perceived cognitive impairments" and "comments from others" (FACT-Cog); "fatigue right now," "usual level of fatigue," and "worst level of fatigue" (BFI-SF); and "cognitive functioning" and "fatigue" (EORTC QLQ-C30); all favored AAP over ENZ. Where significant differences for these scales were not maintained through the full 6-mo period, nonsignificant trends in favor of AAP were observed. **Conclusions:** These 6-mo results continue to suggest that AAP provides favorable outcomes vs ENZ for certain measures of cognition and fatigue in pts with mCRPC.

	Pts with ≥ 1 episode of CMW during first 6 mos of treatment			
	AAP, %	ENZ, %	Odds ratio[a] (95% CI)	*p*
FACT-Cog				
Perceived cognitive impairments	27	56	0.27 (0.13-0.56)	0.0004
Comments from others	20	39	0.38 (0.17-0.85)	0.0191
BFI				
Fatigue right now	42	55	0.46 (0.22-0.95)	0.0365
Usual level of fatigue	40	55	0.42 (0.20-0.86)	0.0174
EORTC QLQ-C30				
Fatigue	31	53	0.36 (0.18-0.73)	0.0047
Appetite loss	20	46	0.28 (0.13-0.61)	0.0013

[a]AAP vs ENZ.

5059 Poster Session (Board #286), Sat, 1:15 PM-4:45 PM

Expression of immune checkpoints (ICs) on circulating tumor cells (CTCs) in men with metastatic prostate cancer (mPC). *First Author: Tian Zhang, Duke University Medical Center, Durham, NC*

Background: Most immune checkpoint inhibitors have shown limited efficacy in unselected men with mPC, and there is limited understanding about which ICs are relevant in mPC. We evaluated ICs on the cell surface of CTCs in patients (pts) with mPC. **Methods:** Pts were enrolled prospectively at the Duke Cancer Center in three cohorts: A) metastatic castration resistant prostate cancer (mCRPC) starting abiraterone acetate (AA) or enzalutamide (enza), B) mCRPC after AA or enza, and C) metastatic hormone sensitive PC (mHSPC). The Cellsearch platform was used to capture EpCAM- and CK-expressing CTCs and analyzed for PD-L1, PD-L2, B7-H3, and CTLA-4 expression at baseline, 12 weeks, and disease progression. **Results:** Through December 2017, we enrolled 18 pts (6 in cohort A, 8 in cohort B, and 4 in cohort C). CTCs were detectable in every cohort. At baseline, B7-H3 was the most prevalent IC while the other ICs were detected less frequently (**Table 1**). PD-L1 expression on CTCs was heterogeneous between and within pts; PD-L1 expression also changed during treatment and upon disease progression (Table 1). Rare CTCs expressed CTLA-4 and PD-L2, mostly in cohort B. **Conclusions:** Patients with mPC have detectable and heterogeneous ICs on CTCs, particularly PD-L1 and B7-H3, which can be monitored over time. B7-H3 was the most prevalent IC on CTCs, regardless of disease state. Our preliminary data suggest that pts with mCRPC post-enza/AA have higher levels of IC expression on CTCs compared with pts with mHSPC and mCRPC prior to enza/AA. We found evidence for heterogeneous CTC expression of CTLA-4 and PD-L2, particularly in men with mCRPC post-AA/enza.

Percentage of CTCs with immune checkpoint over total CTCs at baseline, week 12, and disease progression.

	Median (range) of CTCs at baseline/ week 12/PD	PD-L1 (%) baseline/week 12/PD	PD-L2 (%) baseline/week 12/PD	CTLA-4 (%) baseline/week 12/PD	B7-H3 (%) baseline/week 12/PD
A: mCRPC pre AA/ enza	16 (0-59)/6 (0-50)/ 31 (16-49)	7/4/8	1/2/1	0/0/0	92/53/66
B: mCRPC post AA/ enza	4 (0-54)/1 (0-4)/3 (0-108)	25/17/9	3/50/0	15/50/1	98/80/94
C: mHSPC	3 (0-52)/0 (0-1)/NE	11/100/NE	6/NE/NE	3/NE/NE	68/NE/NE

NE: Not evaluable; PD: disease progression

5060 Poster Session (Board #287), Sat, 1:15 PM-4:45 PM

The association of *BRCA1* and *BRCA2* mutations on prostate cancer risk, frequency, and mortality: Systematic review and meta-analysis. *First Author: Mok Oh, University of Arizona College of Pharmacy, Tucson, AZ*

Background: A prior meta-analysis (Fachal, Prostate, 2011) suggested no association between *BRCA1* mutation and prostate cancer (PCa). Several additional *BRCA2* studies have shown an association with PCa risk and mortality. We conducted a systematic review and meta-analysis of *BRCA1* and *BRCA2* studies to estimate PCa risk in *BRCA* mutation carriers, evaluate the frequency of *BRCA* mutation carriers in PCa patients (pts) and compare survival rate among *BRCA* mutation carriers and non-carriers. **Methods:** PubMed/ MEDLINE, Embase and Cochrane databases were searched for relevant studies for the above objectives. Meta-analyses were conducted using unadjusted odds ratio (OR) with 95% confidence interval (95%CI) for PCa incidence; frequency (%) of BRCA mutation in PCa pts; and hazard ratio (HR) with 95%CI for cancer-specific survival (CSS) and overall survival (OS). Random effects analyses were performed for overall *BRCA* (*BRCA1* or *BRCA2*), with subgroup analyses for *BRCA1* and *BRCA2* separately. **Results:** 10 cohort, 10 case-control, 38 frequency and 11 survival studies were included. Being a *BRCA* carrier was associated with a significant increase in PCa risk (OR 1.97, 95%CI 1.60-2.42), with *BRCA2* mutation being associated with a greater risk of PCa (OR 2.72, 95%CI 2.10-3.54) than *BRCA1* (OR 1.39, 95%CI 1.07-1.81). The frequency of *BRCA1* and *BRCA2* carriers in PCa patients was 1.8% and 2.7% respectively. OS (HR 2.21, 95%CI 1.64-2.30) and CSS (HR 2.63, 95%CI 2.00-3.45) were significantly worse among *BRCA2* carriers compared to non-carriers, whereas OS (HR 0.47, 95%CI 0.11-1.99) and CSS (HR 1.07, 95%CI 0.38-2.96) were not statistically significant when comparing *BRCA1* carriers and non-carriers. **Conclusions:** Meta-analyses revealed a 1.97-fold greater risk of prostate cancer in overall *BRCA* mutation carriers. This elevated PCa risk was attributable largely to a 2.72-fold greater risk of PCa in *BRCA2* carriers and a moderate 1.39-fold greater risk in *BRCA1* carrier. *BRCA2, but not BRCA1,* mutations were associated with higher PCa mortality. *BRCA* mutation may be a clinical factor to stratify high-risk patients and provide clinical strategies for more effective targeted treatments for patients with PCa.

5061 Poster Session (Board #288), Sat, 1:15 PM-4:45 PM

Differences in genomic signatures and opportunities for targeted and immunotherapy treatment between castrate-resistant *TMPRSS2:ERG* fusion-positive and -negative refractory acinar (CRPC) and neuroendocrine prostate cancer (CRNEPC). *First Author: Leszek Kotula, Upstate Medical University, Syracuse, NY*

Background: We hypothesized that sub-categorization of *TMPRSS2* fusion status would impact therapy opportunities in patients with clinically advanced CRPC and CRNEPC. **Methods:** CGP was performed on FFPE samples of 2,424 CRPC and 143 CRNEPC. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined by principal components analysis of optimal homopolymer loci. **Results:** All (100%) CRPC and CRNEPC were advanced and therapy resistant. *TMPRSS2*+ CRPC features significantly more *TP53* and *PTEN* GA, whereas *TMPRSS2*- CRPC featured more *MYC* and *ATM* GA; differences in *BRCA2* and *RB1* GA were not significant. *RB1* GA were significantly more frequent in CRNEPC than CRPC, whereas GA in *AR* and *ATM* were more frequent in CRPC. *TP53* GA frequencies were higher in *TMPRSS2*+ CRNEPC than in *TMPRSS*+ CRPC, whereas GA in *PTEN* and *MYC* were similar in comparative groups. Median TMB was higher in CRNEPC than CRPC, and higher in *TMPRSS2*- compared with *TMPRSS*+ tumors; TMB was more often ≥10 or ≥20 mut/Mb in *TMPRSS2*- tumors. MSI-High status was more frequently identified in the *TMPRSS2*- CRPC and CRNEPC groups. **Conclusions:** The 31% frequency of *TMPRSS2*+ CRPC in this study, lower than the 46% reported in early stage disease (TCGA data) suggests that this biomarker may be linked to a favorable prognosis. For CRNEPC, the higher frequency of *TMPRSS2*- tumors is not as striking. CGP reveals significant differences in both targetable GA and markers of immunotherapy response between *TMPRSS*+ and *TMPRSS2*- prostate tumors.

	TMPRSS2:ERG+ CRPC (755)	*TMPRSS2:ERG*- CRPC (1,669)	Significance	*TMPRSS2:ERG*+ CRNEPC (57)	*TMPRSS2:ERG*- CRNEPC (86)	Significance
Median Age (years)	66	65		64	66	
GA/tumor	4.5	4.3	NS	4.9	5.3	NS
TP53	55%	39%	P < 0.0001	60%	65%	NS
PTEN	45%	27%	P < 0.0001	51%	25%	P < 0.0001
AR	25%	22%	NS	11%	10%	NS
MYC	9%	14%	P = 0.0004	9%	11%	NS
BRCA2	8%	10%	NS	7%	14%	NS
ATM	4%	7%	P = 0.0032	0%	5%	NS
RB1	8%	6%	NS	58%	52%	NS
MSI-High	1%	3%	P = 0.01	0%	3%	NS
TMB median (mut/Mb)	1.7	2.7	NS	2.7	3.6	NS
TMB ≥ 10 mut/Mb	3%	6%	P = 0.04	2%	18%	P = 0.003
TMB ≥ 20 mut/Mb	2%	4%	P = 0.01	2%	7%	NS

5062 Poster Session (Board #289), Sat, 1:15 PM-4:45 PM

Prevalence of homologous recombination deficiency (HRD) mutations in localized prostate cancer according to Gleason grade: Implications for neoadjuvant clinical trial design. *First Author: Catherine Handy, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: Approximately 5-10% of men with localized prostate cancer have homologous recombination deficiency (HRD) mutations, yet it is unknown if these vary by Gleason score. In order to help design neoadjuvant trials for the HRD+ population and to minimize the number-needed-to-screen, we sought to determine if the prevalence of HRD mutations is influenced by Gleason grade. **Methods:** 484 localized prostate adenocarcinoma cases with somatic DNA sequencing data and Gleason grade information were interrogated using The Cancer Genome Atlas (TCGA) repository. HRD mutations were defined as pathogenic lesions in the following genes: *ATM, BRCA1/2, CDK12, CHEK1/2, FANCA, FANCD2, FANCL*, *GEN1, NBN, PALB2, RAD51* and *RAD51C*. A separate analysis was also conducted restricting the gene list to *BRCA1/2* and *ATM*, since deficiencies in these genes have the strongest association with PARP-inhibitor response. R software was used for analyses. **Results:** The prevalence of (any) HRD mutation was 11.6%, 10.8%, 14%, 16.8% and 25.0% for Gleason sums 6, 7, 8, 9 and 10, respectively. When analyzed using Grade Groups, the prevalence of (any) HRD mutation was 11.6%, 6%, 17.8%, 14% and 17% for Grade Groups 1, 2, 3, 4 and 5, respectively (Table). Those in Grade Group 3 and greater had 2.5 times higher odds of harboring at least one HRD mutation compared to those in Grade Groups 1 and 2 (16.8% vs 7.3%, P= 0.002). When specifically considering only *BRCA1/2* or *ATM* lesions, the mutation prevalence was 6.1 times higher in Grade Group 3 and above compared to Grade Groups 1 and 2 (8.9% vs 1.6%, P= 0.0006) (Table). **Conclusions:** HRD mutations in general, and *BRCA1/2/ATM* mutations specifically, are enriched in localized prostate cancers with Gleason Grade Group 3 and higher (*i.e.* primary pattern 4 and higher). We propose that these patients could be targeted for neoadjuvant (or adjuvant) clinical trials using PARP inhibitors in HRD+ populations.

HRD mutation prevalence by gleason grade group.

	At least 1 HRD mutation			At least 1 *BRCA1/2/ATM* mutation		
Grade Group		**N**	**Total**		**N**	**Total**
1	11.6 %	5	43	2.3%	1	43
2	6.0 %	9	149	1.3%	2	149
3	17.8 %	18	101	10.9%	11	101
4	14.0 %	7	50	8.0%	4	50
5	17.0 %	24	141	7.8%	11	141

5063 Poster Session (Board #290), Sat, 1:15 PM-4:45 PM

Early changes in PSA and association with outcomes in mCRPC patients. *First Author: Pasquale Rescigno, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Declines in prostate specific antigen (PSA) levels at 12-weeks are currently used to evaluate treatments response in metastatic castration resistant prostate cancer (mCRPC). Early PSA fall by 30% at 4-weeks (PSA4w30) has been previously shown to be associated with better outcome in mCRPC in a small single-centre cohort. **Methods:** We identified mCRPC patients who had received Abiraterone Acetate (AA) between 06.01.06 and 08.09.17 in 13 cancer centres worldwide. Eligible patients had PSA levels assessed at baseline, after 4-weeks and/or 12-weeks of treatment. PSA response was defined as a ≥30% decline from baseline and PSA progression as a ≥25% increase from baseline. Association with overall survival (OS) was analysed using landmark multivariable Cox regression adjusting for previous chemotherapy, including cancer centre as a shared frailty term. **Results:** We identified 1057 patients who had received AA (447 pre-chemotherapy, 610 post-chemotherapy), with 835 patients having PSA values available at 4 and 12 weeks. Overall, 372/835 (44.5%) had PSA4w30; this associated with longer OS (mOS 22vs15 months; HR = 0.62; 95%CI 0.53–0.72; p < 0.001). A ≥30% PSA decline at 12-weeks (PSA12w30) associated with a lower mortality (mOS 22vs14; HR = 0.57; 95%CI = 0.48–0.67; p < 0.001). Sensitivity analyses confirmed the association between PSA4w30 and OS when pre- and post-chemotherapy cohorts were analysed separately. PSA4w30 strongly correlated with PSA12w30 (ρ = 0.92; p < 0.001). In total, 320/372 (86%) patients with a PSA decline at 4-weeks had a PSA decline at 12-weeks. Conversely, 11/835 (1.3%) patients progressed at 4-weeks and then met the criteria for PSA12w30. PSA4w30 remained correlated with OS (HR = 0.56; 95%CI = 0.48–0.65; p < 0.001) in multivariate analyses including other established prognostic factors in mCRPC (baseline ALP, LDH, Hb, M status and Gleason at diagnosis). **Conclusions:** PSA changes in the first 4-weeks of AA therapy are strongly associated with clinical outcome in mCRPC patients and should be prospectively evaluated in early treatment switch decision trials.

5064 Poster Session (Board #291), Sat, 1:15 PM-4:45 PM

Molecular and clinical implications of *CHD1* loss and *SPOP* mutations in advanced prostate cancer. *First Author: Pasquale Rescigno, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: *CHD1* deletions (*CHD1*del) and *SPOP* mutations (*SPOP*mut) frequently co-occur in prostate cancer (PCa) with lower frequencies observed in castration-resistant PCa (CRPC). Responses to standard treatments in this subset of patients have not been previously reported. We studied the molecular and clinical characteristics of *CHD1*del/*SPOP*mut metastatic CRPC (mCRPC) analyzing CHD1 presence/loss during disease progression and correlation to response to Abiraterone acetate (AA). **Methods:** We identified mCRPC patients who had hormone naïve (HNPC) and CRPC tumor samples available: these were analyzed for CHD1, PTEN and ERG expression by immunohistochemistry (IHC). *SPOP* status was determined by targeted next generation sequencing (NGS). Correlations with *CHD1/SPOP* status and clinical outcomes and responses to AA were analysed using Cox-regression and Log-Rank analyses. **Results:** Tumor samples from 89 patients who had progressed from HNPC to CRPC were analyzed in a cohort enriched for *SPOP*mut. CHD1 protein loss was detected in 11 (15%) and 13 (17%) of HNPC and mCRPC biopsies, respectively. Comparison of CHD1 protein levels were feasible in 56 matched, same patient HNPC and mCRPC biopsies. CHD1 protein status correlated in 55 of 56 cases of the matched samples (98%). We identified 22 patients with somatic *SPOP*mut, with 6 of these mutations not reported previously in PCa, including one (p.A187T) located in the BTB domain in an area reported to be necessary for homodimerisation and other two located in residues (E50, R121) previously associated with endometrial cancer. *SPOP*mut and/or CHD1 loss was associated with a higher response rate to AA (SPOP: OR = 14.50 p = 0.001; CHD1: OR = 7.30, p = 0.08) and a longer time on abiraterone (SPOP: HR = 0.37, p = 0.002, CHD1: HR = 0.50, p = 0.06). **Conclusions:** *SPOP* mutated mCRPCs are strongly enriched for CHD1 loss and seem to be likely sensitive to AA. We envision that determination of *SPOP/CHD1* status might serve treatment selection in mCRPC.

5065 Poster Session (Board #292), Sat, 1:15 PM-4:45 PM

Analysis of genomic alterations in matched circulating tumor cell DNA (CTC DNA) and plasma tumor DNA (ctDNA) in men with metastatic castration resistant prostate cancer (mCRPC). *First Author: Santosh Gupta, Medical Oncology, Duke University, Durham, NC*

Background: CTC and ctDNA-based, actionable genomic alterations are being increasingly utilized for precision oncology therapies. However, the concordance of genomic alterations in CTC DNA vs. ctDNA is not established. **Methods:** After CTC/ctDNA isolation, we performed whole genome copy number alteration (CNA) analysis in 88 men with mCRPC treated with enzalutamide (E) or abiraterone acetate (A) (n = 72), and radium-223 (n = 16). We performed comparative genomic hybridization (aCGH) and low-pass whole genome sequencing (~0.1x, lpWGS) for CNA assessment and evaluated the concordance between gains/losses in matched CTCs, ctDNA and germline DNA in 63 samples; 32 from 16 men receiving radium-223, and 31 from 16 men receiving E/A. **Results:** Of the 88 enrolled men with mCRPC, 51% had ≥5 Cellsearch CTCs. We identified common genomic gains in 63 CTCs and matched ctDNA in FOXA1 (56 vs. 75%), KDM6A (51 vs. 21%), AR (48 vs. 64%), MYCN (30 vs. 5%), and MYC (18 vs. 24%). Common copy losses included ZFHX3 (60 vs. 44%), FGFR2 (43 vs. 32%), PHLPP1 (33 vs. 33%), BRCA1 (29 vs. 30%), and RB1 (13 vs. 21%). We analyzed AR copy gain status in 21 ctDNA specimens by aCGH and lpWGS, finding a concordance of 89%; detection correlated with high ctDNA content and CTC number. However, we found only 33% AR gain concordance in 38 CTC aCGH samples vs ctDNA lpWGS samples, and 63% AR gain concordance for CTC aCGH vs. ctDNA aCGH samples collected at the same time points. In 63 matched CTCs and ctDNA samples, we observed high concordance in gain of FOXA1 (91%) and AR (63%), moderate concordance for gain of MYC (55%), NCOR2 (41%), loss of ZFHX3 (53%) and PHLPP1 (48%), but low concordance for gain of KDM6A (25%) and loss of BRCA1 (39%), RB1 (38%), and FGFR2 (37%). **Conclusions:** Detection of genomic alterations at the whole genome level is feasible in ctDNA and CTC DNA and concordance across ctDNA platforms was high. However, we found variable concordance in CTC DNA vs. ctDNA copy number alterations depending on the specific gene, type of alteration, ctDNA concentration, and CTC enumeration likely reflecting biologic variability or differences in assay sensitivity. Clinical trial information: NCT02269982, NCT02204943.

5066 Poster Session (Board #293), Sat, 1:15 PM-4:45 PM

Prostate cancer (PCa) incidence and severity in hypogonadal men treated with testosterone compared to untreated controls: Experience from 6,500 patient-years from a controlled registry study. *First Author: Ahmad Haider, Private Urology Practice, Bremerhaven, Germany*

Background: EAU Guidelines state that there is no evidence that testosterone (T) treatment in hypogonadal men increases PCa risk. **Methods:** 412 symptomatic men with T≤350 ng/dL received T undecanoate 1000 mg every 3 months following an initial 6-month interval for up to 12 years (T-group). 393 hypogonadal men (age range 51-74) decided against testosterone (CTRL). Total observation time covered approximately 6,500 patient-years. PCa was excluded by transrectal ultrasound, digital rectal examination and PSA measurement before treatment/observation initiation. Examinations were repeated between one and four times per year. Biopsies were performed when indicated according to EAU Guidelines. **Results:** In the T-group, 11 men (2.7%) were diagnosed with PCa. In CTRL, 35 (8.9%) were diagnosed with PCa. The mean baseline age of PCa patients was 65.3 years in the T-group and 63.7 in CTRL. In the T-group, the average time span between the day of first injection and positive biopsy was 386 days (range: 260-546). In CTRL, PCa was diagnosed at any time during the observation time. In the T-group, radical prostatectomy was performed in all men. All but 2 patients had a Gleason score (GS) ≤6, and all had a primary GS of 3. Tumor grade was G2 in all 11 (100%), tumor stage T2a in 7 (64%), T2b in 3 (27%), and T2c in 1 (9%) patient(s). In CTRL, radical prostatectomy (RP) was performed in all but 6 patients who received radiation therapy (RT). 7 patients received RP+RT. GS was ≤6 in 2 patients, 7 men had a GS of 7, 16 a GS of 8, and 10 a GS of 9. 4 men had a primary Gleason score of 3, 22 had 4, and 9 had 5. Tumor grade was G2 in 8 (22.9%) and G3 in 27 (77.1%) patients, tumor stage T2a in 2 (5.7%), T2c in 1 (2.0%), T3b in 13 (37.1%) and T3c in 19 (54.3%) patients. In CTRL, biochemical recurrence occurred in 10 (28.6%) patients. These patients received androgen deprivation therapy (ADT). 12 (34.3%) patients died of whom 7 were on ADT. In the T-group, no biochemical recurrences or deaths occurred during the observation time. **Conclusions:** PCa incidence and severity in testosterone-treated hypogonadal patients were less compared to untreated hypogonadal controls.

5067 Poster Session (Board #294), Sat, 1:15 PM-4:45 PM

Clinical qualification of plasma androgen receptor (p*AR*) status and outcome on abiraterone acetate (AA) plus prednisone or dexamethasone (+P/D) in a phase II multi-institutional study in metastatic castration resistant prostate cancer (mCRPC). *First Author: Anuradha Jayaram, Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, Sutton, United Kingdom*

Background: p*AR* gene aberrations in mCRPC patients (pts) may be associated with worse outcome on AA+P/D. **Methods:** This was an international, multi-institutional, open-label phase 2 study of AA (1000mg QD) and 1 of 4 steroid regimens in asymptomatic, chemo-naïve mCRPC pts (NCT01867710). A pre-defined exploratory objective was to evaluate the association of p*AR* status and radiographic progression free survival (rPFS), PFS and time of long-term ADT to randomisation. We used a validated droplet digital PCR assay to classify pts as p*AR* copy number (CN) gain. **Results:** Baseline plasma DNA was collected from 151 pts of the 164 intention-to-treat pts; 135 pts were available for p*AR* CN analysis, excluding samples with long-fragment DNA. 21(15%) pts had *AR* CN gain. There was a significant association for *AR* gain and shorter rPFS (median 5.7 months [m]:p*AR* gain vs 23.7 m:p*AR* normal; HR: 2.78; 95% CI 1.34 - 4.6; p = 0.004) and PFS (median, 4.90m: p*AR* gain vs 16.2m: p*AR* normal; HR: 2.28; 95% CI 1.3 - 4; p = 0.004). Multivariate analysis is in Table 1. PSA ≥50% decline was 65% for p*AR* normal vs 53.3% for p*AR* gain. (OR: 0.6; 95% CI, 0.2 – 1.7; = 0.33). The time from start of long-term ADT to randomisation, was significantly shorter in pts with *AR* CN gain at castration resistance (8m: p*AR* gain vs 29.5m: p*AR* normal; p = 0.004). **Conclusions:** In this prospectively defined cohort, p*AR* normal in chemo-naïve mCRPC pts had a significantly longer rPFS with AA+P/D. Previous data suggests shorter response to ADT associates with primary resistance to AA +P/D. The novel observation that these pts are enriched for p*AR* gain provides a biological rationale for this. Clinical trial information: NCT01867710.

	rPFS			PFS		
	HR	95% CI	*p*	HR	95% CI	*p*
***AR* Gain (yes vs no)**	2.5	1.2- 5.3	0.01	2.1	1.1 – 4.14	0.03
LDH > ULN vs < ULN	1.1	0.62 – 2.04	0.07	1.1	0.67 – 1.93	0.63
ALP > ULN vs < ULN	0.9	0.5 – 1.7	0.8	1.1	0.61 – 1.79	0.87
Disease Site						
Bone/bone +Lymph node(LN) vs LN	0.5	0.24 – 1.14	0.1	0.6	0.27 – 1.16	0.12
Visceral vs Bone/Bone+LN	1.1	0.14 – 8.16	0.95	1.3	0.17 – 9.78	0.80
Visceral vs LN	0.5	0.06 – 3.87	0.50	0.4	0.06 – 3.39	0.43
≥ 5 Bone mets vs < 5	1.0	0.52 – 2.09	0.12	1.3	0.69 – 2.36	0.44
Baseline PSA	1	1	0.17	1	1	0.66

5068 Poster Session (Board #295), Sat, 1:15 PM-4:45 PM

Association of high CD8+ tumor infiltrating lymphocytes at prostatectomy with improved survival of prostate cancer patients. *First Author: Yuanquan Yang, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: High $CD8^+$ tumor infiltrating lymphocytes (TILs) are associated with improved survival in many solid tumors. However, its prognostic value in prostate cancer (PCa) is unclear. **Methods:** Tumor microarrays of 290 patients with localized PCa who underwent radical prostatectomy (RP) at Roswell Park Comprehensive Cancer Center were retrospectively analyzed using immunohistochemistry. High risk patients were preferentially included to ensure adequate post-RP events for correlation. Six malignant and three benign cores from each patient were stained with anti-CD8 antibody (Dako, M7103). $CD8^+$ cells were scored using Aperio (Leica Biosystems). Patients with < 5-year follow-up were excluded. The $CD8^+$ cell density was dichotomized at 25th percentile. Clinical outcomes collected from a prospective quality assurance database were compared in high vs low TIL group. PSA persistence and recurrence were defined using NCCN prostate cancer guidelines. **Results:** 230 patients with median age 61 years met follow-up requirement. There were no significant differences in age, Gleason sum (GS), diagnostic PSA, margin status and pTNM stage between high vs low TIL group. High TILs were associated with improved 5-year overall survival (OS) (98% vs 91%, p = 0.008) and PCa-specific survival (99% vs 95%, p = 0.041) when compared to low TILs. High intratumoral/benign CD8 ratio (> 1) was associated with improved metastasis-free survival (p = 0.031). The median biochemical recurrence (BCR)-free survival was longer in high TIL group (62 vs 42 m). However, statistical significance was not reached (p = 0.18). The prognostic import of high TILs was independent of surgical pathology. In subgroup analysis, it was also associated with improved 5-year OS (97% vs 88%, p = 0.042) in GS > 7 or pT3/4 patients (n = 149, 65%) and prolonged BCR-free survival (NR vs 58 months, p = 0.036) in GS < = 7 and < = pT2 patients. In contrast, the CD8 density of benign cores was not associated with clinical outcomes. **Conclusions:** High $CD8^+$ TILs are independently associated with improved survival after RP in this majority of high-risk PCa population. This observation suggests that immunomodulation aimed at promoting $CD8^+$ TILs may be beneficial.

5069 Poster Session (Board #296), Sat, 1:15 PM-4:45 PM

Treatment outcomes for patients (Pts) with metastatic castration resistant prostate cancer (mCRPC) pts and DNA damage repair gene mutations. *First Author: Steven Yip, BC Cancer Agency Vancouver Cancer Centre, Vancouver, BC, Canada*

Background: DDRm occur in 15-30% of pts with mCRPC. While BRCA2 germline mutations are linked to aggressive local disease, outcomes in pts with mCRPC and DDRm continue to be characterized. **Methods:** Leukocyte DNA from 631 consecutive mCRPC pts were screened for germline ATM, BRCA1/2, CDK12, and PALB2 truncating mutations using targeted sequencing. 312/631 were assessed for somatic DDRm (sDDRm) and homozygous deletions in the same genes, using matched plasma cell-free DNA. Additional pts with gDDRm were identified through our hereditary cancer program (HCP). We examined time from androgen deprivation therapy (ADT) initiation (± docetaxel) to CRPC; time to PSA progression (TTPP), PSA response (50% decline from baseline), and objective response rate (ORR) on 1st-line AR-targeted therapy, docetaxel, PARP inhibitor, platinum-based chemotherapy, and radium-223 for mCRPC; and overall survival (OS). Outcomes in pts with DDRm and pts with DDR wild-type (WT) status (with available clinical data, n = 113) were compared using the log-rank test. **Results:** gDDRm and sDDRm were identified in 33/631 (5.2%, BRCA2 = 25) and 35/312 (11.2%, BRCA2 = 13) pts, respectively. The HCP identified an extra 3 BRCA2 and 1 BRCA1 pts. Across 59/72 pts with available clinical data, 23/59 (39.0%) presented with de novo metastatic disease. Median time to CRPC from ADT (± docetaxel) initiation was 12.1 mo (gDDRm = 12.5 mo, sDDRm = 11.5 mo). The Table displays outcomes in pts with DDRm. All pts with DDRm had a TTPP on 1st-line AR-targeted therapy of 3.6 mo vs 7.4 mo in WT pts (p = 0.002). Median OS from the time of ADT initiation and time of CRPC was 41.5 mo (gDDRm = 41.5 mo, sDDRm = 43.5 mo) and 28.4 mo (gDDRm = 28.4 mo, sDDRm = 20.9 mo), respectively. **Conclusions:** In our cohort, pts with DDRm have poor AR-targeted therapy outcomes. Encouraging responses were observed with docetaxel, PARP inhibitors and platinum-based therapy.

	AR-Targeted Therapy	Docetaxel Chemo	PARP Inhibitor	Radium-223	Platinum Chemo
N	46	13	7	11	4
Median TTPP in mo (95% CI)	3.6 (2.7-5.8)	5.0 (2.7-6.9)	11.3 (5.5-NR)	3.0 (0.3-4.6)	NR (NR-NR)
PSA Response (N)	54% (25/46)	54% (7/13)	14% (1/7)	9% (1/11)	75% (3/4)
ORR (N)	3% (1/32)	45% (5/11)	50% (3/6)	0% (0/6)	50% (2/4)

5070 Poster Session (Board #297), Sat, 1:15 PM-4:45 PM

Tumor-infiltrating lymphocytes in biallelic-CDK12 mutated prostate cancer. *First Author: Maialen Barrero, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Cyclin-dependent kinase 12 (CDK12) mutations have been described in lethal prostate cancer (PCa) and are reported to impact DNA repair including homologous recombination repair, and associate with an inflamed phenotype. Biomarker studies evaluating tumor infiltrating lymphocytes (TILs) enumeration have reported their prognostic and predictive utility. Here we evaluate the clinical outcomes and the immune-infiltrate characteristics of a cohort of PCa patients with biallelic CDK12 mutations. **Methods:** 418 PCa patients were sequenced in our Institution with targeted next-generation sequencing between February 2015 and December 2017. Biallelic-CDK12 cohort (n = 11) was compared to a control group (n = 47), including other mutations and monoallelic-CDK12 alterations. Immunofluorescence (IF) was performed on primary or metastatic tumor samples to identify TILs. Lymphocyte infiltration per cell type was examined using a negative binomial regression model with the sum of tumor area included as an exposure term. Kaplan-Meier method and Cox model were used for the survival analyses. **Results:** Among 418 patients sequenced, 20 were CDK12 mutant (4.8%), of which 11 (2.6%) had biallelic mutations. The median overall survival (OS) from diagnosis was 7.6 years for the control group and 10.0 years for the biallelic-CDK12 cohort (HR 0.63; 95%CI 0.27-1.51; P = 0.30). One biallelic-CDK12 mutated patient was excluded from IF analysis due to poor quality tumor tissue. TIL counts/mm^2 were significantly higher in CDK12 mutated tumors, with higher CD4$^+$ (95%CI 0.11-1.94; P = 0.03), CD8$^+$ (95%CI 0.24-2.18; P = 0.02) and overall T cell counts (95%CI 0.09-1.73; P = 0.03). No significant difference was noted for CD4$^+$/FOXP3$^+$ (95%CI -1.49-0.69; P = 0.47). **Conclusions:** This is the first study reporting survival outcomes and TILs characteristics in biallelic-CDK12 mutated PCa. Despite being limited by the retrospective design and limited sample size, these pilot data provide a rationale to further explore the role of biallelic-CDK12 mutations in PCa as a predictive biomarker for immunotherapy.

5071 Poster Session (Board #298), Sat, 1:15 PM-4:45 PM

Impact of treatment sequence on the outcomes of metastatic castration resistant prostate cancer patients (mCRPC) with germline BRCA2 mutations: A subanalysis of the PROREPAIR-B study. *First Author: Nuria Romero-Laorden, Hospital Universitario La Princesa, Madrid, Spain*

Background: Germline mutations in BRCA2 have been identified in 3-5% of mCRPC patients. PROREPAIR-B (Castro et al ESMO 2017) is the first prospective study to report a worse survival from mCRPC associated to these mutations. Significant interactions between treatment-type (androgen signaling inhibitors:ASI/Taxane) and *BRCA2* status for cause-specific survival (CSS) from 1st line (1L; p = 0.015) and 2nd line (2L; p = 0.006) were identified. In this exploratory subanalysis, we report mCRPC outcomes according to *BRCA2* status and treatment sequence. **Methods:** PROREPAIR-B (NCT03075735) is a prospective multicentre observational cohort study. Patients who were taxane- and ASI-naïve at time of mCRPC, and who were treated or intended to treat with any of these two sequences: a) 1L ASI, 2L taxane; or b) 1L taxane; 2L ASI were elegible. Enpoints: assessment of the impact of *BRCA2* on CSS, PFS from 1L initiation to clinical/radiological progression on 2L or death (PFS2). Analyses were stratified according to treatment sequence. **Results:** 348 out of 419 patients were eligible: 190 (7 *BRCA2*) for the ASI-taxane and 158 (7 *BRCA2*) for the taxane-ASI sequence. Patients in the taxane-ASI cohort were significantly younger (p < 0.001) and have worse ECOG (p = 0.002), higher PSA (p = 0.007), elevated LDH (p < 0.001) and elevated ALP (p = 0.01) compared to the ASI-taxane group, but there were not significant differences between *BRCA2* patients in both groups. No significant differences in outcomes between *BRCA2* carriers and non-carriers were observed with the ASI-Taxane sequence: CSS (median 24.0 vs 31.1 months, p = 0.9) and PFS2 (18.9 vs 21.1 months, p = 0.6). Conversely, in the taxane-ASI sequence BRCA2 status was associated to significantly worse CSS (10.7 vs 28.4 m, p < 0.001) and PFS2 (8.6 vs 17.1 m; p < 0.001). In the multivariable analyses *BRCA2* remained an independent prognostic factor for CSS (HR 2.95; CI95% 1.21-7.15) and PFS2 (HR 5.50; CI95% 2.35-12.89). **Conclusions:** These results suggest that the outcomes of *BRCA2* mutation carriers may differ according to treatment sequences. This contributes to explain the differences in outcomes reported by previous series. Clinical trial information: NCT03075735.

5072 Poster Session (Board #299), Sat, 1:15 PM-4:45 PM

Association of changes in the B-cell receptor (BCR) repertoire with overall survival after sipuleucel-T (sip-T) treatment for prostate cancer. *First Author: Li Zhang, University of California San Francisco, San Francisco, CA*

Background: Sip-T, an autologous cellular immunotherapy for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), induces antibody responses to prostatic acid phosphatase and secondary antigens (antigen spread) that correlate with improved survival (Sheikh 2013, GuhaThakurta 2015); however, little is known about cancer immunotherapy-induced changes to the BCR repertoire. We evaluated the correlation between BCR diversity/dynamics and overall survival (OS) after sip-T. **Methods:** mCRPC pts (N = 52) received sip-T (wk 0, 2, 4) with enzalutamide (NCT01981122; Petrylak 2018). Blood samples were collected at wk 0, 2, 4, 6, 26, and 52. BCR diversity was assessed by clonality in samples from 19 pts. Dynamics of BCR repertoire changes were evaluated by the proportion of overlapping clones at two time points (Zhang 2017). Correlations between OS and BCR diversity/dynamics were analyzed by logrank test and Cox proportional hazards models. **Results:** There was minimal overlap of BCR clones from wk 0 to later time points suggesting clonal shuffling in BCR repertoire. BCR clonality peaked at wk 6 (wk 6 vs wk 0, p = 0.039; wk 6 vs wk 2, p = 0.030), indicating focusing of the BCR repertoire during and soon after sip-T. Clonality decreased from wk 6 to wk 26 and wk 52 (p = 0.049 and 0.037, respectively), reflecting long-term increase in diversity after sip-T. The proportion of overlapping clones from wk 0 to wk 2 and wk 0 to wk 4 were inversely correlated with OS during sip-T (p = 0.048 and p = 0.043, respectively) showing that a lower proportion of overlapping clones predicted better OS. Thus, greater changes in BCR repertoire during treatment, including creation of new clones and disappearance or reduction in frequency of preexisting clones, were associated with an OS benefit. **Conclusions:** Sip-T led to focusing of BCR repertoire during and soon after treatment, which may signify the magnification of relevant clones and transition of clones out of the periphery. Greater dynamic change in the BCR repertoire induced by sip-T correlated with longer survival. These findings corroborate the prior association between the breadth of antigen spread and OS after sip-T. Clinical trial information: NCT01981122.

5073 Poster Session (Board #300), Sat, 1:15 PM-4:45 PM

A pre-specified statistical model based on four kallikrein markers in blood to predict advanced pathology on radical prostatectomy. *First Author: Thomas Steuber, Martini-Clinic Prostate Cancer Center Hamburg-Eppendorf, Hamburg, Germany*

Background: Four kallikrein markers in blood – commercially available as the 4Kscore – has been shown to be highly predictive of Gleason Grade Group (GGG) 2 or higher prostate cancer at biopsy. However, tissue sampling and grading at biopsy is an imperfect gold standard and may miss aggressive disease. We measured the kallikrein in cryopreserved blood in patients undergoing radical prostatectomy at a tertiary referral center during 2000 - 2010, during which it was common to treat GGG1 prostate cancer. **Methods:** Aggressive disease was defined as primary Gleason grade 4, any grade 5, seminal vesicle invasion, extra-capsular extension (ECE) or lymph node invasion. ECE was excluded in a sensitivity analysis. A second sensitivity analysis excluded patients with low scores from the kallikrein panel, who may never have been biopsied had they received a 4Kscore. We assessed improvement in discrimination when the kallikrein panel was added to a base model using established clinical predictors: age, prostate specific antigen, clinical stage and grade. We also examined a model that included number of positive cores and mm of cancer. We pre-specified that we would separately assess men with GGG1 – where the decision concerns confirmatory biopsy – and GGG2 – where the decision would concern treatment vs. active surveillance. **Results:** The cohort included 2284 men with data on cores for 1294. The kallikrein panel was significantly associated with advanced pathology after adjusting for clinical variables ($P < 0.001$). Overall, the panel added 0.014 to the AUC of clinical model, with larger effects within GGG1 (0.047) and GGG2 (0.017). Results were similar when cores data were included and not sensitive to alternative definitions of advanced disease, or exclusion of patients with low panel risks. Decision curve analysis confirmed the additional value of the panel in appropriate ranges for decision thresholds: 5 – 20% for confirmatory biopsy and 20 – 60% for treatment. **Conclusions:** The kallikrein panel is strongly associated with pathologic outcome, and can be used to make subsequent management decisions for patients found with GGG1 or GGG2-cancer at biopsy and the need for confirmatory biopsy and treatment.

5074 Poster Session (Board #301), Sat, 1:15 PM-4:45 PM

Plasma androgen receptor (p*AR*) status and activity of taxanes in metastatic castration resistant prostate cancer (mCRPC). *First Author: Vincenza Conteduca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Meldola, Italy*

Background: Plasma *AR* (p*AR*) gain identifies CRPC with worse outcome on abiraterone (abi) or enzalutamide (enza). We aimed to evaluate whether taxanes in CRPC are active regardless of *AR* status **Methods:** Between May 2011 and June 2017, pretherapy plasma samples were collected from 115 evaluable patients (pts) prior to abi/enza-naïve docetaxel (doce) and 130 prior to cabazitaxel (caba) in biomarker protocols at 19 different Institutions. We used droplet digital PCR to assess p*AR* copy number (CN). Primary objective was to evaluate associations of p*AR* gain with treatment outcome. In addition, after incorporating updated data from our prior study of 73 chemotherapy-naïve abi/enza pts, we also investigated if p*AR* could have a differential impact on taxanes compared with abi/enza pts. Both taxanes were administered at standard or reduced-dose at the discretion of treating physician **Results:** We observed *AR* gain in 32 (27.8%) doce pts. No differences were observed in OS/PFS (HR 1.2 95%CI 0.74-1.96 p = 0.45; HR 0.77 95%CI 0.51-1.17 p = 0.21 respectively) or PSA decline ≥50% (OR 1.0 95%CI 0.99-1.0 p = 0.75). A significant interaction was observed between p*AR* and doce vs abi/enza for OS (p = 0.003) and PFS (p = 0.013). In addition, we showed *AR* gain in 24 (37.5%) caba pts and confirmed no association of *AR* status with OS/PFS/PSA response. As an exploratory analysis, we reported in *AR* gained pts treated with initial reduced dose of taxanes a meaningful shorter OS (HR 2.15 95%CI 1.13-4.06 p = 0.019) in doce pts and a trend toward a worse OS in caba pts (HR 1.67 95%CI 0.94-2.95 p = 0.079). Multivariable analysis, adjusting for *AR* CN, LDH, alkaline phosphatase, hemoglobin, PSA, sites of metastasis, age, showed only liver metastasis as an independent predictor of OS in doce and caba pts (HR 2.78 95%CI 1.13-6.85 p = 0.026; HR 6.6195%CI 1.65-26.56 p = 0.008 respectively). **Conclusions:** p*AR* gained pts do not have a worse outcome when treated with taxanes when compared to p*AR* normal pts. This contrasts with a significantly worse outcome for p*AR* gained compared to p*AR* normal when treated with abi or enza and introduce the opportunity to use p*AR* status to select for doce vs abi/enza in mCRPC. Prospective evaluation in a randomized trial is warranted

5075 Poster Session (Board #302), Sat, 1:15 PM-4:45 PM

Exploration of the cGAS-STING pathway in prostate cancer. *First Author: Emma Reilly, Almac Diagnostics, Craigavon, United Kingdom*

Background: Recent studies have demonstrated limited success of immune checkpoint therapies in unselected prostate cancer. We therefore assessed an immune based DNA Damage Repair Deficiency (DDRD) assay, that we previously reported represents activation of the cGAS STING pathway, in the TCGA prostate cancer dataset to investigate the presence of targetable immune biology. In order to assess if immune therapy could have a role in treating high risk disease, we applied a second assay (the prostate cancer metastatic signature-PCM) that predicts the risk of metastatic recurrence for early prostate cancer. **Methods:** 498 samples with RNA sequencing data were scored with the PCM and DDRD assays. Integrative analysis was performed on 488 samples with RNA sequencing, promoter site methylation, somatic mutation and somatic copy number variation. The subgroups were assessed for leukocyte infiltration and the expression of n = 6 immune checkpoint targets. The viability of reproducing those subgroups with RNA sequencing alone was tested in the TCGA dataset and an independent validation dataset of 321 resected primary prostate cancers. Cox proportional hazards regression analysis was performed for biochemical recurrence and metastatic events in both datasets. **Results:** Integrative analysis identified four patient subgroups characterised primarily by variances in copy number and genomic mutation. One of these subgroups 'Metastatic-like DDRD' had significantly higher PCM scores and DDRD immune scores compared to the other subgroups ($p < 2E-12$). This subgroup of patients showed elevated immune signalling ($p < 2e-6$) and greater genomic instability with amplification of 8q and a higher incidence of TP53 mutations. The 'Metastatic-like DDRD' subgroup was found to have a significant association with poor survival outcome in TCGA (multivariable: $p < 0.008$) and the independent dataset (multivariable: $p < 0.01$). **Conclusions:** We have identified and validated a poor prognostic subgroup, representing 10-20% of early prostate cancer patients that are at increased risk of developing metastatic disease and present with targetable immune biology. These patients may represent a viable target population for immune checkpoint and DNA damaging therapies in prostate cancer.

5076 Poster Session (Board #303), Sat, 1:15 PM-4:45 PM

Germline variant alleles in rs12422149 of *SLCO2B1* and response to abiraterone acetate (AA) in men with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Andrew W Hahn, University of Utah Hunstman Cancer Institute, Salt Lake City, UT*

Background: Predictive biomarkers of response to AA in advanced prostate cancer are needed. *SLCO2B1* encodes a protein that mediates transport of AA into tissue. A pre-clinical study showed that variant alleles in select single nucleotide polymorphisms (SNPs) for *SLCO2B1*, rs12422149 and rs1789693, result in higher tumor tissue AA levels (Mostaghel EA, *Clin. Can. Res.*, 28389510). In an exploratory analysis, we found a non-significant trend towards improved progression-free survival (PFS) in men with variant alleles for rs12422149 but not for rs1789693 on AA in mCRPC patients. Here, we interrogate the correlation of variant alleles in rs12422149 with PFS on first-line therapy with AA in men with new mCRPC. **Methods:** Clinical data and samples were analyzed from a prospective prostate cancer registry at the University of Utah. Genotyping was performed using the Illumina OmniExpress genotyping platform. Primary endpoint was PFS on first-line AA in men with mCRPC. We performed a pre-specified multivariate Cox regression analysis to assess the independent predictive value of rs12422149 on PFS on AA. **Results:** Of 401 men with advanced prostate cancer genotyped. 323 were homozygous wild type for rs12422149 (80.5%), 74 were heterozygous (18.5%), and 4 were homozygous variant (1.0%). In a multivariate analysis of 79 men treated with first-line AA for mCRPC, men heterozygous for rs12422149 had significantly improved median PFS compared to the homozygous group (8.9 months vs. 6.3 months, HR 0.46, 95% CI 0.23-0.94, p=0.03) (Table). **Conclusions:** In this first clinical validation of pre-clinical data reported by Mostaghel, et al., variant alleles in rs12422149 of *SLCO2B1* are common and predict improved response to first-line AA In men with mCRPC. These findings need external validation.

	rs12422149 GG (n=63)	rs12422149 AG (n=16)	rs12422149 AA (n=0)	p value*
log PSA at AA Initiation	3.22 (1.47)	3.60 (1.40)	NA	0.36
Gleason				0.35
4	2 (3%)	0	0	
5-6	4 (6%)	3 (19%)	0	
7	14 (22%)	2 (12%)	0	
8-10	43 (69%)	11 (69%)	0	
Cox Regression results:				
Median PFS (months)	6.3	8.9	NA	
Hazard rate	1.0	0.462 (p=0.034)	NA	
HR CIs	NA	0.23-0.94	NA	

*p values are comparisons across the two observed genotypes

5077 Poster Session (Board #304), Sat, 1:15 PM-4:45 PM

Long-term patterns in race-specific, distant metastasis-free survival following radiation treatment for prostate cancer. *First Author: Jennifer Cullen, Center for Prostate Disease Research, Rockville, MD*

Background: Racial differences in prostate cancer (PCa) outcomes are widely observed, irrespective of risk stratum at diagnosis. The primary study aim was to compare distant metastasis-free survival (DMFS) for African American (AA) and Caucasian American (CA) military health care beneficiaries undergoing radiation therapy (RT) for PCa over 20+ years. **Methods:** A retrospective cohort study of Center for Prostate Disease Research Multi-Center National Database enrollees was conducted. Eligibility requirements included a diagnosis with biopsy-confirmed PCa between January 1, 1989 and December 31, 2013, primary treatment ($<$ 6 months post-diagnosis) with external beam radiation therapy (EBRT) or brachytherapy (BRY), and $\geq$2 years follow-up. EBRT combined CT-based, 3D conformal, and intensity modulated RT (IMRT). DMFS was compared across race using Kaplan Meier (KM) estimation curve analysis, stratified by treatment type (EBRT vs. BRY). Multivariable (MV) Cox Proportional Hazards (PH) analysis was used to model DMFS as a function of race, stratified by treatment type (EBRT vs. BRY), controlling for clinical covariates. **Results:** Of the 4,299 eligible men who had primary RT, 2,022 (77.6%) had EBRT and 583 (22.4%) had BRY (N = 2605). Among EBRT patients, 28% were AA and 66% were CA. For BRY patients, 18% were AA and 77% were CA. Median follow up times and ages were 6.7 and 69.8 years for EBRT patients and 6.9 and 65.4 years for BRY, respectively. In KM analysis race did not predict DMFS for EBRT group (p = 0.56) but there were significant racial differences among BRY group (p = 0.013). Table 1 shows DMFS estimates by race and treatment group. In MV Cox PH models, race did not predict DMFS among EBRT patients (p = 0.695); however, among BRY group, AA men had a 4.7-fold increased probability of developing distant metastasis compared to CA men (p = 0.045), controlling for age at RT, year of treatment, and NCCN risk stratum. **Conclusions:** In this racially diverse, equal access health care system, comparable DMFS was observed across patient race over this 20+ years for EBRT but not BRY patients who had significantly poorer DMFS. Subsequent work will examine cancer-specific survival, comorbidity, and prostate volume.

5078 Poster Session (Board #305), Sat, 1:15 PM-4:45 PM

Evaluation of an immunotherapeutic DNA-vaccine in biochemically relapsed prostate cancer. *First Author: Neal D. Shore, Carolina Urologic Research Center, Myrtle Beach, SC*

Background: The DNA immunotherapy, INO-5150 (PSA and PSMA) +/- INO-9012 (IL-12) was assessed for safety, immunogenicity and the effect on PSA kinetics in biochemically recurrent prostate cancer patients (pts). **Methods:** Phase I, open-label, multi-center study included pts with rising PSA after surgery and/or RT, PSA doubling time (PSADT) $>$ 3 months (mos), testosterone $>$ 150 ng/dL, no concurrent ADT and no evidence of metastases by conventional imaging. Safety, immunogenicity and efficacy were evaluated in 4 treatment arms in 60 planned pts (A: 16, 2mg INO-5150; B: 15, 8.5 mg INO-5150; C: 15, 2mg INO-5150+1mg INO-9012; D: 16, 8.5mg INO-5150+ 1mg INO-9012). Pts received 4 IM doses of vaccine followed by electroporation on day 0, wks 3, 12 and 24 and followed for 72 wks. **Results:** The study has concluded and 50/62 (80%) pts completed all visits. 90% of pts had Grade (Gr) 1-3 AEs, primarily injection site reactions which were Gr 1. Across 4 cohorts, 47/61 (77%) of all evaluable pts demonstrated immunogenicity, [35/58 (60%) had IFN-γ reactivity by ELISPOT, 6/61 (10%) and 5/61 (8%) had antibody titers against PSA and PSMA, respectively, and 19/50 (38%) had CD38, Perforin+CD8 T cell responses]. Pts (38%) with CD38 and Perforin + CD8 T cell immune reactivity had attenuated % PSA rise compared to non-reactive pts (p = 0.05, n = 50). Pts with no known progression during the study showed significant differences in $\log_2$PSA change and PSADT pre-treatment baseline (D0) vs wk 27 (post-immunotherapy time point, n = 34, p $<$ 0.0001) or wk 72 (end of follow-up, n = 27, p $<$ 0.0001). Furthermore, pts with D0 PSADT$\leq$ 6 mos and no known progression during the study showed significant differences in $\log_2$PSA change and PSADT in D0 vs wk 27 (n = 15, p $<$ 0.0001) or wk 72 (n = 10, p = 0.002). **Conclusions:** INO-5150 +/- INO-9012 was safe, well tolerated and immunogenic. A clinical effect was demonstrated by evidence of dampening % rise in PSA and increased PSADT in the majority of patients. In patients with no known disease progression during the study, a significant PSA stabilizing effect of the immunotherapy was observed. Additional analyses are ongoing to further elucidate the correlation of immunologic efficacy and clinical benefit. Clinical trial information: NCT02514213.

5079 Poster Session (Board #306), Sat, 1:15 PM-4:45 PM

Ten year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy for 1,503 patients with intermediate risk prostate cancer. *First Author: Barry W. Goy, Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA*

Background: To compare 10-year treatment outcomes of radical prostatectomy (RP) vs external beam radiation therapy (EBRT) vs brachytherapy (BT) for patients with intermediate risk prostate cancer (IRPC). **Methods:** A retrospective analysis using propensity score matching was performed on 1,503 IRPC patients who underwent treatment from 2004 to 2007. 819 underwent RP, 574 underwent EBRT to a median dose of 75.3 Gray, and 110 underwent BT using iodine-125. Biochemical failure was defined by the American Urological Association (AUA) definition of prostate specific antigen (PSA) failure for RP patients, and the American Society of Therapeutic Radiology and Oncology (ASTRO) - Phoenix definition for the EBRT and BT patients. **Results:** Median follow up was 10.0 years for RP, 9.6 for EBRT, and 9.8 for BT (range 1.0-13.4 years). With RP 76.3% had Gleason score 7 vs 72.8% for EBRT vs 57.3% for BT, p = 0.0001. Median initial PSA was 7.4 for RP, 9.4 for EBRT, and 8.3 for BT, p $<$ 0.0001. Neoadjuvant androgen deprivation therapy was given in 58.9% of EBRT patients vs 12.7% of BT vs 0.6% for RP, p $<$ 0.0001. Only 14% of BT received supplemental external radiation. The 10-year freedom from biochemical failure (FFBF) was 82.0% for BT vs 58.0% for RP vs 58.8% for EBRT, p $<$ 0.0001. Subset analysis of unfavorable IRPC patients showed a 10 year FFBF of 81.6% for BT vs 55.8% for RP vs 51.0% for EBRT, p $<$ 0.0001. The 10-year freedom from salvage therapy was 89.5% for BT vs 64.0% for RP vs 73.4% for EBRT, p $<$ 0.0001. There were no significant differences in distant metastases-free survival, prostate cancer-specific survival, or overall survival after adjusting for age. Multivariable analysis between pairwise groups with BT balanced by stabilized inverse probability of treatment weights showed that BT remained an independent predictor for improved FFBF, p = 0.049 for BT vs EBRT, and p $<$ 0.0001 for BT vs RP. **Conclusions:** Brachytherapy using iodine-125 is a reasonable treatment option for IRPC patients. Although BT showed improved FFBF after propensity score matching, this did not impact overall survival.

5080 Poster Session (Board #307), Sat, 1:15 PM-4:45 PM

Long-term androgen deprivation, with or without radiotherapy, in locally-advanced prostate cancer: Updated results from a phase III randomized trial. *First Author: Paul Sargos, Institut Bergonié, Bordeaux, France*

Background: We previsously reported results of a randomized phase III trial comparing androgen-deprivation therapy (ADT) combined with external beam radiation therapy (EBRT) and ADT alone in patients treated with localized cancer. We report here long-term oncological outcomes of this trial. **Methods:** In this multicenter phase III trial, patients with biopsy-proven locally advanced prostate cancer (T3-4) randomly assigned to ADT alone or ADT+EBRT. In both arms, leuprorelin 11.25 mg, subcutaneous, was started within seven days of randomization and continued every three months for three years and oral flutamide (750 mg/day) was administered during the first month. For the ADT-EBRT arm, the whole pelvis was treated at a dose of 46+/-2 Gy and the prostate with a boost from 20 Gy to 28 Gy. Primary endpoint was progression-free Survival (PFS) which included biochemical and clinical events and deaths. Secondary endpoints included overall survival (OS), disease-specific survival (DSS), locoregional progression free survival (LPFS), metastasis-free survival (MFS), biochemical progression free survival (BPFS) and tolerance. Competing-risk analysis was used whenever appropriate. **Results:** With a median follow-up of 7.3 years, 263 patients were included in the Intent-to-treat analyses. The 8-year PFS rate was significantly higher in the ADT+EBRT arm than in the ADT arm (47.9% versus 7.0%; hazard ratio: 0.27, p $<$ 0.0001). The risk of death from prostate cancer was significantly reduced for ADT+EBRT arm as compared to ADT alone (sub-hazard ratio (SHR): 0.48; p = 0.02). The 8-year OS rate was respectively 56.8% in the ADT arm and 65.1% in the ADT+EBRT arm (p = 0.43). LPFS was significantly in favor of ADT+EBRT arm (SHR = 0.61; p = 0.01). MFS was comparable between both arms (p = 0.88). Analysis of toxicities revealed acute lower tolerance (mainly gastro-intestinal and genito-urinary) in the ADT+EBRT arm with a gradual decrease in intensity during follow up from 6 months after the end of EBRT. **Conclusions:** These long-term results confirm the oncological benefit of combining EBRT with ADT in the treatment of locally advanced prostate cancer. Clinical trial information: NCT01122121.

5081 Poster Session (Board #308), Sat, 1:15 PM-4:45 PM

A pharmacodynamic biomarker study of vistusertib (AZD2014), an mTORC1/2 inhibitor, given prior to radical prostatectomy (CANCAP02). *First Author: Simon Pacey, University of Cambridge, Cambridge, United Kingdom*

Background: The effect of novel drugs can be studied in primary prostate cancer (PC), if given prior to radical prostatectomy (RP). Altered PI3K/AKT/mTOR signalling is associated with aggressive primary PC and progression. CanCap02 investigated the effects of vistusertib (AZD2014), an oral, dual mTORC1/mTORC2 inhibitor in men with PC. **Methods:** Men, due for RP, with high volume or aggressive PC consented and received vistusertib, 50mg bd, for 15 days prior to RP. Diagnostic biopsy, attempted intra-operative biopsy and RP tissue were collected for IHC analysis. Adverse events (AE) were graded using CTCAE v4. Blood was collected to determine plasma vistusertib concentrations. The primary endpoint was to measure mTOR1/2 inhibition by immunohistochemistry (IHC). Secondary endpoints were feasibility, safety, tolerability and vistusertib plasma pharmacokinetics. Exploratory objectives included interrogating biological pathways related to mTOR and anti-cancer effects. **Results:** Median age 62 (50 – 69) yrs, 48% intermediate and 52% high risk recurrence. 20/23 pt were evaluable for primary endpoint analysis. The majority of AEs (67%) were Gr1 includin: mucositis, diarrhoea, thrombocytopenia, rash, transaminitis, lymphopenia and hyperglycaemia. Two pts discontinued vistusertib due to AEs (mucositis, thrombocytopenia, raised liver enzymes/ bilirubin) which resolved prior to RP. RP was only delayed in one pt to allow resolution of AE (Gr 1 thrombocytopenia). Vistusetib inhibited mTOR1/2 (pS6, 4EBP1 and NDRG1 were reduced). PSA declined in 3 pt (15%, range -48 to +332%) over two week dosing period. Analysis of tumour PTEN status, tumour infiltrating lymphocytes and Ki67 are ongoing. Mean plasma vistusertib concentration during RP was 738 ± 287 ng/mL. Mean fasting plasma glucose was 4.88 ± 0.56 mmol/L at baseline and rose after vistusertib to 6.16 ± 0.78 mmol/L, correlated with plasma vistusertib levels. **Conclusions:** Vistusertib (50mg bd) is feasible for a two week course prior to RP, mTORC1/ 2 were inhibited in tumour tissue as well as surrogate tests (ie plasma glucose) and in some pt (15% pt) a fall in PSA occurred. The AE profile might be improved by an intermittent dosing schedule. Clinical trial information: NCT02064608.

5082 Poster Session (Board #309), Sat, 1:15 PM-4:45 PM

Neoadjuvant androgen deprivation therapy and enzalutamide: Imaging and pathological responses. *First Author: David James VanderWeele, University of Chicago Medical Center, Chicago, IL*

Background: Neoadjuvant androgen deprivation therapy (nADT) with abiraterone and prednisone for localized disease leads to pathological complete response (pCR) rates of up to 10%. In this study we tested the efficacy of nADT with enzalutamide for patients with high risk, localized disease. We also tested the ability of post-treatment multiparametric MRI (mpMRI) to evaluate response. **Methods:** A single institution trial (NCT02430480) evaluated nADT (goserelin) and enzalutamide 160 mg daily in patients with high risk non-metastatic prostate cancer. Patients underwent MRI-TRUS-guided fusion biopsy at screening and repeat mpMRI followed by radical prostatectomy (RP) after completing six months of therapy. **Results:** Twenty-two patients have completed therapy and undergone radical prostatectomy. Baseline clinical characteristics were typical of those with high risk disease: median PSA 10.3 ng/ml (range 2.1-985.9) and clinical stage by mpMRI cT2-cT4. Following 6 months of therapy, median pre-RP PSA was 0.02 ng/ml (range $<$ 0.02 – 0.35). On final pathology, 0 patients were upstaged, 5 (23%) were unchanged, and 15 (77%) were downstaged, including 4 (18%) with pCR or near pCR (Residual Cancer Burden $<$ 0.001 cc). Five of 9 patients with bulky nodes at baseline were downstaged to pN0. Of 9 patients with pT3 disease at prostatectomy, 6 were cT3 on post-treatment mpMRI. Of 4 patients with pCR or near pCR, 1 was cT0, 1 was cT2, and 2 were cT3 on post-treatment mpMRI. One additional patient had radiographic complete response but was pT3a on pathological review. **Conclusions:** Six months of nADT with enzalutamide has activity in high risk, localized prostate cancer, with a small number of patients having exceptional responses. Standard analysis of mpMRI identifies most patients with persistent T3 disease but does not reliably identify exceptional responses. Evaluation of molecular characteristics that predict exceptional response or intrinsic resistance is on-going. Clinical trial information: NCT02430480.

5083 Poster Session (Board #310), Sat, 1:15 PM-4:45 PM

Effect of rilimogene galvacirepvec/rilimogene glafolivec on intra/peritumoral immune infiltrate in patients with localized prostate cancer undergoing radical prostatectomy. *First Author: James L. Gulley, Genitourinary Malignancies Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: PSA-TRICOM (Prostvac) is a vector-based vaccine designed to generate a robust immune response (IR) against PSA–expressing tumor cells. To date, studies of Prostvac in patients with mCRPC have shown IR in peripheral blood but effects on prostate tumors are unknown. **Methods:** An open label phase 2 study of neoadjuvant Prostvac (NCT02153918) enrolled patients (pts) with localized prostate cancer undergoing radical prostatectomy (RP). Priming vaccination was given followed by boosts on days 15, 29 and 57 prior to RP (~day 64). The 1° objective evaluated increases in CD4 and CD8 cell infiltrate (RP tissue vs. baseline biopsies) by IHC. IR to tumor associated antigens (TAA) was measured using intracellular cytokine staining (ICS) in PBMC from baseline and ~day 63. **Results:** 27 pts (median age 64.8 years) enrolled. All pts received 4 pre-RP vaccine injections. Matched tissue IHC analysis and peripheral IR is available on 24 pts. TAA specific T cell peripheral IR to PSA, Muc-1 or Brachyury were observed in 12/24 (50%) pts post vaccine, with 25% of pts responding to each antigen. Table comparing peripheral IR vs. tumoral IR. Clinical trial information: NCT02153918. 19 pts were evaluable for tissue RNA expression profiles pre/post vaccine and observed upregulation of genes such as RANKL (DC maturation), CCL25 (chemotaxis), and FLT3 (T-cell development) suggests vaccine-induced IRs. Conversely, increased expression of immunosuppressive genes (e.g., FOXP3, IL-10) suggests adaptive resistance post vaccination. **Conclusions:** Prostvac treatment is associated with a ≥2X increase in CD8 and CD4 intra/ peritumoral infiltrate in 17/24 and 21/24 pts, respectively. However only 12/24 had a TAA response in the peripheral blood. Anti-tumor IRs may become broader and more immunologically relevant over time (Ag spreading) and may be underestimated by peripheral IRs to TAA. These data better inform the immunodynamic effects of Prostvac which are incompletely represented by peripheral IR data. Work is ongoing to more fully characterize the IR with multispectral imaging, targeted RNASeq and TCRSeq analysis.

	↑ CD8 Infiltrate		↑ CD4 Infiltrate	
	No	**Yes**	**No**	**Yes**
No Peripheral IR	5	**7**	2	**10**
Peripheral IR	2	**10**	1	**11**
Total		**17/24**		**21/24**

5084 Poster Session (Board #311), Sat, 1:15 PM-4:45 PM

Combination of a therapeutic cancer vaccine and immune checkpoint inhibitors in prostate cancer. *First Author: Ravi Amrit Madan, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: Immune checkpoint inhibitors (ICIs) have yet to demonstrated efficacy as monotherapy in non-MSI-HI prostate cancer. Vaccines may increase immune cells in the tumor microenvironment, potentiating ICIs. **Methods:** This study combines PROSTVAC(P), a pox-viral based vaccine targeting PSA, ipilimumab (Ipi; 1 mg/kg) and nivolumab (Nivo; 240 mg) in patients (pts) with castration resistant prostate cancer (CRPC). The initial regimen was P on Day 1, all 3 agents (PIN) 2 weeks(wks) later, and PIN every 3 wks thereafter. After Ipi was removed the regimen = P on Day 1, P+Nivo on wks 2,4 and then Nivo every 2 wks with P monthly. **Results:** 11 pts enrolled with median age = 75 and PSA = 16.1. 10 were metastatic CRPC, 6 pts had an ECOG PS = 0 (5 PS = 1). 3 pts had grade 3 immune-related adverse events (irAE; all responded to steroids and continued P once complete). Only the first 2 pts were treated with PIN but had cystitis and hepatitis, respectively, after which Ipi was removed from the regimen. Of 9 P+Nivo pts, 1 had transient myocarditis. 1 of 2 pts treated with PIN had an 88% PSA decline and a partial response (PR) for 10+ months. Of the P+Nivo pts, 6 are evaluable for response (on trial $>$ 3 months). The 2 pts with the greatest PSA decline have been evaluated for MSI-HI status, 1 was positive. Some patients have had late PSA declines from intra-study peak PSA. Clinical trial information: NCT01875250. **Conclusions:** Ipi was removed from regimen after first 2 pts had≥Gr 3 irAEs, only 1 irAE from the 9 pts on P+Nivo. P+Nivo may have activity in CRPC, additional follow-up and further MSI-HI testing is warranted.

Pt #	PSA decline > 30% from baseline	Time on study (+ still on study)	Additional information
1 (PIN)	88% (PR)	10+ months	irAE cystitis, treated with steroids MSI-HI negative CDK12 mutation (bi-allelic)
2 (PIN)	n/a	7.2 months	irAE hepatitis, treated with steroids delayed PSA decline of 23% lasting 4.25 months
3 (P+N)	n/a	4.5 months	Off study for 2nd cancer diagnosis, not treatment related
4 (P+N)	97%	7.5+ months	Substantial reduction in bladder mass MSI-HI positive
5 (P+N)	36%	4.8+ months	n/a
6 (P+N)	n/a	4.6+ months	irAE myocarditis, treated with steroids delayed PSA decline of 34% continuing at 2 months
7 (P+N)	n/a	3.5 months	Progressive disease
8 (P+N)	n/a	3.8+ months	delayed PSA decline of 20% lasting 2.5 months

5085 Poster Session (Board #312), Sat, 1:15 PM-4:45 PM

The influence of decision aids on prostate cancer screening preferences: A randomized survey study. *First Author: Kyle Tsai, Northwestern University, Chicago, IL*

Background: Shared decision making between a patient and caregiver is important when discussing prostate cancer (PCa) screening. Decision aids (DAs) are tools intended to facilitate this process and improve patient participation through education, yet little is known about how DAs affect screening preferences. We administered an online survey study to determine how different DAs impact the decision to undergo or recommend a loved one undergo PCa screening. **Methods:** Using ResearchMatch, an online, study recruitment registry, participants matched for age, race, and gender were randomized to one of six different major professional society's free, online DA on PCa screening. We compared pre- and post-DA responses. The primary outcome was change in participant likelihood to undergo or recommend a loved one undergo PCa screening on a scale of 1 (unlikely) to 100 (extremely likely). Secondary outcomes included change in participant comfort with PCa screening based on the average of six, five-point Likert-scale questions. **Results:** Median age was 53 years for the 1,336 participants, and 50% were men. Randomized groups did not differ significantly by race, age, gender, income, marital status, or education level. Likelihood to undergo or recommend PCa screening decreased from 83 to 78 following DA exposure ($p < 0.001$). Reviewing the DAs from the Center for Disease Control or American Academy of Family Physicians did not alter likelihood (both $p > 0.2$), while reviewing the DA from the United States Preventive Services Task Force was associated with the largest decrease (-16.0, $p < 0.001$). Participants reported increased comfort with the decision-making process for PCa screening from 3.5 to 4.1 (out of 5, $p < 0.001$) following exposure to a DA. **Conclusions:** In this online survey, after exposure to most DAs from major professional societies, participants were less likely to undergo or recommend their loved one undergo PCa screening. DAs improved participant comfort with the PCa screening shared decision-making process. These results illustrate how different DAs may disparately influence men and their loved ones about the tradeoffs of PCa screening.

TPS5086 Poster Session (Board #313a), Sat, 1:15 PM-4:45 PM

Investigation of metformin (MET) in patients with castration resistant prostate cancer (CRPC) in combination with enzalutamide (ENZ) vs. ENZ alone: A randomized, open label, phase 2 trial. SAKK 08/14—IMPROVE. *First Author: Christian Alexander Rothermundt, Kantonsspital St Gallen, St Gallen, Switzerland*

Background: The current first-line treatment for patients with CRPC and disease progression is either treatment with abiraterone acetate/prednisone, ENZ, or treatment with docetaxel in more symptomatic patients. There is preclinical data on synergism of ENZ and the biguanide MET: studies on mice orthotopically implanted with ENZ-resistant cells demonstrated that the combination of ENZ and clomipramine or MET significantly reduced tumor growth compared to control groups. Rothermundt et al. previously reported favorable effects of single agent MET in a phase 2 trial: objective PSA responses, disease stabilization and improvement of metabolic endpoints in patients with CRPC. Therefore addition of MET to ENZ might have positive impact on tumor progression, on body composition and insulin sensitivity. **Methods:** This is a prospective 1:1 randomized multicenter phase 2 trial. Primary endpoint is disease control (DC) at 15 months. Progression is defined as having 2 of the following events: radiographic progression, symptomatic/clinical progression, or PSA progression. Secondary endpoints include overall response according to modified RECIST v1.1 and PCWG2 recommendations, event-free survival, adverse events, quality of life, pain and overall survival. Translation research comprises liquid biopsy, metabolomics, hyperglycemia, and pyruvate dehydrogenase substudies. Assuming a 20% difference in the DC rate at 15 months (50% vs. 70% in the combination arm) with alpha 0.10 and power 80%, 168 patients are required in total. Eligibility criteria are as follows: asymptomatic or minimally symptomatic mCPRC (adenocarcinoma) documented by imaging, ongoing androgen deprivation therapy (ADT) with GnRH agonists or antagonists or bilateral orchiectomy, total testosterone levels $\leq$ 1.7 nmol/L, tumor progression at the time of registration, no prior treatment for mCRPC other than ADT, no history of diabetes and metformin use, and adequate organ function. Patients receive either ENZ 160mg qd in combination with MET 850mg bd or ENZ 160mg qd alone. 62 patients have been enrolled since accrual began in March, 2016. Clinical trial information: NCT02640534.

TPS5087 Poster Session (Board #313b), Sat, 1:15 PM-4:45 PM

A phase 2 trial of darolutamide maintenance therapy in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with AR targeting agents and non-progressive on a subsequent taxane (SAKK 08/16). *First Author: Richard Cathomas, Kantonsspital, Chur, Switzerland*

Background: Treatment with the AR targeting agents abiraterone or enzalutamide followed by a taxane is currently the most used treatment for men with mCRPC. Further treatment after response to chemotherapy is only indicated in case of disease progression, with limited treatment options available. Darolutamide is a second-generation oral androgen receptor antagonist which has demonstrated a good safety profile and antitumor activity in mCRPC. This trial evaluates whether the immediate use of darolutamide after successful chemotherapy can prolong radiographic progression-free survival (rPFS) compared to watchful waiting in patients with mCRPC. **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial (NCT02933801) conducted in approximately 19 sites in Switzerland and Italy. Patients with mCRPC are required to have been previously treated with abiraterone and/or enzalutamide and have no evidence of disease progression on subsequent docetaxel or cabazitaxel. Patients (N = 88) will be randomized 1:1 to receive 600 mg darolutamide BID or placebo BIDuntil disease progression. Patients will be stratified by country, WHO performance status (0, 1 vs 2), presence/absence of visceral metastases, enzalutamide vs abiraterone vs both prior to chemotherapy, and planned start of trial treatment after last taxane dose ($<$ 35 days vs $\geq$35 days). The primary endpoint is rPFS at 12 weeks after treatment initiation. The secondary endpoints are rPFS, time to PSA progression, time to symptomatic/clinical progression, event-free survival, overall survival, PSA response (30%, 50%, 90%, and best), duration of PSA response (50%), adverse events, and fatigue. The rPFS rate at 12 weeks after treatment initiation will be compared between the two treatment arms using a one-sided test statistic using the Kaplan–Meier method. Recruitment is ongoing, with the first patient randomized on 20.04.2017. Clinical trial information: NCT02933801.

TPS5088 Poster Session (Board #314a), Sat, 1:15 PM-4:45 PM

A phase I study of ^{177}Lu-DKFZ PSMA 617 combined with the radiosensitizer idronoxil in men with metastatic castrate-resistant prostate cancer (mCRPC) (LuPin trial). *First Author: Megan Crumbaker, The Kinghorn Cancer Centre, St. Vincent's Hospital, Darlinghurst, Australia*

Background: Despite recent treatment advances, mCRPC remains a challenging disease associated with significant mortality and morbidity. Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that is overexpressed in most prostate adenocarcinomas. Radiolabelled peptides which bind PSMA receptors induce internalization of the ligand-receptor complex, allowing concentration of PSMA-bound isotopes within targeted prostate cancer cells. ^{177}Lutetium (^{177}Lu) bound to PSMA ligands has a favorable therapeutic-toxic ratio and yields PSA responses in 30-70% of selected patients. However, responses are often partial and acquired resistance common, suggesting a need to augment the clinical benefit of beta-radiation. Idronoxil is an inhibitor of external NADH oxidase type 2, and has a variety of downstream actions including radiosensitization. Given the reassuring safety data of idronoxil as a single agent, we initiated a phase 1 clinical trial of ^{177}Lu-PSMA plus idronoxil. **Methods:** Sixteen patients will be recruited. Participants will receive up to 6 doses of ^{177}Lu-PSMA at 6-weekly intervals; the first 8 patients will also receive 400mg idronoxil daily for 10 days from day 1 of each cycle, while subsequent patients will receive 800mg daily for 10 days if no major adverse events are noted. Entry criteria include (i) failure of, or (ii) ineligibility to receive both docetaxel and a second-generation androgen pathway inhibitor. Imaging criteria include a PSMA PET that shows significant uptake at all sites of disease with no discordant disease on FDG PET. The primary endpoint is the toxicity (safety, tolerability) of the combination as assessed by CTCAE criteria. Secondary endpoints include PSA response, radiological response, changes in quality of life, radiation dosimetry, overall survival and progression-free survival. Plasma for ctDNA testing will be collected to explore whether DNA repair defects are predictive biomarkers for response and/or mechanisms of resistance. Four of 16 patients have been enrolled, with no significant toxicities or safety concerns as yet.

TPS5089 **Poster Session (Board #314b), Sat, 1:15 PM-4:45 PM**

Phase Ib study of avelumab plus carboplatin in patients with metastatic castration resistant prostate cancer progressing after one line of chemotherapy and one novel androgen receptor axis inhibitor. *First Author: Alejo Rodriguez Vida, Hospital del Mar, Barcelona, Spain*

Background: The management of metastatic castration resistant prostate cancer (mCRPC) has been revolutionized with the approval of several agents improving overall survival. However, despite an initial response, most patients will experience disease progression. New studies assessing new agents are still needed. Recently, several immune check-point inhibitors targeting the PD-1 pathway have been approved for the treatment of several solid tumors. However, their use in mCRPC is still at a very early phase of development. The purpose of this study is to test the safety and efficacy of combining carboplatin with avelumab in pretreated mCRPC patients. Genomic aberrations are frequent in CRPC, especially in advanced cases. By selecting pre-treated patients, we will enrich the amount of genetic aberrations (like high mutational burden or DDR mutations) potentially increasing the likelihood of response to avelumab. Cytotoxic chemotherapy like carboplatin has been shown to induce immunogenic tumor cell death, tumor-antigens release and stimulation of the immune system. It has been hypothesized that this "autovaccination" could be enhanced with the addition of immunotherapy such as avelumab. **Methods:** This is a phase Ib, open-label, single-arm study in patients with mCRPC progressing on at least 1 line of chemotherapy and 1 line of novel androgen receptor axis inhibitors. Inclusion criteria include performance status 0-1 and adequate organ function. Patients will receive 2 cycles of carboplatin AUC5 monotherapy followed by 2 cycles of carboplatin AUC5 plus avelumab 10mg/kg. Maintenance avelumab will continue for up to 2 years. This trial will have 2 stages. In the Safety phase (6 patients) the safety of combining both agents will be analyzed (primary endpoint). If safety is confirmed, an Expansion phase (20 patients) will assess the efficacy of the combination in terms of PSA and radiographic assessment as per PCWG3 (secondary endpoints). As exploratory endpoint, potential immunologic and genomic predictive biomarkers will be analyzed. The trial is open, and enrollment is ongoing. Clinical trial information: 2017-004552-39.

TPS5090 **Poster Session (Board #315a), Sat, 1:15 PM-4:45 PM**

A phase 3 study of androgen annihilation in high-risk biochemically relapsed prostate cancer: An Alliance Foundation trial (AFT-19). *First Author: Rahul Raj Aggarwal, UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Men with biochemically relapsed prostate cancer (BRPC) following prior radical prostatectomy (RP) and a short PSA doubling time (PSADT) are at high risk for the development of metastatic disease and prostate cancer-related mortality. Intermittent androgen deprivation therapy (ADT) is a commonly applied treatment in this disease setting, but fails to achieve prolonged progression-free and treatment-free intervals for the majority of patients (pts). Apalutamide is a next generation androgen receptor (AR) antagonist that has efficacy in non-metastatic castration-resistant prostate cancer (CRPC). Abiraterone acetate, a prodrug of the CYP17 androgen synthesis inhibitor abiraterone, has been shown to prolong survival in both CRPC and metastatic hormone-sensitive prostate cancer. We hypothesize that the addition of apalutamide with or without abiraterone acetate/prednisone, as compared to ADT alone, will prolong disease suppression and potentially eradicate micrometastatic disease with a finite duration of treatment in pts with BRPC. **Methods:** AFT-19 is a randomized, open-label, three arm phase 3 study (first patient enrolled March 2017) of a) degarelix monotherapy compared to each of two experimental arms: b) degarelix plus apalutamide, and c) degarelix plus apalutamide plus abiraterone acetate/prednisone, in pts with BRPC following prior RP without metastases on conventional imaging, and a PSADT of $\leq$ 9 months. Pts are treated for up to 52 weeks in the absence of progression or unacceptable toxicity, and subsequently followed off treatment until PSA progression, defined as serum PSA $>$ 0.2 ng/mL. The primary endpoint is PSA progression-free survival (PFS). Secondary endpoints are 36-month PSA PFS rate, metastasis-free survival, time to CRPC, overall survival, and quality of life. Planned accrual is 504 pts, estimated to provide 85% power to detect a hazard ratio of 0.63 in the comparison of PSA PFS between each experimental arm versus the control arm, with an overall two-sided type I error rate of 0.025 for each comparison. The DSMB last reviewed the trial in November 2017 and recommended that the trial continue as planned. Clinical trial information: NCT03009981.

TPS5091 **Poster Session (Board #315b), Sat, 1:15 PM-4:45 PM**

Talapro-2: A 2-part, placebo-controlled phase 3 study of talazoparib (TALA) with background enzalutamide (ENZA) in metastatic castration-resistant prostate cancer (mCRPC) with DNA damage repair deficiencies. *First Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: ENZA is approved to treat men with mCRPC. TALA is a dual-mechanism PARP inhibitor that inhibits PARP1 and PARP2 catalytic activity and traps PARP on DNA, preventing DNA damage repair and causing cell death in *BRCA1/2*-mutated cells. A combination of TALA with ENZA in DNA damage repair (DDR)+ mCRPC may improve clinical outcomes. **Methods:** Part 1 (P1) is open label to confirm the starting dose of TALA to be given in combination with ENZA. Part 2 (P2) is a double-blind assessment of efficacy and safety. Approximately 352 patients (pts) will be enrolled (P1, n=12; P2, n=340). Eligible pts for both parts are $\geq$18 yrs of age ($\geq$20 in Japan) with asymptomatic or mildly symptomatic mCRPC; ECOG PS $\leq$1; no brain metastases; and who have not been treated with taxanes or novel hormonal therapy (NHT) initiated after the onset of mCRPC. Pts who received cytotoxic chemotherapy (CT), other HT, biologic, or radionuclide therapy within 28 days of screening or who received a prior PARP inhibitor, platinum-based CT, cyclophosphamide, or mitoxantrone are excluded. For P2, pts must have DDR+ mCRPC. In P1, pts will receive open-label TALA 1 mg/d orally with ENZA 160 mg/d. In P2, pts will receive open-label ENZA and will be randomized 1:1 to also receive TALA 0.5-1 mg/d or placebo. The starting dose of TALA for P2 will be determined in P1. Randomization will be stratified by prior treatment with NHT for castration-sensitive prostate cancer or non-mCRPC and prior treatment with taxane-based CT for castration-sensitive prostate cancer (yes/no). For P1, the primary endpoint is safety; the secondary endpoint is pharmacokinetics of TALA and ENZA. For P2, the primary endpoint is radiographic progression-free survival (rPFS); key secondary endpoints include overall survival, objective response in measurable soft tissue disease, PSA progression, and time to initiation of cytotoxic CT. Efficacy will be assessed by radiographic assessments every 8 wks through week 25 and every 8-12 wks thereafter. P2 analysis for rPFS is powered at 90% using a 2-sided log-rank test with alpha of 0.05. Clinical trial information: NCT03395197.

TPS5092 **Poster Session (Board #316a), Sat, 1:15 PM-4:45 PM**

A prospective phase 2/3 multicenter study of ^{18}F-DCFPyL PET/CT imaging in patients with prostate cancer: Examination of diagnostic accuracy (OSPREY). *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Accurate localization of sites of disease is essential for delivering optimal care to patients with prostate cancer. This is especially true for patients who may have distant disease either at initial staging or at relapse and may benefit from curative local primary or salvage treatments. ^{18}F-DCFPyL (PyL) is a novel, high specific activity, highly selective, low-molecular weight prostate-specific membrane antigen (PSMA)-targeted PET radiopharmaceutical. This trial seeks to analytically validate the performance characteristics of PyL PET/CT for the detection of metastatic and/or recurrent prostate cancer. **Methods:** This is a multi-center, open-label, phase 2/3 study evaluating the diagnostic performance of PyL PET/CT in patients with at least high-risk (as defined by NCCN guideline v3.2016) prostate cancer prior to radical prostatectomy [cohort A] or radiologically confirmed metastatic/recurrent prostate cancer [cohort B]. A total of approximately 400 subjects will be enrolled in the study. All patients must be at least 18 years of age with histologically confirmed adenocarcinoma of the prostate. A single administration of PyL (9 $\pm$ 1 mCi [333 $\pm$ 37 MBq]) is administered 1-2 hours prior to PET/CT imaging on Day 1. The primary objective is to assess the diagnostic performance (sensitivity and specificity) of PyL PET/CT in the detection of metastatic prostate cancer within the pelvic lymph nodes relative to histopathology in pre-prostatectomy patients [cohort A], as determined by independent central review. Key secondary objectives include safety and tolerability of PyL, diagnostic performance of PyL PET/CT in the detection of prostate cancer within sites of distant metastasis or local recurrence [cohort B], and pharmacokinetic parameters of PyL in a subset of subjects. The clinical impact of PyL PET/CT imaging on the intended management of prostate cancer patients will also be assessed as an exploratory endpoint. Clinical trial information: NCT02981368.

TPS5093 Poster Session (Board #316b), Sat, 1:15 PM-4:45 PM

ODENZA: A study of patient preference between ODM-201 (darolutamide) and enzalutamide in men with metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Geraldine Martineau, Clinical Research Department, Institut Gustave Roussy, Villejuif, France*

Background: In recent years, the treatment of mCRPC has evolved and next-generation androgen receptor (AR)-axis targeting drugs (enzalutamide (ENZ), and abiraterone) have been approved and are routinely used. Darolutamide (DARO) is a new next-generation AR inhibitor which has shown strong activity and minimal toxicity in two phase I-II trials ARADES (Fizazi, Lancet Oncol 2014) and ARAFOR (Massard, Eur Urol 2016) and is currently evaluated in a study in men with non-metastatic CRPC (ARAMIS trial). In contrast to ENZ, DARO does not significantly penetrate the blood-brain barrier in vivo, and this may reduce the risk of fatigue, cognitive impairment, and seizure. Assessing patient preference between DARO and ENZ may contribute further differentiating between these two agents. **Methods:** ODENZA is a prospective, randomized, open-label, multicenter, cross-over phase II trial assessing patient preference between DARO and ENZ (NCT03314324). It was initiated in November 2017. Eligibility criteria include: men with asymptomatic or mildly symptomatic mCRPC, performance status 0-1, no prior next generation AR axis-targeted agent. The randomization is stratified on performance status and prior treatment with a taxane for CSPC. 250 patients will be randomized 1:1 to: 12-week ENZ followed by 12-week DARO or 12-week DARO followed by 12-week ENZ. The primary endpoint is patient preference between DARO and ENZ, assessed after the second treatment period. A two-sided binomial test with a power of 80% and a bilateral α of 0.05 will be used. Secondary endpoints include: reasons for patient preference, dose modifications and time to dose modification, safety, fatigue (BFI), cognitive function as assessed by Cogstate computerized cognitive tests, depression screening (CES-D) test, frequency of falls, PSA declines using Waterfall plots after each treatment period, Progression-Free Survival (PFS), association between 4-weeks PSA value and PFS, incidence of cancer progression or death, and tumor response. The study is recruiting. By February 13, 2018, 10 patients have been enrolled. Clinical trial information: NCT03314324.

TPS5094 Poster Session (Board #317a), Sat, 1:15 PM-4:45 PM

A phase II trial of enzalutamide, docetaxel and androgen deprivation therapy (ENZADA) in patients with metastatic castrate sensitive prostate cancer (mCSPC). *First Author: Earle Frederick Burgess, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC*

Background: The addition of docetaxel (Doc) or abiraterone to androgen deprivation therapy (ADT) in men with mCSPC improves survival. Whether the triple combination of ADT, Doc and next generation endocrine therapy further improves patient outcome is unknown. Enzalutamide (Enz) is a potent anti-androgen that has activity in the advanced, castration-resistant setting. Preclinical data support the use of Enz in combination with Doc. Enz inhibits the ABCB1 drug efflux pump implicated in Doc resistance, and Doc may eradicate Enz-resistant clones harboring the androgen receptor splice variant 7 (ARv7). The combination of Enz with Doc at standard doses was safe in the phase I setting. This study tests the hypothesis that men with newly diagnosed mCSPC may benefit from adding Enz to standard Doc and ADT. **Methods:** This is a phase II, single arm trial of Enz plus Doc and ADT in men with newly diagnosed mCSPC. The study is designed to enroll 39 eligible participants who must have metastatic prostate adenocarcinoma with confirmed soft tissue and/or skeletal metastasis, ECOG 0-2, and PSA $\geq$ 5. Subjects who previously received up to 3 years of ADT with radiation for localized disease are eligible if ADT was discontinued $>$ 6 months before diagnosis of mCSPC and testosterone recovery is confirmed. Prior treatment with cytotoxic chemotherapy or next generation endocrine therapy is not allowed. Patients will be stratified by volume of metastatic disease. Treatment consists of Doc 75 mg/m2 IV every 3 weeks for 6 cycles and Enz 160 mg daily commencing at enrollment and continued until radiographic progression or study withdrawal. Continuous ADT is required during the study period. The primary endpoint is 12-month PSA complete response rate. Secondary endpoints include adverse events, best PSA response, radiographic objective response, time to castration resistance, progression free and overall survival. Exploratory biomarker analysis includes sequential measurement of circulating tumor cell (CTC) levels and CTC ARv7 status during study treatment. Clinical trial information: NCT03246347.

TPS5095 Poster Session (Board #317b), Sat, 1:15 PM-4:45 PM

Phase II trial of rucaparib (Without ADT) in patients with metastatic hormone-sensitive prostate cancer harboring germline DNA repair gene mutations (TRIUMPH). *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: The clinical activity of PARPi in patients with homologous recombination DNA-repair mutations and metastatic prostate cancer has now been established. Focusing specifically on patients with a germline mutation in a pre-specified group of DNA-repair genes, we hypothesize that targeted therapy with PARPi should be sufficient to induce a clinical response irrespective of hormonal (castration-sensitive/resistant) status. For men with metastatic hormone sensitive prostate cancer (mHSPC), this trial would also provide an alternative to ADT. **Methods:** This study is a multicenter, open-label, single arm Phase II trial. Eligible patients are those with mHSPC without prior ADT. All patients must have a documented germline mutation in a homologous recombination DNA-repair gene (*BRCA1, BRCA2, ATM, CHEK2, NBN, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM*). Patients on trial must be ineligible for or decline standard-of-care hormonal treatment. A mandatory tumor biopsy will be performed prior to therapy. A second, optional tumor biopsy is planned after three months of therapy. Patients will be treated with Rucaparib 600mg po twice daily. Patients will be followed monthly with clinic visits and safety labs with PSA. The primary endpoint is the proportion of patients with a $\geq$ 50% decrease in PSA from baseline (PSA_{50} response). A total enrollment of 30 patients is planned to detect an improved PSA_{50} response rate from 50% to 75% with 90% power (one sided type I error of 0.1). The total number of patients allowed with a non-*BRCA1*, -*BRCA2*, or –*ATM* mutations will be capped at 10. For patients who do not respond to PARPi, we have incorporated safety rules into the study design to take patients off study at first signs of progression. Secondary endpoints include safety, progression-free survival, and objective response. Exploratory analysis will involve biomarker discovery including somatic DNA mutation analysis, RNA expression analysis, and immunohistochemistry for DNA damage markers. Clinical trial information: NCT03413995.

TPS5096 Poster Session (Board #318a), Sat, 1:15 PM-4:45 PM

CRLX101 plus olaparib in patients with metastatic castration-resistant prostate cancer. *First Author: Gang Chen, NCI/NIH, Bethesda, MD*

Background: Prostate cancer is the most commonly diagnosed cancer among men in the United States. While prostate cancer is initially responsive to androgen deprivation therapy (ADT), most patients will develop castration-resistant disease. In the past several years, despite multiple new therapeutics (docetaxel, abiraterone and enzalutamide) have been approved by FDA, the majority patients will become resistant to treatments in 2-3 years. Therefore, it is necessary to find new treatments in metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This phase II expansion cohort will evaluate the efficacy and safety of CRLX101 plus Olaparib in patients with mCRPC. CRLX101 is a nanoparticle drug conjugate with a camptothecin (CPT) payload that provides durable inhibition of topoisomerase I (Top1) specifically in the tumor. CPT stabilizes the Top1-DNA cleavage complex during DNA replication and prevents Top1-mediated DNA relegation, ultimately leads to apoptosis. Poly ADP ribose polymerase (PARP) plays a role in the repair of topoisomerase I-induced DNA damage. By inhibiting PARP, Olaparib may increase the potency of CPT and thus olaparib plus CRLX101 offers a potential treatment option in patients with mCRPC. Synergistic activity between camptothecin and olaparib has been shown in preclinical data. The primary endpoint of this study is overall response rate (ORR), the secondary endpoints include safety and progression-free survival (PFS), duration of response and PSA responses. Clinical trial registry number of this study is NCT02769962. **Results:** N/A. **Conclusions:** N/A. Clinical trial information: NCT02769962.

TPS5097 **Poster Session (Board #318b), Sat, 1:15 PM-4:45 PM**

c15-148: Phase I/II trial of concurrent chemohormonal therapy using enzalutamide and cabazitaxel in patients with metastatic castration resistant prostate cancer (mCRPC). *First Author: Julie Nicole Graff, VA Portland Health Care System, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: The management of mCRPC has been both enhanced and complicated by the rapid emergence of at least five new agents that can lengthen survival. While great strides have been made in developing new agents for mCRPC, response rates and duration have remained modest, and men ultimately succumb to their disease. Historically, combined chemohormonal therapy has not improved outcomes for patients with prostate cancer, but earlier trials were hindered by lack of efficacious chemotherapy and weaker hormonal agents. In this study, we aim to determine if potential synergistic effects between two newer and more effective agents can be identified and exploited for therapeutic effect, and to obtain correlative biological information that may offer predictive and response value. **Methods:** An initial 3-12 study subjects will be treated with cabazitaxel at 25 mg/m^2 on day 1 and enzalutamide 160 mg daily every 21 days. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The trial will proceed to phase II stage at the dose of 25 mg/m^2 if 0/3 or 1/6 patients receiving 25 mg/m^2 had DLT. The dose de-escalation will happen if $\geq$2/3 or $\geq$2/6 patients receiving 25 mg/m^2 had DLT. The trial will proceed to Phase II stage at the dose of 20 mg/m^2 if 0/3 or 1/6 patients receiving 20 mg/m^2 had DLT. In the absence of treatment delays due to adverse events, treatment with cabazitaxel and enzalutamide will continue for 6-10 cycles. Patients may then continue enzalutamide monotherapy on a 28-day cycle until progression or limiting toxicity. For the phase I portion of this trial an initial 3 study subjects were treated with cabazitaxel at 25 mg/m^2 on day 1 and enzalutamide 160 mg daily every 21 days; no DLTs occurred. These subjects will be permitted to continue on cabazitaxel and enzalutamide until progression and will be included in the final analysis of efficacy. The phase II patients are treated with 25 mg/m2 cabazitaxel and 160 mg enzalutamide. The trial is open at 2 sites and managed by the Prostate Cancer Clinical Trials Consortium (PCCTC). Clinical trial information: NCT02522715.

TPS5098 **Poster Session (Board #319a), Sat, 1:15 PM-4:45 PM**

The GENTleMEN study: Genetic testing for men with metastatic prostate cancer in Washington state and beyond. *First Author: Heather H. Cheng, University of Washington, Seattle, WA*

Background: Germline DNA repair gene mutations are present in ~10% of patients with metastatic prostate cancer (mPC) irrespective of age at diagnosis or family history, and have potential profound implications for treatment, clinical trial selection and family counseling. However, patient/provider lack of awareness, limited access to genetic counseling services, variable insurance coverage and high out-of-pocket costs are known barriers. To remove these barriers and to assess feasibility and acceptability, we are conducting a research study, Genetic Testing for Men with Metastatic Prostate Cancer (GENTleMEN) that offers germline genetic testing to all men in Washington State with mPC. **Methods:** GENTleMEN is a prospective, observational study. Informed consent is provided via internet access (www.gentlemenstudy.org). Participants complete a HIPAA-compliant, RedCap (web-based) questionnaire including demographics, self-reported family cancer history and validated instruments including GAD7, PHQ9, Cancer Distress, Risk Perception, Decision Conflict, Knowledge of and Concern with Genetic Testing (~40 min). Supporting medical data are uploaded by the participant or, with permission, by the study team. Germline genetic testing is performed on a saliva sample via the CLIA-certified Color Genomics 30-gene targeted panel of cancer predisposition genes (www.color.com) through mail, and results are returned by email and/or phone. Men who test positive for pathogenic or likely pathogenic germline variants are required to receive results by phone from a genetic counselor and are strongly encouraged to share results with their medical providers and families. The study offers follow-up support and access to clinical trials, research and registry participation. **Conclusions:** Germline genetic testing is expected to become increasingly pertinent to the care of men with mPC and their families. The GENTleMEN study is investigating a novel mechanism to supplement existing genetics services and remove barriers to germline genetic testing. (*NCT number pending)*

TPS5099 **Poster Session (Board #319b), Sat, 1:15 PM-4:45 PM**

Phase II neoadjuvant and immunologic study of B7-H3 targeting with enoblituzumab in localized intermediate- and high-risk prostate cancer. *First Author: Eugene Shenderov, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: B7-H3 is part of the B7 superfamily and is an immune checkpoint expressed on multiple tumor types. B7-H3 inhibition limits tumor growth by enhancing cytotoxic T lymphocyte function through engagement with an unknown receptor. B7-H3 is highly expressed in prostate cancer (PCa) and is negatively correlated with both biochemical recurrence and metastasis. Enoblituzumab is a humanized Fc-optimized B7-H3–targeting antibody that induces antibody-dependent cellular cytotoxicity (ADCC). To date, approximately 180 patients have received Enoblituzumab monotherapy in a phase I study, with good tolerability. To determine the antitumor, immunological and biological effects of B7-H3 inhibition in high-risk localized PCa, we are currently conducting a neoadjuvant and pharmacodynamic phase II study (NCT02923180). *We hypothesize that neoadjuvant enoblituzumab treatment will be feasible, safe, and will produce a robust antitumor immune responses that will correlate with clinical outcomes in high-risk prostate patients undergoing prostatectomy.* **Methods:** In this investigator-initiated single-center, single-arm, open-label phase II neoadjuvant trial we plan to enroll 32 patients with localized PCa (16/32 accrued). Patients must have clinical stage T1c–T3b, N0, M0 disease and Gleason sum 7-10. Eligible patients undergo a pre-treatment prostate biopsy and receive enoblituzumab at a dose of 15mg/kg IV weekly for 6 doses beginning 50 days prior to radical prostatectomy. Fourteen days after the last dose of enoblituzumab, prostate glands are harvested at the time of radical prostatectomy, and prostate tissue is examined for the secondary pharmacodynamic endpoints. The primary co-endpoints are (1) to characterize safety and tolerability of enoblituzumab treatment in the neoadjuvant setting, and (2) to estimate clinical benefit based on PSA0 response (PSA $<$ 0.1 ng/mL) 12 months after radical prostatectomy. Secondary endpoints include evaluation of anti-tumor effects consistent with enoblituzumab's proposed mechanism of action (apoptosis, proliferation), ADCC markers, and assessment of immunologic correlates (CD8, FOXP3, PD-L1 expression). Clinical trial information: NCT02923180.

TPS5100 **Poster Session (Board #320a), Sat, 1:15 PM-4:45 PM**

Apalutamide + abiraterone + leuprolide with stereotactic, ultra-hypofractionated radiation (AASUR) in very high risk prostate cancer (PCa). *First Author: Sean Matthew McBride, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Radiotherapy and long course (18-28 months) androgen deprivation therapy (ADT) is a current standard of care in very high risk PCa; however, biochemical failure remains frequent. We hypothesize that stereotactic, hypofractionated radiotherapy (SBRT) delivered with a total of 6 months of apalutamide, abiraterone (Abi), and leuprolide will result in a superior 3-year rate of biochemical control compared to the historical control of conventionally fractionated radiation therapy (42-48 treatments) and long term ADT in pts with very high risk PCa (Gleason 9-10 or 2 high risk features or $>$ 4 Gleason 8 cores). The regimen, if proven in a phase 3 setting, would enable very high risk PCa pts to receive curative therapy with potentially decreased morbidity compared with extended androgen ablation. **Methods:** We present a single arm, phase 2 trial to determine the efficacy of anti-androgen therapy combined with SBRT in very high risk PCa, with the proportion of pts who have had biochemical failure (nadir+2) by 36-months post completion of anti-androgen therapy as the primary endpoint. Eligible pts will receive 6 months of leuprolide, abi, and apalutamide to begin 3 months prior to SBRT with continuation 3 months post-SBRT. Pts will be assessed every 4 weeks ($\pm$1 week) (cycle = 28 days) throughout study treatment, and at least once during SBRT. A prostate biopsy will be required prior to the start of SBRT; 2 additional biopsies (at 24 months and, if applicable, metastatic progression) will be performed; partial exome analyses using the MSKCC genomic platform (IMPACT) will be performed on all biopsies; additional correlatives include circulating tumor cell evaluation and cell-free DNA measurement pre and post treatment. Interim analysis will ensure early trial termination should toxicities exceed historical controls. 32 of planned 58 pts have been enrolled. The trial is open at 5 sites and managed by the Prostate Cancer Clinical Trials Consortium and funded by Janssen. Clinical trial information: NCT02772588.

TPS5101 Poster Session (Board #320b), Sat, 1:15 PM-4:45 PM

A multicenter, randomized, controlled trial comparing the occurrence of major adverse cardiovascular events (MACEs) in patients (pts) with prostate cancer (pc) and cardiovascular disease (CVD) receiving degarelix (GnRH receptor antagonist) or leuprolide (GnRH receptor agonist). *First Author: Susan F. Slovin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Background: Epidemiological studies showed an association between GnRH agonists and a long-term increased risk of CVD, early after treatment initiation and with a higher risk seen in pts with pre-existing CVD. Retrospective pooled safety analyses of 6 randomized trials showed that significantly fewer pts treated with the GnRH receptor antagonists, degarelix, had a CV event or death compared with pts receiving a GnRH receptor agonist. In those studies showing an increased CV risk, Androgen-Deprivation Therapy (ADT) was primarily with GnRH receptor agonists. The mechanistic differences between GnRH antagonists and agonists, including testosterone surge and time to suppression at initiation, effect on follicle-stimulating hormone and on GnRH receptors e.g. T-lymphocytes in atherosclerotic plaque, raises the possibility of different CV risk profiles. The PRONOUNCE trial is the first to prospectively assess whether a GnRH agonist/antagonist can worsen pre-existing CVD; assess the impact of GnRH agonist/antagonist on CV risk biomarkers; and effects on the immune system. **Methods:** PRONOUNCE is a multi-center, randomized, controlled trial of 900 men with pc and concomitant CVD, assessing adjudicated MACEs, i.e. myocardial infarction (fatal, non-fatal), stroke (fatal, non-fatal), or death in pts randomized 1:1 to either degarelix or leuprolide according to label recommendations for up to one year. Eligibility include pre-defined CVD, metastatic or locally advanced pc; high-risk disease with plan for definitive radiation therapy (RT); recurrence after local therapy with PSA doubling time $<$ 12 months; or salvage RT with neoadjuvant/adjuvant ADT for at least 12 months. Serum samples are collected for the analysis of various CV, inflammatory, and immune biomarkers. The primary endpoint will be based on Kaplan-Meier estimator of survival function and stratified for age group and region. Interim analysis is scheduled when 50% of MACE events have occurred allowing the DSMB to recommend for sample size correction. Clinical trial information: NCT02663908.

5500 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602. *First Author: Takashi ONDA, Department of Gynecology, Kitasato University School of Medicine, Sagamihara, Japan*

Background: We conducted a phase III non-inferiority trial comparing upfront primary debulking surgery (PDS) and neoadjuvant chemotherapy (NAC) for stage III/IV ovarian, tubal and peritoneal cancers (JCOG0602). Two preceding studies, EORTC55971 and CHORUS demonstrated non-inferior overall survival (OS) of patients treated with NAC. We have already reported reduced invasiveness of NAC setting treatment (NACT) compared to PDS setting treatment (PDST) in analysis of short-term outcomes of JCOG0602. This is a final analysis including primary endpoint of OS. **Methods:** Target cancer was diagnosed by 1) imaging studies (CT and/or MRI), 2) cytology of ascites, pleural effusions or fluids obtained by tumor centesis, and 3) CA125 $>$ 200 U/ml and CEA $<$ 20 ng/ml. Patients were randomized to PDS arm (PDS followed by 8 cycles of paclitaxel and carboplatin, i.e. TC regimen) and NAC arm (4 cycles of TC, interval debulking surgery [IDS], 4 cycles of TC). Planned sample size was 300 with 3-year OS of 25% in PDS arm, 30.3% in NAC arm and non-inferiority margin of hazard ratio (HR) of 1.161 (these corresponds to median OS of 18 months in PDS arm, 20.9 months in NAC arm and non-inferiority margin of 2.5 months), one-sided alpha of 5% and 80% power. **Results:** From Nov 2006 to Oct 2011, 301 patients (149 PDS arm and 152 NAC arm) were randomized. Median OS was 49.0 months in PDS arm and 44.3 months in NAC arm. HR was 1.052 [90.8%CI 0.835-1.326] and one-sided non-inferior p value was 0.24. Median progression-free survival was 15.1 months for PDS arm and 16.4 months for NAC arm (HR: 0.987 [95%CI 0.774-1.259]). In PDS arm 147/149 underwent PDS. 49 of them and 130/152 in NAC arm underwent IDS. Complete resection was achieved in 12% (17/147) of PDS and 31% (45/147) of PDS $\pm$ IDS in PDS arm and in 64% (83/130) of IDS in NAC arm. Optimal surgery (maximum residual tumor $<$ 1cm) was achieved in 37% (55/147) of PDS and 63% (92/147) of PDS $\pm$ IDS in PDS arm and in 82% (107/130) of IDS in NAC arm. **Conclusions:** The non-inferiority of NAC arm was not confirmed and NACT cannot be always a substitute for PDST. Further studies may be necessary to demonstrate a role of NACT for more limited target. Clinical trial information: UMIN000000523.

5501 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): A NRG Oncology/Gynecologic Oncology Group (GOG) study. *First Author: Robert L. Coleman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: GOG-0213 is an international, open-label, randomized phase 3 trial in women with PSOC with two objectives: 1) to study the addition of B to paclitaxel/carboplatin concurrently and as maintenance; and 2) to evaluate the impact of SSC. The primary endpoint is overall survival (OS). We previously reported the results of Objective 1 [HR 0.829; 95% CI: 0.683-1.005; p = 0.056) Coleman RL, et al Lancet Oncol 2017], and now report the outcomes of Objective 2. **Methods:** From Dec-2007 until Jun-2017, 485 women with investigator-determined resectable PSOC were randomized 1:1 to SSC followed by PBC (n = 240) or PBC alone (n = 245). Stratification factors included the platinum-free interval (PFI). Surgical candidacy was predicated on the likelihood to achieve complete resection (R_0). For Objective 2, the use of B was investigator's choice. The primary endpoint reached maturity for a pre-specified interim analysis in Nov-2017. Results are based on 2-sided alpha = 0.05. **Results:** 215/240 (90%) evaluable patients who were randomized to SSC underwent the procedure. R_0 was achieved in 63%. Adjuvant B was common (84%). Median follow-up duration is 34.6 mos. The HR for death (SSC vs. none) is 1.28 (95%CI: 0.92-1.79) corresponding to a median OS of 53.6 mos vs. 65.7 mos, respectively. There is a significantly different effect of SCC on OS in those receiving PBC+B vs. those who did not (p = 0.022). The HR for death (SCC vs. none) among 77 patients receiving PBC is 2.18 (95% CI: 0.86 – 5.51), while the HR for death among 408 patients receiving PBC+B is 1.03 (95% CI: 0.57 – 1.88). The median progression-free survival was 18.2 mos in the SSC cohort vs.16.5 mos without SCC, HR: 0.88 (95% CI: 0.70 – 1.11). One patient died due to complications from SSC. No new safety signals were observed. **Conclusions:** SSC can be safely performed in patients with PSOC, but did not improve OS in this population. Additional analyses (e.g. impact of PFI, SSC outcome, disease burden and chemotherapy regimen on OS by SSC allocation) are underway and will be presented. Clinical trial information: NCT00565851.

5502 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer. *First Author: Daniel Jacob Margul, Northwestern University, Chicago, IL*

Background: Surgery is the primary treatment modality for early cervical cancer. Compared to open (ORH), a robotic (RRH) or laparoscopic (LRH) approach to radical hysterectomy may have decreased morbidity, but the influence of surgical approach on survival, specific perioperative complications, and costs is unknown. **Methods:** The 2010-2013 National Cancer Database (NCDB) was used to evaluate the 5-year survival (5YS) of women with stage IB1 cervical squamous cell carcinoma or adenocarcinoma after radical hysterectomy performed open or by minimally invasive surgery (MIS). Survival times were estimated with the Kaplan-Meier method. Multivariable Cox proportional-hazards model (CPH) was used to adjust for measured confounders. The 2010-2015 Premier Healthcare Database was used to compare complications, length of stay (LOS), readmission rates, and hospitalization costs between ORH, RRH, and LRH. All p-values are two-sided. **Results:** From the NCDB, 982 and 910 women underwent ORH versus MIS radical hysterectomy, respectively. Women with a tumor size $\geq$ 2 cm who underwent MIS radical hysterectomy had decreased survival compared to women who underwent ORH (5YS (95% CI): 81.3% (75.6%-87.3%) versus 90.8% (87.7%-93.9%); hazard ratio (95% CI) 2.14 (1.36-3.38), P $<$ 0.001). From Premier, 2830 women had radical hysterectomy: 45.1% (1277) ORH, 48.9% (1384) RRH, and 6% (169) LRH. ORH was associated with longer LOS compared to RRH or LRH (days, median (IQR): ORH 3 (3-5); RRH 1 (0-2); LRH 0 (0-2), P $<$ 0.001). ORH also had a higher composite complication rate than RRH or LRH (ORH 44.9%; RRH 13.9%; LRH; 12.4%, P $<$ 0.001), with increased bowel injuries, infections, electrolyte or fluid disorders, transfusions, and ileus (all P $\leq$ 0.001) associated with ORH. Thirty-day readmission rates were similar (ORH 2.3%; RRH 1.4%; LRH 1.8%, P = 0.17). Total surgical hospitalization costs favored MIS (P $<$ 0.001 between groups) with median (IQR) values: ORH $12080 (8957-16052); RRH $11562 (8636-14600); LRH $9649 (7478- 13010). **Conclusions:** MIS is associated with decreased morbidity and costs. However, among women with $\geq$ 2 cm stage IB1 cervical cancer, MIS was associated with significantly decreased survival.

5503 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

ZoptEC: Phase III randomized controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (NCT01767155). *First Author: David S. Miller, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Zoptarelin (AEZS-108, AN-152, ZEN-008) is a luteinizing hormone-releasing hormone (LHRH)-cytotoxic hybrid molecule composed of doxorubicin chemically linked to the carrier molecule D-Lys6-LHRH. The primary objective of this study was to compare the overall survival (OS) of patients treated with zoptarelin vs doxorubicin. The secondary objectives included comparing efficacy based on progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), and safety. **Methods:** In an international multi-center trial, patients with advanced, recurrent, or metastatic endometrial cancers who had failed prior platinum and taxane therapy were centrally randomized 1:1 to zoptarelin (267mg/m2) or doxorubicin (60 mg/m2), I.V. every 21 days for up to nine cycles. **Results:** Zoptarelin was given to 256 patients and doxorubicin to 255 for a median of 5 vs 4 cycles respectively. The median OS for patients treated with zoptarelin was 10.9 months compared to 10.8 months for patients treated with doxorubicin (HR = 1.06; C.I. 0.87, 1.30). PFS was 4.7 months for both (HR = 0.89, C.I. 0.71, 1.11). ORR was 12% vs 14% and CBR was 54% vs 52% (p = NS). The most common grade $>$ 2 adverse events were Neutropenia 47% vs 45%, Leukopenia 21% vs 18%, and Anemia 20% vs 15%. Febrile neutropenia was seen in 9% vs 4%. Absolute decline of LVEF from baseline of $>$ 15% or absolute value $<$ 45% was found in 7% vs 13%. **Conclusions:** Zoptarelin did not improve OS, PFS, ORR, CBR, or adverse events compared to doxorubicin as second line therapy for advanced endometrial cancers. Clinical trial information: NCT01767155.

5504 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Phase I trial of olaparib (PARP inhibitor) and vistusertib (mTORC1/2 inhibitor) in recurrent endometrial, ovarian and triple negative breast cancer. *First Author: Shannon Neville Westin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We sought to determine the recommended phase II dose (RP2D) of olaparib (O) and vistusertib (V) and evaluate molecular markers of response. **Methods:**Two oral schedules for V were explored with O tablet BID. Arm 1: BID continuous (5 dose levels (DL)) and Arm 2: BID 2 days on/5 days off (4 DL). Clinical benefit rate (CBR) was defined as objective response or stable disease ≥ 6 cycles by RECIST 1.1. Patients (pts) were evaluable for response if they received at least 1 cycle (28 days). An expansion phase (n = 30) was performed at RP2D of Arm 2 with biopsies at baseline and 28 days. **Results:** 74 pts were enrolled, 8 with BRCA mutation (11%). Median prior therapies was 4 (1-8). There were 2 DLTs on Arm 1 at DL 5 (O 300mg/V 50mg; G4 thrombocytopenia, G3 allergic reaction). There were 3 DLTs on Arm 2. 2 DLTs at DL 1 (O 100mg/V 125mg; G3 neutropenia > 7 days (n = 1); G3 hyperglycemia (n = 1)) and 1 DLT at DL1b (O 200mg/V 100mg; G3 fatigue). RP2D of Arm 1 was O 200mg/V 50mg. RP2D of Arm 2 was O 300mg/V 100mg. Most common adverse events (≥20%) were nausea (84%, G3/4 4%), anemia (83%, G3/4 15%), hyperglycemia (76%, G3/4 3%), fatigue (73%, G3/4 11%), leukopenia (55%, G3/4 9%), increased creatinine (50%, G3/4 0%), headache (42%, G3/4 0%), vomiting (41%, G3/4 5%), hypercholesterolemia (41%, G3/4 0%), diarrhea (39%, G3/4 0%), hypertriglyceridemia (38%, G3/4 1%), thrombocytopenia (38%, G3/4 14%), mucositis (28%, G3/4 4%), transaminitis (28%, G3/4 1%), constipation (28%, G3/4 1%), and pain (28%, G3/4 1%). Of 64 evaluable pts, response rate (RR) across all DL was 19% with median duration 14 mo (4-34). CBR was 34%. RR was 27%, 20%, and 6% for endometrial, ovarian, and breast cancer, respectively. Among 49 evaluable pts treated on Arm 2, RR was 19% and CBR 37%. In Arm 2, RR was 31%, 15%, and 8% for endometrial, ovarian and breast cancer, respectively. Among 6 endometrial cancer responders (3 endometrioid, 3 serous), PI3K pathway, ARID1A, or FBXW7 mutations were common (67%). **Conclusions:** The combination of olaparib and vistusertib is well tolerated with durable anti-tumor activity. Promising response was seen in both histologies of endometrial cancer. Assessment of molecular correlatives of response will be presented. Clinical trial information: NCT02208375.

5505 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Adjuvant gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high-grade leiomyosarcoma: A phase III GOG study. *First Author: Martee Leigh Hensley, Memorial Sloan Kettering Cancer Center and Weil Cornell Medical College, New York, NY*

Background: We conducted a phase III trial to determine whether adjuvant chemotherapy with gemcitabine-docetaxel followed by doxorubicin improves survival compared to observation in women with resected, uterus-confined, high grade LMS. **Methods:** Women with uterus-confined high grade LMS, confirmed disease-free by post-resection imaging, were randomly assigned to treatment with gemcitabine-docetaxel x 4 cycles, followed by doxorubicin x 4 cycles (CHEMO) or to observation (OBS). All were followed by CT or MR imaging every 4 mos for 3 yrs, then every 6 mos for 2 yrs for recurrence. The primary endpoint was overall survival. **Results:** The study was opened with international collaboration. 38 of the target accrual of 216 patients (pts) were enrolled, after which the study was closed for National Cancer Institute-defined accrual futility. 20 pts were assigned to CHEMO and 18 to OBS. 3 pts assigned to CHEMO never received treatment. Among the 17 pts treated with at least one cycle of CHEMO grade 3 or 4 toxicities were observed in 47%; among 18 pts assigned to OBS, 1 had grade 3 hypertension. There were 6 deaths, (5 - CHEMO, 1-OBS), all due to disease. Over 48 mos, the restricted mean survival time (RMST) for OS in the CHEMO arm was estimated to be 34.3 mos (95% CI: 25.3 mos – 43.3 mos); RMST for OS in the OBS arm was estimated to be 46.4 mos (95% CI: 43.6 mos – 49.1 mos). There were 8 recurrences in each arm. Over 24 mos, the RMST for RFS in the CHEMO arm was estimated to be 18.1 mos (95% CI: 14.2 mos – 22.0 mos) and the RMST for RFS in the OBS arm was estimated to be 14.6 mos (95% CI: 10.3 mos – 19.0 mos). The difference in RMST comparing the CHEMO arm to the OBS arm was estimated as 3.4 mos (95% CI: -2.4 mos – 9.3 mos). Neither survival outcome comparison is considered statistically robust due to the small sample size and low number of events. **Conclusions:** Despite international collaboration to answer the critical question of the role of adjuvant chemotherapy in early-stage uterine LMS, this study was closed for accrual futility. While sample size and number of events preclude robust statistical comparison, observed OS and RFS data do not suggest superior outcomes for patients treated with adjuvant chemotherapy. Clinical trial information: NCT01533207.

5506 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: The randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17. *First Author: Sandro Pignata, Istituto Nazionale Tumori "Fondazione G.Pascale"-IRCCS, Naples, Italy*

Background: Bevacizumab (BEV) is approved in recurrent ovarian cancer (rOC) for patients not previously treated with the drug. Our study aimed at evaluating whether the addition of BEV to a platinum-based chemotherapy prolongs progression-free survival (PFS) for rOC patients who had already received it during first line. **Methods:** FIGO stage IIIB-IV rOC patients relapsing at least 6 months after last dose of platinum, who had received BEV during first-line treatment, ECOG PS≤2, were randomized to 6 cycles of platinum-based doublets (carboplatin/paclitaxel or carboplatin/gemcitabine or carboplatin/PLD) with or without BEV administered concomitant with chemotherapy and as maintenance until disease progression. The primary endpoint is PFS. With 90% power in detecting a 0.67 HR, with 2-sided α error 0.05, 265 events were needed. All efficacy analyses are done on an intention-to-treat basis. PFS and OS curves are estimated by Kaplan-Meier method, and compared with a two-sided log-rank test. Toxicity is graded according to NCI-CTCAE v 4.0. **Results:** 405 pts were enrolled. Median age was 61; 64% of patients had progressed ≥12 months after last dose of platinum and 72% of patients after completion of first-line BEV maintenance. With a median follow-up of 20.3 months, 304 PFS events and 147 deaths were recorded. Median PFS was 8.8 months and 11.8 months without and with BEV, respectively (HR 0.51, 95%CI: 0.41-0.64, p < 0.001). Median OS was 27.1 months and 26.7 months without and with BEV, respectively (HR 1.00, 95%CI: 0.73-1.39, p = 0.98). Severe (≥G3) hypertension (27.5% vs 9.7%, p < 0.001) and proteinuria (4% vs 0, p = 0.007) were more frequent with BEV. **Conclusion:** This study shows that for rOC patients previously treated with BEV in first line relapsing ≥6 months after last platinum, rechallenge with BEV in combination with platinum-based doublets is associated with a significantly prolonged PFS, with no unexpected toxicity.Supported by Roche. Clinical trial information: NCT01802749.

5507 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Correlation of imaging and plasma-based biomarkers to predict response to bevacizumab in epithelial ovarian cancer (EOC): A GOG 218 ancillary data analysis. *First Author: Megan Buechel, University of Oklahoma Health Science Center, Oklahoma City, OK*

Background: Increasing measures of adiposity can correlate with poor oncologic outcomes and lack of response to antiangiogenic therapies. Limited data exists on the impact of subcutaneous fat and visceral fat density(SFD/VFD) on oncologic outcomes. IL-6 has been suggested as a predictive serum biomarker for overall survival (OS) with use of bevacizumab (bev) in EOC. **Methods:** 1249 patients(pts) (67%) from GOG 218 with imaging measurements were included in the OS analysis. Predictive analyses for bev responsiveness used pts who received chemotherapy (CT) + placebo and placebo maintenance and CT + bev and bev maintenance (851 pts). Of these, 522 pts (61%) had IL-6 measurements. SFD and VFD were calculated utilizing Hounsfield units (HU). Proportional hazards models were used to assess the association between BMI, SFD, and VFD with OS. Spearman correlation was used to assess the relationship between IL-6 and VFD. **Results:** Demographic characteristics for pts included in this analysis did not differ from the entire cohort. Increased SFD and VFD showed an increased HR for death (HR per 1-SD increase 1.12, 95% CI:1.05-1.19 p = 0.0009 and 1.13, 95% CI: 1.05-1.20 p = 0.0006 respectively). OS curves for high SFD and VFD show the most separation within quartiles (difference of ~10 months between the 2nd and 4th quartiles). In the predictive analysis, VFD showed a significantly different effect in the two treatment groups (p = 0.025). High VFD showed an increased hazard for death in the placebo group (HR per 1-SD increase 1.22, 95% CI: 1.09-1.37). However, in the bev group there was no effect seen (HR per 1-SD increase: 1.01, 95% CI: 0.90-1.14). OS curves show median OS of 45 vs 47 months in the VFD low groups and 36 vs 42 months in the VFD High groups on placebo versus bev respectively. There was no correlation between IL-6 and high VFD (r = 0.02, p = 0.57). **Conclusions:** High SFD and VFD may be prognostic biomarkers for EOC. High VFD may be a predictive biomarker for use of bev. Pts with high VFD improved their OS curve to the low VFD group with the addition of bev. A similar association was seen with IL-6; however, high IL-6 and high VFD occur in different populations. Further biomarker study is warranted.

5508 Oral Abstract Session, Tue, 9:45 AM-12:45 PM

Cost-effectiveness of maintenance therapy in advanced ovarian cancer: Paclitaxel, bevacizumab, niraparib, rucaparib, olaparib, and pembrolizumab. *First Author: Juliet Elizabeth Wolford, University of California, Irvine, Orange, CA*

Background: Acquired drug resistance remains the greatest clinical hurdle in advanced ovarian cancer suggesting that effective maintenance therapies are lacking. We evaluated cost-effectiveness of available strategies, adjusting for pre-treatment medication costs, infusion center charges, and costs of managing adverse events. **Methods:** Registration trial data was used to obtain toxicity and median PFS for a) paclitaxel (GOG 212); b) bevacizumab (GOG 218, ICON 7, OCEANS, GOG 213); c) niraparib (NOVA), olaparib (SOLO-2), rucaparib (ARIEL-3); and d) pembrolizumab. Because anti-angiogenesis therapy was studied in different populations, each trial was modeled separately. As phase III randomized trials involving checkpoint inhibition in ovarian cancer are not mature, data for pembrolizumab (available via agnostic indication) were obtained from the phase IB ovarian cohort of KEYNOTE-028. Costs of germline/somatic BRCA testing and those associated with management of neuropathy and immune-mediated adverse events, including endocrinopathies, also factored into the model. Utilizing a Markov chain, patients transitioned through response, hematological and non-hematological complications, progression, and death. Using Medicare data, the costs of infusions and managing toxicities were estimated. Incremental cost-effectiveness ratios (ICER) and quality of adjusted life-months gained were determined for each therapy. **Results:** Maintenance paclitaxel was most cost-effective at $870/PFS month. Expected costs of PARP inhibitors (PARPi(s)) prior to progression were approx. $471,989 (18.8x paclitaxel, 6.9x pembrolizumab, and 2.2-2.7x bevacizumab). Comparing pembrolizumab to PARPi(s) in BRCA-deficient patients, anti-PD-1 maintenance yielded ICERs per month of life gained of $20,032 (niraparib), $18,444 (rucaparib), and $17,520 (olaparib). **Conclusions:** Using PFS as the benchmark, high costs of maintenance PARPi(s)/immunotherapy are not mitigated by adjusting for the sequelae that may manifest with maintenance chemotherapy/VEGF inhibition. In terms of economic toxicity, the current trend to study novel combinations is problematic.

5509 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Dendritic cell vaccine (DCVAC) with chemotherapy (ct) in patients (pts) with epithelial ovarian carcinoma (EOC) after primary debulking surgery (PDS): Interim analysis of a phase 2, open-label, randomized, multicenter trial. *First Author: Lukas Rob, Department of Obstetrics and Gynaecology, University Hospital Kralovske Vinohrady, Prague, Czech Republic*

Background: Most pts with EOC relapse after PDS and ct. Autologous DCVAC can present tumor antigens to elicit a durable immune response. We hypothesized that adding DCVAC to ct could improve outcomes, including progression-free survival (PFS). **Methods:** Key eligibility criteria were FIGO stage III EOC (serous, endometrioid, or mucinous), PS 0 - 2, post-PDS with $<$ 1cm maximal residuum and no prior systemic therapy. We randomized pts up to 6 weeks after PDS, 1:1:1, into arm A (A; DCVAC concomitantly with ct), arm B (B; DCVAC sequentially after ct) and arm C (C; ct alone). Pts were stratified by tumor residuum (0 or $<$ 1cm). Ct consisted of 6 cycles of carboplatin (AUC 5 - 7) and paclitaxel (175mg/m^2). Pts in A and B were to receive 10 doses of DCVAC (1×10^7 DCs/dose). The primary endpoint was investigator-assessed PFS. Key secondary endpoint was overall survival (OS). **Results:** Between November 2013 and March 2016, 99 pts were randomized in 3 countries (A/B/C, 34/34/31). Median age was comparable in all arms (range, 61.5 - 62.0 years). The % of pts with complete cytoreduction was 85% in A and B, and 84% in C. At the planned interim analysis, the ITT population included 31 pts in A, 30 pts in B, and 31 pts in C; pts who failed leukapheresis (LP) or manufacturing were excluded. A mean of 9.6 and 9.5 doses of DCVAC were administered in A and B, respectively. Median follow-up time was 26.8 months (range, 3.24 - 43.0; 1 pt withdrew informed consent early in the trial). Median PFS was 18.3 months in A, 24.3 months in B, and 18.6 months in C. Compared to C, PFS hazard ratios (95% CI) were 1.08 (0.53 - 2.21) in A and 0.43 (0.18 - 1.03) in B. The gain in PFS in the sequential arm was statistically significant ($p = 0.05$), and this was supported by the same trend in OS. Median OS was not reached in any arm (14% events). There were no grade $\geq$ 3 adverse events (AEs) related solely to DCVAC and it did not worsen the side effects of ct. Most common LP-related AEs were mild pyrexia and moderate hypocalcemia. **Conclusions:** DCVAC improved PFS when administered sequentially after ct. This provides a promising maintenance treatment option delaying progression of the disease. Clinical trial information: NCT02107937.

5510 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Clinical data from the DeCidE^1 trial: Assessing the first combination of DPX-Survivac, low dose cyclophosphamide (CPA), and epacadostat (INCB024360) in subjects with stage IIc-IV recurrent epithelial ovarian cancer. *First Author: Oliver Dorigo, Stanford Cancer Institute, Stanford, CA*

Background: DPX-Survivac is a novel T cell activating therapy containing a mix of HLA class I peptides designed to evoke a T cell response against survivin and previously optimized for immunogenicity when delivered with intermittent metronomic cyclophosphamide (CPA). It can induce robust, sustained and specific T-cell responses in subjects with ovarian cancer. Epacadostat (E) is a potent and selective inhibitor of indoleamine 2,3-dioxygenase 1 that may reverse tumor-associated immune suppression. This Phase 1b is evaluating if a *de novo* tumor-specific T cell response, combined with the alteration of the immune suppression will result in clinical benefits. **Methods:** Subjects with advanced ovarian cancer (stage IIc-IV with evidence of disease progression) were treated with DPX-Survivac (2x 0.25 mL priming doses q3w and up to 6x 0.1 mL boosting doses q8w), metronomic CPA (50 mg BID on alternating weeks), and epacadostat (up to 300 mg BID). Primary endpoints include safety and immunogenicity. Secondary endpoints include objective response by modified RECIST v1.1. **Results:** Fourteen subjects were enrolled in the initial dose cohort (E 100 mg BID), 10 of which were considered evaluable. The incidence of adverse events has been collected and the presence of survivin-specific activated T-cells detected in the blood. Three subjects reached an objective response of PR with 1 subject attaining a response of PR within 8 weeks of beginning treatment. Two subjects reached SD followed by PR, one of which is still ongoing, maintained for more than 6 months post-response; both have had disease control for more than 12 months. A best response of SD was shown in 3 of 10 subjects, with an additional subject showing SD (+6%) after an initial PD (+26%). **Conclusions:** The first triple combination of DPX-Survivac, low dose CPA, and epacadostat resulted in clinical responses in subjects with recurrent ovarian cancer. The combination was well-tolerated and immunogenicity to DPX-Survivac was demonstrated. The rate of response observed so far in this study is promising and warrants additional development. Clinical trial information: NCT02785250.

5511 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: Interim results from the phase 2 KEYNOTE-100 study. *First Author: Ursula A. Matulonis, Dana-Farber Cancer Institute, Boston, MA*

Background: Data from the KEYNOTE-028 study (NCT02054806) suggested that pembrolizumab (pembro) has clinical activity in patients (pts) with PD-L1+ advanced ovarian cancer (AOC). We assessed the antitumor activity and safety of pembro in pts with recurrent AOC in the ongoing, 2-cohort, phase 2 KEYNOTE-100 study (NCT02674061). **Methods:** Key eligibility criteria included epithelial ovarian, fallopian tube, or primary peritoneal cancer, confirmed recurrence following front-line platinum-based therapy, ECOG PS 0/1, and provision of a tumor sample for biomarker analysis. Cohort A pts received $\leq$2 prior chemotherapy lines for recurrent AOC and had a platinum-free or treatment-free interval (PFI/TFI) of $\geq$3 to 12 mo. Cohort B pts received 3-5 prior chemotherapy lines and had a PFI/TFI of $\geq$3 mo. Pts received pembro 200 mg Q3W IV for 2 yrs or until progression, death, unacceptable toxicity, or consent withdrawal. Tumor imaging was performed every 9 wks for 1 yr and every 12 wks thereafter. Primary study endpoint was ORR per RECIST v1.1 by independent central review for both cohorts and by tumor PD-L1 expression. The effect of PD-L1 expression on ORR was tested with the combined positive score (CPS) assay. Cutpoints were established using the first 100 pts enrolled into Cohort A (training set). Validation was performed among all subsequent pts enrolled. Training set results are presented here. Complete results (n = 378) will be available for presentation. **Results:** 378 pts were enrolled in KEYNOTE-100. 97/100 training set pts had analyzable results. Mean ($\pm$SD) age for this group was 61 ($\pm$12) yr, 68% had ECOG PS 0, and 77% had high grade serous disease. ORR was 9% (95% CI, 4, 17). ORR was higher in pts with PD-L1 expression: 14% (8/59) with CPS $\geq$1 and 25% (5/20) with CPS $\geq$10. 73% of pts had treatment-related (TR) AEs and 17% had grade 3-5 TR AEs. There was 1 TR death in a pt with Stevens-Johnson syndrome. **Conclusions:** Pembro monotherapy was associated with antitumor activity in pts with recurrent AOC. ORR increased with PD-L1 expression, better defining a population benefiting from single agent pembro. No new safety signals were identified in this population. Clinical trial information: NCT02674061.

5512 Clinical Science Symposium, Sun, 9:45 AM-11:15 AM

Association of high tumor mutation (TMB) with DNA damage repair (DDR) alterations and better prognosis in ovarian cancer. *First Author: Wenjuan Tian, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: Defects in DNA damage repair (DDR) system may lead to genomic instability and manifest as increased tumor mutation burden (TMB) in multiple types of cancers. But the prognostic value of TMB and association between DDR and TMB in ovarian cancer is still unclear. **Methods:** Whole-exome sequencing data of 434 ovarian tumors from The Cancer Genome Altas (TCGA) and next generation sequencing (NGS) data of 93 ovarian tumors from 3D Medicines were analyzed to explore the association between 21 cancer-related DDR genes and TMB, defined as number of somatic non-synonymous mutations. We also performed analysis of clinical data from TCGA to identify the impact of TMB on ovarian cancer prognosis. **Results:** 27.4% of ovarian tumors in TCGA and 40.9% in 3D Med harbored at least one DDR alteration. The most frequently mutated genes were POLE (21%), BRCA1 (5.1%), BRCA2 (4.1%), ATM (3.0%), FANCA (2.5%), PALB2 (2.3%), FANCD2 (2.1%), and ATR (2.1%) in TCGA, and BRCA1 (12.9%), BRCA2 (10.8%), ATM (5.4%), RAD51 (3.2%), BRIP1 (3.2%), FANCD2 (3.2%), and PALB2 (3.2%) in 3D Med. Any DDR alteration was significantly associated with higher TMB in both TCGA ($P < 0.00$) and 3D Med ($P = 0.021$). Any two DDR gene alterations were associated with even much higher degree of TMB in both TCGA ($P < 0.00$) and 3D Med ($P = 0.03$) compared with DDR wild type. Co-mutated TP53 and any DDR significantly associated with higher TMB in both TCGA ($P < 0.00$) and 3D Med ($P = 0.02$). Prognosis analysis was performed on patients from TCGA. High TMB (cut off as median) was associated with significantly longer DFS (16.4m vs. 14.1m, HR 0.83, $P = 0.04$) and OS (41.0m vs. 32.1m, HR 0.77, $P < 0.00$). Moreover, median PFS for patients with and without DDR alterations was 19.2m and 16.7m ($P = 0.07$). Median OS was 54.6m and 41.5m respectively ($P = 0.02$). **Conclusions:** DDR deficiency is prevalent in ovarian cancer and associated with higher TMB. High TMB was associated with more favorable DFS and OS in ovarian cancer patients. Our results suggest that DDR gene alterations may correlated with anti-tumor immunity in forms of increased TMB, which is known to increase the neoantigen load of tumors. This may assist with the selection of ovarian cancer patients likely to benefit from immunotherapy.

5514 Poster Discussion Session; Displayed in Poster Session (Board #241), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

QUADRA: A phase 2, open-label, single-arm study to evaluate niraparib in patients (pts) with relapsed ovarian cancer (ROC) who have received ≥3 prior chemotherapy regimens. *First Author: Kathleen N. Moore, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: PARP inhibitors (PARPi) are approved as active treatment only for pts with *BRCA* mutations. The PARPi niraparib demonstrated increased PFS vs placebo in the maintenance setting of platinum (plat) responsive ROC. Niraparib was effective regardless of *BRCA*mut or homologous recombination deficiency (HRD) status, but an increased treatment effect was observed in the HRDpos population. QUADRA (NCT02354586) evaluated niraparib active treatment in ROC pts. Based on the results of NOVA, the primary objective in QUADRA was to determine ORR in plat sensitive, HRDpos patients. **Methods:** Eligible pts had grade 2 or 3 serous ROC, ≥3 prior lines of chemo and measurable disease. Pts were evaluated for *BRCA*mut and HRD status (MyChoice HRD Test). HRDpos included germline or tumor *BRCA* mutation or an HRD score ≥42. Pts received niraparib 300 mg once daily until progression; treatment emergent adverse events (TEAEs) were managed with dose reduction to 200 or 100 mg. The primary endpoint was ORR per RECIST v1.1. **Results:** 463 pts were treated. Median age was 65 (range: 29-91). 162 pts were plat refractory; 152 plat resistant; 118 plat sensitive; 31 unknown. In HRDpos, plat sensitive pts who had received ≥3 regimens (median: 3 [range: 3-9]), without prior PARPi ($N = 51$) ORR was 27.5% (95% CI: 15.9%, 41.7%); DCR was 68.6%; DOR was 9.2 mos. Of the 51 pts, ORR was 38.9% (7/18) in *BRCA*mut and 21.2% in *BRCA*wt pts (7/33). 260 (56.2%) pts had grade ≥3 treatment-related TEAEs. The most common grade ≥3 TEAEs were thrombocytopenia (27.9%), anemia (24.9%), and neutropenia (12.4%). Grade ≥3 thrombocytopenia was 27.5% at 300 mg, 4.7% at 200 mg, and 2.7% at 100 mg. Hematologic TEAEs were most frequent in the first month and decreased in frequency and severity after dose reduction during months 2-3. **Conclusions:** Niraparib demonstrated durable anti-cancer activity in this heavily treated, HRDpos ROC population (4th line or greater), including *BRCA*wt pts. Toxicities, consistent with previous niraparib studies, were manageable with dose reduction and generally resolved within 3 mos. Final data including ORR in the total population ($N = 463$) and results in other subgroups will be presented. **Disclosure** Funded by TESARO, Inc. Clinical trial information: NCT02354586.

5515 Poster Discussion Session; Displayed in Poster Session (Board #242), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Apatinib, a novel VEGFR inhibitor, combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer: A single-arm, open-label, phase 2 study. *First Author: Chunyan Lan, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Anti-angiogenic therapy combined with chemotherapy could improve the outcome of platinum-resistant ovarian cancer. Apatinib is an oral tyrosine kinase inhibitor which selectively inhibits VEGFR2. We assessed the efficacy and safety of combination of apatinib and oral etoposide, which has the advantage of home administration without an infusion pump and hospitalization, in patients with platinum-resistant or platinum-refractory ovarian cancer. **Methods:** In this phase 2, single-arm, open-label study, we included patients aged 18-70 years with platinum-resistant or platinum-refractory ovarian cancer. Patients received oral etoposide 50 mg on days 1 to 14 in a 21-day cycle for a maximum of six cycles. In addition to the chemotherapy, apatinib 500 mg was administered orally once daily. The primary endpoint was objective response rate by RECIST version 1.1. A Simon two-stage design was employed. This study was registered with ClinicalTrials.gov, number NCT02867956. **Results:** Between Aug 10, 2016 and Nov 9, 2017, 35 patients were enrolled. At data cutoff (Dec 31, 2017), 20 (57.1%) of 35 patients had discontinued study, and 15 (42.9%) patients remained on treatment. The reasons for treatment discontinuation included disease progression (n = 10), adverse events (n = 4), consent withdrawal (n = 2), lost of follow-up (n = 2), and others (n = 2). Objective responses were achieved in 19 (54.3%; 95% CI: 36.6–71.2) of 35 patients and disease control was obtained in 30 (85.7%; 95% CI: 69.7–95.2) patients. The median progression-free survival was 8.1 months (95% CI: 2.8–13.4). The most common grade 3 or 4 adverse events were neutropenia (41.2%), fatigue (32.4%), anaemia (29.4%), and mucositis (23.5%). No treatment-related death was recorded. All of the adverse events were manageable. Dose reductions occurred in 82.4% of the patients for apatinib and 76.5% of the patients for oral etoposide. **Conclusions:** The combination of apatinib with oral etoposide shows promising activities and manageable toxicities in patients with platinum resistant or refractory recurrent ovarian cancer, and warrants further study in phase 3 trials. Clinical trial information: NCT02867956.

5516 Poster Discussion Session; Displayed in Poster Session (Board #243), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). *First Author: Anna Fagotti, Policlinico A. Gemelli Foundation, Rome, Italy*

Survival analyses from a randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer with high tumor load (SCORPION trial). Background: Previous randomized multicenter trials determined that neoadjuvant chemotherapy (NACT) was non-inferior to primary debulking surgery (PDS) for both progression-free (PFS) and overall survival (OS) in advanced epithelial ovarian cancer (AEOC). We investigated whether NACT was superior to PDS in terms of PFS and postoperative morbidity in AEOC patients, endowed with high tumor load (HTL), in a single Institution committed toward maximal surgical effort. **Methods:** This was a superiority, randomized phase III trial registered on clinicaltrials.gov (No. NCT01461850). Tumor load was assessed by a laparoscopy predictive index (PI; Fagotti score). Women included had stage IIIC-IV disease and PI between 8 and 12 (HTL). They were randomly assigned (1:1 ratio) to undergo either PDS followed by adjuvant chemotherapy, or NACT followed by interval debulking surgery (IDS) and chemotherapy. Carbo-taxol based chemotherapy was performed in both arms. Co-primary outcome measures were PFS and postoperative complications; secondary outcomes were OS, and quality of life (QoL). Results on postoperative complications and QoL were previously published. Survival analyses were performed on intention-to-treat analysis (ITT), using Kaplan-Meier method. **Results:** From October 2011 to November 2016, 171 women were randomly assigned to PDS (n = 84) vs. NACT (n = 87). All were included in the ITT analysis. Overall median FU was 42 months (95% CI: 30-50 months). As of March 11, 2018, 137 (80.1%) disease progressions and 74 deaths (43.3%) had occurred. There was no significant difference for PFS between patients who underwent PDS vs. NACT (15 vs. 14 months) (HR = 1.06, 95%CI: 0.77-1.46; p = 0.72 log-rank test). Median OS was 41 months in the PDS arm and not reached in the NACT arm. Eighty-four women had PDS and 74 had IDS. Optimal residual tumor (≤ 1 cm) was obtained in 78 (92.8%) vs. 74 (100%) patients, respectively (p = 0.02). Seven (8.3%) deaths for post-operative complications were registered in the PDS vs. 0 in the NACT arm (p = 0.01). **Conclusions:** NACT was not superior to PDS in terms of PFS for AEOC patients endowed with HTL receiving maximal surgical effort. Clinical trial information: NCT01461850.

5517 Poster Discussion Session; Displayed in Poster Session (Board #244), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: A NRG oncology/Gynecologic Oncology Group (GOG) study. *First Author: Robert Allen Burger, Department of Obstetrics & Gynecology, Division of Gynecologic Oncology, University of Pennsylvania, Philadelphia, PA*

Background: GOG 0218 is a double-blind, placebo-controlled, phase 3 randomized trial studying chemotherapy with and without concurrent BEV, and with concurrent BEV followed by maintenance BEV for advanced stage ovarian carcinoma. In 2010, at a median follow-up of 17.4 months (m), the trial met its primary endpoint demonstrating improvement in progression-free survival (PFS) for patients receiving BEV with and following chemotherapy compared to chemotherapy alone: median PFS 14.1 vs 10.3m, respectively; HR 0.717; 95% CI, 0.625-0.824; $p < 0.001$ [Burger RA, et al N Engl J Med 2011]. With extended follow-up, we report on the key secondary endpoint, final OS. **Methods:** 1,873 women with newly diagnosed, incompletely resected stage III or stage IV ovarian cancer received six 21-day cycles of carboplatin (AUC 6) IV and paclitaxel (175 mg/m^2 BSA) IV chemotherapy alone (control) vs chemotherapy plus BEV (15 mg/kg body weight) IV cycles 2-6 (BEV-initiation) vs chemotherapy plus BEV cycles 2-22 (BEV-throughout). OS was analyzed in the intention-to-treat (ITT) population. The database was locked on Jan. 17, 2018 at a median follow-up of 102.9m. **Results:** After 1,491 (79.6%) deaths, 204 patients (10.9%) are alive with a progression event, and 178 (9.5%) are alive without progression. Comparing BEV-throughout to control, the hazard of death (HR) is 0.96; 95% CI, 0.85-1.09; p = 0.53. For BEV-initiation vs control, HR is 1.06; 95% CI, 0.94-1.20; p = 0.34. The relative HR for stage IV patients was reduced for BEV-throughout compared to control (HR 0.774). While the median survival times for stage IV control and stage IV bevacizumab-initiation were 32.6 and 34.5 mos., respectively, the median OS (42.8m) for stage IV BEV-throughout patients was similar to the median OS (control, 44.3m; BEV-initiation, 42.9m; BEV-throughout, 44.2m) of stage III patients. **Conclusions:** In the ITT analysis, there were no survival differences between patients receiving BEV compared to chemotherapy alone. Patients with FIGO stage IV disease may derive a survival advantage from BEV when administered with and following front-line chemotherapy. Clinical trial information: NCT00262847.

5518 Poster Discussion Session; Displayed in Poster Session (Board #245), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

AGO-OVAR 16: A phase III study to evaluate the efficacy and safety of pazopanib (PZ) monotherapy versus placebo in women who have not progressed after first line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer—Overall survival (OS) results. *First Author: Ignace Vergote, BGOG & University Hospital Leuven, Leuven, Belgium*

Background: AGO-OVAR 16 study investigated PZ, an oral multi-kinase inhibitor of VEGFR-1, -2, -3, PDGFR-α and -β and c-Kit. This study was designed to test efficacy, safety and tolerability of PZ maintenance after first-line chemotherapy in newly diagnosed advanced ovarian cancer (AOC). The results of final analysis of OS following last patient last visit (LPLV) after prespecified futility criteria were met during 3rd OS interim analysis (IA) are reported. **Methods:** Inclusion criteria: Patients with histologically confirmed AOC; prior treatment of surgical debulking and at least five cycles of platinum-taxane chemotherapy with no evidence of progression; and no bulky disease or disease requiring imminent therapy. Nine hundred and forty patients were randomized in a 1:1 ratio to receive either 800 mg PZ once daily or placebo for up to 24 months unless disease progression, toxicity, withdrawal of consent, or death. The Primary endpoint (investigator assessed progression-free survival (PFS) was met (J Clin Oncol. 2014 Oct 20; 32: 3374-82). The 3rd IA of OS (key secondary endpoint) confirmed futility (conditional power $< 1\%$), and led to study closure and a final analysis after LPLV. **Results:** The final OS analysis was conducted after 494 (89.7% of the planned 551) events occurred. No difference was observed in OS between PZ and placebo. The HR was 0.960 (95% CI: 0.805, 1.145), and the median OS was 59.1 months in PZ and 64.0 months in placebo. For the East Asian patients, similar to the first three OS IA, a numerical negative trend was observed favoring placebo (HR = 1.332, 95% CI: 0.863, 2.054). Exploratory analyses showed a trend for a longer time to first subsequent anticancer therapy or death with PZ over placebo (HR = 0.829, 95% CI: 0.713, 0.965) with a median estimate of 19.0 and 14.5 months, respectively, suggesting that the PFS benefit remained with additional data maturity. **Conclusions:** Although PZ prolonged PFS, OS benefit was not demonstrated. Clinical trial information: NCT00866697.

5519 Poster Discussion Session; Displayed in Poster Session (Board #246), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase 2 biomarker trial of combination cediranib and olaparib in relapsed platinum (plat) sensitive and plat resistant ovarian cancer (ovca). *First Author: Joyce F. Liu, Dana-Farber Cancer Institute, Boston, MA*

Background: The combination of cediranib (ced) and olaparib (olap) improves progression-free survival and overall response rates (ORR) in women with recurrent plat sensitive high-grade serous (HGS) ovca compared to olap alone. However, the activity of this combination in plat resistant disease has not been characterized and biomarkers of response are poorly understood. We conducted a Phase 2 study to assess the activity of ced/olap in plat resistant ovca and to identify biomarkers of response (NCT02345265). **Methods:** Patients (pts) across 11 centers were enrolled to two cohorts (plat sensitive or resistant ovca). All pts received ced 30mg daily and olap tablets 200mg BID. Eligibility included pts with recurrent HGS or *BRCA*-related ovca. Pts had measurable disease by RECIST 1.1, the ability to take POs, available archival tissue, and biopsiable disease. No prior anti-angiogenics in the recurrent setting or prior PARP inhibitor was allowed. All pts underwent mandatory pre-treatment and on-treatment biopsies and had the option of undergoing a post-progression biopsy. **Results:** 72 pts were enrolled, with 70 pts receiving treatment (35 plat sensitive and 35 plat resistant). The ORR in plat sensitive pts was 77% (90%CI 63-88%), with 3 confirmed CRs and 24 confirmed PRs. 22 of 27 responders remain progression free with a median follow-up of 7 months. Ten of the plat sensitive responders had a germline *BRCA* mutation, 8 were wild type, and 9 had not been tested. Disease control rate (DCR; SD at 16wks + CR + PR) was 91%. The ORR in plat resistant pts was 20% (90% CI 11-38%) with 7 confirmed PRs. Median duration of response was 6 months and DCR 43% in plat resistant patients. Among the 7 pts with confirmed response in the plat resistant cohort, 3 had germline *BRCA* mutation, 3 were wild type, and 1 had not been tested. **Conclusions:** Ced/olap demonstrated clinical activity in women with recurrent plat sensitive and plat resistant ovarian cancer. While the presence of germline *BRCA* mutation was correlated with increased likelihood of response, confirmed responses were observed in *BRCA* wild type pts with plat resistant disease. Molecular studies are ongoing to investigate additional predictive biomarkers. Clinical trial information: NCT02345265.

5520 Poster Discussion Session; Displayed in Poster Session (Board #247), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Significant overall survival improvement in proliferative subtype ovarian cancer patients receiving bevacizumab. *First Author: Stefan Kommoss, Department of Women's Health, Tuebingen University Hospital, Tuebingen, Germany*

Background: We previously demonstrated that bevacizumab may differentially improve ovarian cancer progression-free survival (PFS) depending on TCGA molecular subtypes. Despite recent progress in the molecular biology of epithelial ovarian cancer, results have not yet translated into individualized treatment options or improved disease outcome. In the current study we correlated mature overall survival data with TCGA molecular subtypes in ovarian cancer patients from the AGO-OVAR11 (ICON7) trial. **Methods:** Whole genome DASL gene expression arrays were performed on FFPE tissues from the AGO OVAR11 (ICON7) trial. Patients were stratified into four TCGA molecular subtypes. Correlation between molecular subtype and the efficacy of randomly assigned therapy with bevacizumab was assessed. **Results:** Among all four TCGA suptypes, only patients with tumors of the proliferative subtype had a statistically significant benefit from the addition of bevacizumab to standard chemotherapy. Median PFS and OS of proliferative subtype patients was 22.17 and 52.43 months respectively if bevacizumab was added to standard chemotherapy but only 12.0 and 35.27 months in the control arm group of patients. Thus anti-angiogenic therapy resulted in a median improvement of PFS of 10.2 months (HR 0.48 [95%CI 0.3-0.76], p = 0.002) and in a median improvement of overall survival (OS) of 17.2 months (HR 0.54 [95%CI 0.3-0.9], p = 0.021) among TCGA proliferative subtype patients. The remaining three non-proliferative subtypes showed no statistically significant improvement of PFS or OS after addition of bevacizumab. **Conclusions:** We demonstrate for the first time significant OS benefit in patients with TCGA proliferative molecular subtype. Our findings may help to develop molecularly stratified treatment strategies and hold potential to ultimately improve outcome in patients with ovarian cancer.

5521 Poster Discussion Session; Displayed in Poster Session (Board #248), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Genomic mutation profiles of paired ovarian cancers (OC) across time. *First Author: Julia Fehniger, NYU Langone Medical Center, New York, NY*

Background: Prior studies demonstrate the clonal heterogeneity of ovarian tumors but do not address the relationship between genomic alteration profiles and treatment selection. We analyzed comprehensive genomic profiling (CGP) results from paired recurrent OC tumor samples to identify changes in somatic mutations over time. **Methods:** DNA from two or more FFPE tumor samples collected serially during the course of clinical care from 49 OC patients in the Clearity Foundation Data Repository was analyzed for genomic mutations (Mut), microsatellite instability (MSI), tumor mutation burden (TMB), and loss of heterozygosity (LOH) by hybrid-capture, next-generation sequencing of up to 315 genes (Foundation Medicine, Cambridge, MA). Genomic profiles were compared between samples from the same patient excluding sub-clonal mutations and genes/biomarkers not assessed across assays. 5 pairs were excluded due to poor quality metrics. **Results:** 22 sample pairs compared primary tumor to recurrence (PR) and 22 pairs compared two or more recurrences (RR). The majority of patients had stage III/ IV (34/77%) and primary platinum-sensitive disease (30/68%). OC was diagnosed at a median age of 57.3 yrs (range 34.5-76.9 yrs). Most tumors demonstrated serous histology (31/70%). Between sample pairs the median number of treatments was 3 for the PR (range 1-13) and 2 for the RR (range 1-7) groups. There was a median of 2 Mut/per OC sample (range 0-5), with a minority (12/27%) of pairs with any discordant mutations (dMut; 9 gains; 5 losses). 36 (82%) OC had *TP53* Mut and all were concordant. Four *BRCA1* Mut were identified (9% of OC) and all four were conserved between sample pairs. dMut were identified in *ARID1A* for 4 (9%) patients and *RB1* for 2 (5%). No dMut were targetable with FDA-approved therapies, but could impact enrollment in clinical trials. We found no significant clinical associations for patients with discordant alterations. **Conclusions:** The majority of targetable mutations from CGP of paired OC specimens are concordant over time, despite inter-current chemotherapy and associated clonal selection. For those genes with discordant findings, attention to specimen selection may be warranted in the clinical development of drugs targeting associated pathways.

5522 Poster Discussion Session; Displayed in Poster Session (Board #249), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Pembrolizumab treatment of advanced cervical cancer: Updated results from the phase 2 KEYNOTE-158 study. *First Author: Hyun Cheol Chung, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)*

Background: The KEYNOTE-158 study (NCT02628067) is a phase II basket study investigating the antitumor activity of pembrolizumab, an IgG4 anti-PD-1 monoclonal antibody, in 11 cancer types. An updated analysis of all 98 patients (pts) included in the cervical cancer cohort is presented. **Methods:** Key eligibility criteria for this cohort included histologically or cytologically confirmed advanced cervical cancer, progression on or intolerance to ≥1 line of standard therapy, ECOG PS 0 or 1, and provision of a tumor sample for biomarker analysis. Pts received pembrolizumab 200 mg Q3W for 2 y or until progression, intolerable toxicity, or physician or patient decision. Tumor imaging was performed every 9 wks for the first 12 mo, and every 12 wks thereafter. PD-L1 positivity, defined as a combined positive score (CPS) ≥1, was evaluated retrospectively by IHC. Primary endpoint was ORR assessed per RECIST v1.1 by independent central radiology review. Secondary endpoints included DOR, PFS, OS, and safety. **Results:** 98 pts were treated. Median age was 46.0 (range, 24-75) y, 65.3% had ECOG PS 1, and 93.9% had stage M1 disease. 83% of enrolled pts had PD-L1+ tumors. As of the August 23, 2017 data cutoff, the median follow-up duration was 10.3 mo (range, 0.6 to 18.0 mo). ORR was 13.3% (95% CI, 7.3%-21.6%), with 3 CR and 10 PR. 17 pts had SD, and the DCR was 30.6%. All 13 responses were in pts with PD-L1+ tumors, and the ORR was 16.0% (95% CI, 8.8%-25.9%) in the PD-L1-positive cohort (N = 81). 9 of 13 responses were ongoing after ≥9 mo follow-up. Median DOR had not been reached (range, 3.7+ to 12.4+). Median (95% CI) PFS and OS were 2.1 mo (2.0-2.2 mo) and 9.4 mo (7.9-13.4 mo), respectively. Treatment-related AEs occurred in 65.3% of pts, and the most common were hypothyroidism (10.2%), decreased appetite (9.2%), fatigue (9.2%), and diarrhea (8.2%). 11.2% of pts had treatment-related grade 3-4 AEs. **Conclusions:** Similar to the initial report, durable antitumor activity and manageable safety were demonstrated with pembrolizumab in advanced cervical cancer. Clinical trial information: NCT02628067.

5523 Poster Discussion Session; Displayed in Poster Session (Board #250), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Neoadjuvant chemotherapy with cisplatin and gemcitabine followed by chemoradiation with cisplatin in locally advanced cervical cancer: A phase II, prospective, randomized, trial. *First Author: Samantha Silva, Instituto do Cancer do Estado de São Paulo, São Paulo, Brazil*

Background: Chemoradiation with cisplatin (CRT) is the standard treatment for patients (pts) with locally advanced cervical cancer (LACC). However, 40% of pts has disease relapse. Adjuvant chemotherapy with gemcitabine plus cisplatin improves overall survival, with high toxicity. The role of the addition of neoadjuvant chemotherapy (NAC) to definitive CRT is still a matter of debate. We conducted a trial to investigate if NAC with cisplatin and gemcitabine followed by CRT would improve outcomes. **Methods:** LACC pts (FIGO IIB-IVA) were randomized to 3 cycles of NAC with cisplatin 50 mg/m^2 D1 and gemcitabine 1000mg/m^2 D1 and D8 followed by standard CRT with weekly cisplatin 40mg/m^2/w/6w plus pelvis radiotherapy (50.4Gy) followed by brachytherapy (BCT) or to the standard CRT and BCT alone. Progression-free survival (PFS) in 3 years was the primary endpoint. Secondary endpoint were response rate (RR), overall survival (OS) and toxicity. Kaplan-Meier method was used for survival analysis and curves were compared using log-rank test. RR was evaluated using chi-square test **Results:** Between July 2012 and July 2017, 107 pts were randomized. Pts characteristics were similar between groups. Median age was 47 years. The majority of the patients had squamous cell carcinoma (87.8%), and FIGO stage IIB (42.9%) or IIIB (44.8%). Median follow up was 25.5 months. PFS rates at 3 years were 41.1% (CI 95% 26.5-55.2%) in NAC group and 59.6% in the CRT alone group (CI 95% 42.5-73.1%), with an absolute difference of 18% (HR 1.48, CI 95% 0.86-2.82, p = 0.13). OS rates in 3 years were 74.2% (CI 95% 58.4-84.7%) and 81.9% (CI 95% 65.2-91.1%), respectively (HR 1.64, CI 95% 0.71-3.77, p = 0.23). CRT alone had superior complete RR (54% NAC vs 82% CRT alone, p = 0.002). No difference was seen in overall RR (92.7% NAC vs 94% CRT alone, p = 0.77). QoL improved after treatment in both groups when compared with baseline. **Conclusions:** This study showed that NAC is associated with inferior complete RR in comparison with standard CRT alone in the treatment of LACC, which is probably associated with the trend towards inferior PFS in NAC group. There was no statistically significant difference in OS. Clinical trial information: NCT01973101.

5524 Poster Discussion Session; Displayed in Poster Session (Board #251), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

PARAGON: A phase 2 study of anastrozole (An) in patients with estrogen receptor(ER) and / progesterone receptor (PR) positive recurrent/metastatic granulosa cell tumors/sex-cord stromal tumors (GCT) of the ovary. *First Author: Susana N. Banerjee, The Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: GCTs occur predominantly in postmenopausal women and arise from sex cord stromal cells of the ovary. They generally have a good prognosis but can metastasize / recur after surgery. Patients (pts) are commonly treated with antiestrogens as GCTs frequently express high ER and/or PR. The pooled response rates with a range of hormonal therapies in the literature are ~ 70 % based on case reports and small retrospective series which form the evidence base for clinical practice. Aromatase inhibitors (AIs) are reported to be particularly active. There are no reported phase 2 studies of antiestrogens in GCT. We report the results of a phase 2 trial of anastrozole, an AI in recurrent / metastatic GCT. To our knowledge this is the first prospective trial of hormonal therapy in GCTs. **Methods:** Postmenopausal women with ER/PR +ve metastatic GCT measurable by RECIST v1.1 and/or elevated Inhibin were eligible for inclusion. Pts received An 1 mg daily until progression or unacceptable toxicity. The primary endpoint was clinical benefit rate (CBR) at 12 weeks. **Results:** There were 41 pts entered. 3 pts without measureable disease had an elevated Inhibin. 1 pt received prior tamoxifen. 1 pt was not evaluable for 3-month (m) CBR. The CBR at 3m was 80.0% which included 1 (2.5%; 95% CI: 0.4 – 12.9%) partial response (PR) and 77.5% stable disease. 8 (20%) had progressive disease by 3m. Median PFS was 8.6 m (95% CI 5.5 – 13.5m). There were delayed responses beyond 3 m with a total 4 pts (9.8%; 95% CI 3.9% – 22.5%) with a RECIST PR. 23 (59%) pts were progression free at 6m (1 pt was censored at 3 m and 16 had progressed by 6 m). 2 pts remain on treatment at 14.8 m and 53.5 m. An was well-tolerated with only 1 grade 3 toxicity – arthralgia. 1 pt stopped An due to side effects. **Conclusions:** This is the first prospective trial of hormonal therapy in GCTs. Although there was a high CBR, the objective response rate to An was much lower than the pooled results of the response rate to hormonal therapy reported in retrospective series. Translational research on tumor specimens is underway for predictors of response/resistance to An which will inform future studies. Clinical trial information: 12610000796088.

5525 Poster Session (Board #252), Mon, 1:15 PM-4:45 PM

A phase 1/2A trial of synthetic DNA vaccine immunotherapy targeting HPV-16 and -18 after chemoradiation for cervical cancer. *First Author: Yasmin Hasan, Department of Radiation and Cellular Oncology, The University of Chicago Hospitals, Chicago, IL*

Background: DNA immunotherapies targeting HPV oncogenes, E6 and E7, have demonstrated clinical efficacy in pre-invasive cervical lesions. Here, we assessed the feasibility of chemoradiation and adjuvant MEDI0457 (INO-3112), a DNA-based immunotherapy targeting HPV-16 and HPV-18 E6 and E7 oncogenes, followed by electroporation (EP) with the CELLECTRA device, in locally advanced and recurrent cervical cancer patients. **Methods:** Safety and immunogenicity of MEDI0457 were assessed in HPV-16- or HPV-18-positive newly-diagnosed inoperable (Cohort 1, C1) or persistent and/or recurrent disease (Cohort 2, C2) cervical cancer patients treated with standard therapy. MEDI0457 was delivered with EP on day 0, weeks 4, 8, and 12. The primary endpoint was to evaluate safety and tolerability. Secondary objectives included clinical response (PET-CT, clinical exam) and immune responses against HPV antigens as measured by Interferon-g (IFNg) secretion by peripheral blood mononuclear cells and anti-E6/E7 antibody titers. **Results:** As of Jan 23, 2018, 10 patients (7 C1, 3 C2) with stage IB1-IV HPV 16 (n = 7) or 18 (n = 3) cervical cancers received MEDI0457 after conventional therapy. Treatment-related adverse events were all Grade 1, primarily injection site related. At up to 60 weeks of follow-up, all C1 patients remain alive with no evidence of disease clinically and on PET/CT. Of 3 C2 patients, 1 died, 1 had persistent disease and one remains free of disease. Antibody responses against HPV oncoproteins were detected in up to 60% of patients (anti-HPV16 E6 response: 5/10 patients, anti-HPV18 E6 response: 3/10 patients, anti-HPV16 E7 response: 4/10 patients, anti-HPV18 E7 response 6/10 patients). IFN-g responses were detected in 4/7 C1 patients while no IFN-g response was detected in C2 patients. **Conclusions:** Adjuvant MEDI0457 is feasible after chemoradiation for locally advanced and/or recurrent cervical cancer. More than half of the patients developed detectable immune responses to HPV antigens after treatment. These results support further study into the efficacy of adding DNA therapy with CELLECTRA EP to chemoradiation for HPV-related cancers. Clinical trial information: NCT02172911.

5526 Poster Session (Board #253), Mon, 1:15 PM-4:45 PM

Phase II clinical trial of eribulin (E) in advanced/recurrent cervical cancer. *First Author: Jocelyn Garcia, Los Angeles County Hospital/ University of Southern California, Los Angeles, CA*

Background: Eribulin (E), a Halichondrin B analog from the marine sponge H. okadai has clinical efficacy in pretreated metastatic breast cancer patients (pts) and preclinical antitumor activity in squamous cell carcinoma (SCC). We conducted a 2-stage Phase 2 study of E in pts with advanced/recurrent CC to examine its clinical activity and evaluate potential predictors of response. **Methods:** Pts with advanced/recurrent CC after ≤1 prior CT regimens, measurable disease and ECOG performance status ≤2 were treated with E (1.4mg/m^2 IV day 1 and 8, every 21 days) with tumor assessments every 2 cycles. Primary endpoint was 6-month progression-free survival PFS_6; secondary were best overall response (RECISTv1.1), toxicity (CTCAEv4.03) and overall survival (OS); and exploratory were associations of tumor and serum GRP78 as well as apoptosis/proliferation markers, unfolded protein response markers and tubulin sub-types with clinical activity. 30 evaluable pts would ensure 80% power when the true PFS_6= 26% with a 1-sided α ≤0.1 (H_o: PFS_6= 10%). A prespecified futility analysis gating stage 2 was set if 0/15pts showed at least SD at 6 months. Immunohistochemistry was performed on archival tumor samples and serial serum GRP78 levels were quantified by ELISA. **Results:** 32 pts were enrolled, median age 51 years (range 29-76), 22 had SCC, the median number of cycles was 4 (range 1-29). 26 pts had received prior pelvic irradiation. 29 pts had received prior CT with cisplatin/gemcitabine (12) and cisplatin/paclitaxel/bevacizumab (12) as the most common regimens. 6/32 pts (18.8%) achieved > PFS_6; median PFS is 2.6 months (95%CI: 1.2, 4.2). Median OS is 6.6 months (95% CI: 4.4, 12.7). Two pts were inevaluable for response having received less than 2 cycles. Among the 30 evaluable pts, 6 (20%) had a partial response and 11 (37%) had stable disease (clinical benefit rate 57%). 2 pts remain on study having received 21 and 29 cycles. Grade 3/4 adverse events occurring in > 10 % of pts are anemia (12pts), neutropenia (7pts) and leukopenia (6pts). 1 pt was removed from study due to paresthesia after 7 cycles. Analysis of correlative predictors of response is ongoing. **Conclusions:** Eribulin shows evidence of activity in recurrent/advanced CC with a favorable toxicity profile. Clinical trial information: NCT01676818.

5527 Poster Session (Board #254), Mon, 1:15 PM-4:45 PM

Propensity score-matched analysis of systemic chemotherapy versus hysterectomy for patients with residual cervical disease after definitive radiotherapy/concurrent chemoradiotherapy. *First Author: Munetaka Takekuma, Department of Gynecology, Shizuoka Cancer Cener Hospital, Shizuoka, Japan*

Background: Patients with persistent cervical cancer after definitive radiotherapy/concurrent chemoradiotherapy (RT/CCRT) have a poor prognosis. Salvage hysterectomy (HT) is considered curative treatment; however, very little data exists showing the survival advantage of HT over standard therapy. **Methods:** Patients with persistent cervical cancer treated with definitive RT/CCRT at 35 institutions from 2005–2014 were reviewed retrospectively. Those who underwent a HT for residual cervical disease after definitive RT/CCRT were matched (histology, FIGO stage at initial treatment, brachytherapy application, age and performance status at diagnosis of residual tumor, diameter and parametrial invasion by residual tumor, and the number of lymph node tumors at diagnosis, etc.) with propensity scores for patients who underwent systemic chemotherapy (CT). Oncologic outcomes between the two groups using a propensity score matched–cohort analysis were compared. **Results:** A total of 142 patients with residual cervical disease after definitive RT/CCRT were included after matching (HT: 71, systemic CT: 71). A difference in all background factors between HT and CT groups was not observed. At a median follow-up of 4.6 years, 33 (46.5%) and 47 deaths (66.2%) occurred in HT and CT groups, respectively. Median overall survival was 3.8 and 1.5 years in HT and CT groups, respectively (p= 0.0019, hazards ratio [HR] 2.438, 95% confidence interval [CI] 1.362–4.361), and median progression-free survival was 2.7 and 0.7 years, respectively (p= 0.0046, HR 2.235, 95% CI 1.262–3.960). Increasing tumor size was significantly associated with a high incomplete resection rate (p= 0.0385, Odds Ratio 0.941, 95% CI 0.888–0.997). The cut-off value for the residual tumor diameter regarding complete resection after receiver operating characteristic (ROC) analysis was 11 mm (sensitivity 70%, specificity 86.9%). **Conclusions:** Salvage HT may be considered curative treatment for patients with residual cervical disease after definitive RT/CCRT. The diameter of residual tumor is important in selecting appropriate candidates for HT.

5528 Poster Session (Board #255), Mon, 1:15 PM-4:45 PM

Preliminary results from CECILIA, an open-label global safety study of bevacizumab (BEV), carboplatin (C) and paclitaxel (P) therapy for metastatic, recurrent or persistent cervical cancer (CC). *First Author: Andres Redondo, Medical Oncology Department, Hospital Universitario La Paz, Madrid, Spain*

Background: Adding BEV to chemotherapy (cisplatin + P or topotecan + P) for advanced (a)CC significantly improved overall and progression-free survival (PFS) in the overall population in GOG240. The CECILIA study (NCT02467907) is evaluating BEV with more widely used CP. **Methods:** The primary objective is to determine the safety of BEV + CP for aCC, defined by the frequency and severity of gastrointestinal (GI) perforation/fistula, GI-vaginal fistula and genitourinary (GU) fistula. Eligible patients (pts) have metastatic/recurrent/persistent CC not amenable to curative surgery and/or radiotherapy (RT). Pts with ongoing bladder/rectal involvement, prior cobalt RT, history of fistula/GI perforation, or bowel resection ≤6 weeks or chemoRT ≤3 mo before the first dose are excluded. Pts receive BEV 15 mg/kg, P 175 mg/m^2 and C AUC 5 q3w until progression, unacceptable toxicity or consent withdrawal. If BEV, C or P are stopped for adverse events (AEs), the remaining drug(s) can be continued alone. We report preliminary findings after ≥6 mo follow-up in all pts. **Results:** Between Jul 2015 and Dec 2016, 150 pts in Europe, South/Central America and South Africa began treatment. At study entry, 20% had persistent disease, 54% recurrent disease and 26% stage IV at diagnosis; 73% had squamous cell carcinoma, 71% had received prior RT (as part of chemoRT in 58%) and 59% prior platinum. At the data cutoff (12 Jun 2017), median follow-up was 11.2 mo. Median BEV duration was 9 cycles (range 1–28; 42 pts still on therapy). Grade 3/4 AEs occurred in 67% of pts, most often hematologic AEs and hypertension; 5 AEs (3%) were fatal. GI perforation/fistula occurred in 4.0% of pts (95% CI 1.5–8.5%), GI-vaginal fistula in 4.0% (1.5–8.5%) and GU fistula in 4.0% (1.5–8.5%), giving an overall rate of 18 fistula/GI perforations in 15 pts (10.0% [95% CI 5.7–16.0%]). All but 1 pt with fistula/GI perforation had received prior RT. PFS results are immature. **Conclusions:** These preliminary results suggest that BEV can be combined with CP in carefully selected pts. The fistula/GI perforation incidence was in line with GOG240. Final results are expected in 2019. Clinical trial information: NCT02467907.

5529 Poster Session (Board #256), Mon, 1:15 PM-4:45 PM

Comparison of different adjuvant therapy after radical surgery in early stage cervical carcinoma: A 3-arm randomized control study. *First Author: He Huang, Sun Yat-sen University Cancer Center, Guang Zhou, China*

Background: To determine whether the addition of concurrent chemotherapy (CCT) or sequential chemotherapy (SCT) to adjuvant pelvic radiotherapy (RT) will improve prognosis of patients with early-stage cervical carcinoma who had adverse pathological factors. **Methods:** After radical surgery, patients with FIGO stage IB1 to IIA2 cervical cancer who had one or more of the following pathological factors were recruited: lymph node metastases (LNM), positive parametrium or margins (PPM), lymphatic vascular space involvement (LVSI), deep invasion of cervical stroma (DIS). Eligible patients were randomized to the three groups. Group A underwent 50 GY pelvic RT alone. Group B received concurrent weekly cisplatin and RT (CCRT). Group C received paclitaxel and bolus cisplatin every three weeks for two cycles before RT, followed by two cycles of chemotherapy (SCRT). **Results:** From February 2008 to August 2015, a total of 1055 cases were randomized and eligible for evaluation, with 352 cases in group A, 348 in group B and 355 in group C. The disease-free survival (DFS) was 132.3 month in group C versus 94.4 month in group A and 92.3 month in group B ($P = 0.047$), and the corresponding overall survival (OS) were 140 month, 105.4 month and 99.5 month ($P = 0.20$). In the intergroup analysis, a better DFS was found in group C (87 months) than the other two groups (79 month in group B and 69 months in group A, $P < 0.05$) among patients with LNM or/and PPM (high risk). While there was no significant difference in DFS was found between three groups in the patients with DIS and/or LVSI (intermediate risk), or in those patients who had indications for adjuvant treatment according to Sedlis Criteria. Alopecia (87.1%, $P < 0.05$) and pelvic lymph cyst (14.1% $P < 0.05$) were significantly higher in group C. There is no significant difference of grade 3/4 hematologic and gastrointestinal toxicities between group B and C. **Conclusions:** SCRT brought a better DFS in patients especially with high-risk cervical carcinoma. The sequential strategy may constitute an alternative treatment for the high-risk patients. However, CCRT and SCRT did not show survival benefit in patients with intermediate risk factors. Clinical trial information: NCT00806117.

5530 Poster Session (Board #257), Mon, 1:15 PM-4:45 PM

Association between pap abnormalities and HPV infection in participants in HPV vaccine clinical trials. *First Author: Evan Meyers, Duke University, Durham, NC*

Background: Few studies have reported the burden of Pap abnormalities associated with the specific HPV types targeted by HPV vaccines. The purpose of this analysis is to estimate prevalence of HPV anogenital infection, by baseline Pap results, in participants of 3 worldwide trials of the quadrivalent HPV vaccine (placebo and vaccine groups, FUTURE I, II, III), and to estimate incidence of Pap abnormalities by HPV infection status at enrollment (placebo only, FUTURE I, III). **Methods:** Among 16,949 young women (YW) age 15-26 years (FUTURE I, II) and 3,674 adult women (AW) age 24-45 (FUTURE III), HPV prevalence (measured with PCR for 14 HPV types) was estimated at enrollment for women with: atypical squamous cells of undetermined significance (ASC-US) (n = 781 YW, 115 AW), low-grade squamous intraepithelial lesion (LSIL) (n = 993 YW, 115 AW), and high-grade squamous intraepithelial lesion or atypical squamous cells- cannot exclude HSIL (HSIL/ASC-H) (n = 157 YW, 30 AW).

Cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) over 4 years (placebo only), by baseline HPV status, was estimated for 1,481 (YW) and 1,701 (AW). **Results:** Prevalence of any 9-valent (9v) vaccine type (6/11/16/18/31/33/45/52/58) among women with ASC-US, LSIL, or ASC-H/HSIL at enrollment was 47%, 67%, and 89%, respectively (YM), and 29%, 55%, and 93%, respectively (AW). Prevalence of any non-vaccine type (35/39/51/56/59) among women with ASC-US, LSIL, or ASC-H/HSIL was 32%, 64%, and 47%, respectively (YM), and 24%, 54%, 38%, respectively (AW). Over 48 months, cumulative incidence of high-grade Pap abnormalities (HSIL/ASC-H) among women with any high-risk 9v HPV type at enrollment was 8% (YW) and 6% (AW); cumulative incidence among women with no measured HPV infection at enrollment was 2% (YW) and 0.4% (AW). **Conclusions:** While the 9-valent vaccine will substantially reduce Pap abnormalities associated with HPV types that cause 90% of cervical cancers, non-vaccine HPV types also contribute to Pap abnormalities. These findings underscore the need for vaccination to protect against 9 HPV types, as well as the ongoing need for cervical cancer screening. Clinical trial information: NCT00090220.

5531 Poster Session (Board #258), Mon, 1:15 PM-4:45 PM

The clinical utility of prospective molecular characterization in advanced cervical and vulvovaginal cancer. *First Author: Claire Frances Friedman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The molecular landscape of recurrent cervical and vulvovaginal cancers is undefined. We sought to determine the clinical impact of performing next generation sequencing (NGS) in these patients (pts). **Methods:** 82 pts consented to an IRB-approved protocol for the prospective sequencing of tumor and matched normal with MSK-IMPACT (NCT01775072), a NGS assay of up to 468 cancer-associated genes. Hotspot mutations were annotated using the OncoKB knowledge base (OncoKB.org). **Results:** We analyzed 90 samples. There was no significant difference in the incidence of mutations between primary (45%) and metastatic (mets) (55%) specimens. In the 5 pts with paired mets and 2 with matched primary and mets, the molecular profiling was identical in all but one pt that gained a TP53 mutation. We identified likely therapeutically actionable mutations in 44% of pts. Using OncoKB, we found that 8.5% of patients had a level 2B oncogenic alteration (See Table). Other alterations that have a lower level of clinical evidence included mutations in PIK3CA, ERBB2, AKT, and FGFR3 (n = 29, 35%). In this cohort, 32 pts (39%) enrolled in at least one clinical trial, half of which (n = 15) were genotype-matched. Among these pts, 11 (73%) had stable disease or partial responses (PR). Overall, 24% of patients received checkpoint blockade; two patients without evidence of somatic hypermutation achieved a PR. **Conclusions:** Prospective NGS of cervical and vulvovaginal cancer informs management of patients through the identification of potentially actionable mutations.

Age at Dx (med, range)	46 (22-86)
Histology (n, %)	
Cervical Adenosquamous	7 (9%)
Cervical Squamous	25(30%)
Endocervical Adenocarcinoma	26 (32%)
Gastric Type	7 (9%)
Other Cervical	8 (10%)
Vulvovaginal carcinoma	9 (11%)
Sample Type (n, %)	
Primary	40 (45%)
Metastatic	50 (55%)
Hotspot Mutations (n, %)	
OnkoKB Level 2B: Biomarker to an FDA approved drug in another indication BRCA2, ERBB2 amp, KIT	7 (8.5%)
OncoKB Level 3B: Biomarker is likely predictive of response to a drug in another indication, but neither FDA approved PI3K, AKT1, ERBB2 mut, FGFR3	29 (35%)
OncoKB Level 4: Biomarker is likely predictive of response to a drug, but neither FDA approved BRAF, HRAS, NF1, PTEN	9 (11%)

5532 Poster Session (Board #259), Mon, 1:15 PM-4:45 PM

Unexpected lymphatic drainage pathways of cervical cancer: Insights of the sentinel lymph node biopsy. *First Author: Vincent Balaya, Hopital Européen Georges Pompidou, Paris, France*

Background: Sentinel lymph nodes (SLNs) can be observed in various territories. An intraoperative surgical strategy is needed to find all relevant SLNs and limit the risk of missed SLN. The aim of this study was to define an anatomically based surgical algorithm to identify sentinel lymph nodes (SLNs). **Methods:** We analyzed the data of two prospective multicentric trials on SLN biopsy for cervical cancer (SENTICOL I and II) in women undergoing surgery for early-stage cervical cancer. SLN detection was realized with a combined labeling technique (Patent blue and radioactive tracer). **Results:** A total of 377 patients with 1186 intraoperative detected SLNs were analyzed. 201 SLNs were only blue, 291 SLNs were only hot and 685 SLNs were blue and hot. The SLNs were located in the ilio-obturator or extern iliac area in 82.1 % of cases (974/1186) corresponding to the upper parametrial pathway (UPP) and 362 patients (96%) had at least one SLN in these areas. The SLNs were located in other unexpected areas in 17.9% of cases (212/1186). 130 patients (34.5%) had at least one SLN in an unexpected area and 14 (3.7%) patients had SLNs only in in an unexpected area. 176 SLNs (14.8%) were located in the lower parametrial pathway (LPP) with 45 in the parametrium (3.8%), 109 in the common iliac area (9.2%), 22 in the promontory area (1.9%)) whereas 36 SLNs (3%) were located in the infundibulo-pelvic pathway (IPP) with 26 in the paraaortic area (1.9%), and 13 in other areas (1.1%). The lymphatic drainage was exclusively through the UPP in 57.2% of cases (679/1186), through the UPP and another pathway in 40.8% of cases (484/1186) and exclusively through the LPP or the IPP in 1.9% of cases (23/1186). **Conclusions:** The SLNs search should begin in the ilio-obturator and external iliac area. Other territories should be explored in the absence of SLNs in this first level or as a complement. Pelvic dissection should be done only in case of absence of SLN in all territories.

5533 Poster Session (Board #260), Mon, 1:15 PM-4:45 PM

AMPATH Oncology: Baseline HPV detection in Kenyan women enrolled in a longitudinal study of modifiable factors predicting cervical dysplasia. *First Author: Darron R. Brown, Indiana University School of Medicine, Indianapolis, IN*

Background: Cervical cancer is caused by oncogenic HPV types. Kenyan women, HIV-infected or uninfected were studied to define modifiable factors predicting incidence and persistence of HPV and cervical dysplasia. **Methods:** From 9/21/2015 to 10/4/2016, 223 women ages 18 to 45 years old with normal VIA at enrollment were enrolled in a longitudinal study in Kenya. Cervical swabs, behavioral data, and other data were collected. HPV typing was performed on clinician-obtained cervical swabs using the Roche Linear Array. **Results:** Analysis of 219 evaluable participants was done, including 115 HIV-infected (median age 36 years) and 104 HIV-uninfected women (median age 33 years) (p = .0009). Among HIV-infected women, 86.8% were receiving antiretroviral therapy (ART); median duration between HIV diagnosis and enrollment was 7.2 years (IQR 4.1-10.3); median CD4 count was 471 (IQR 310-612). There was a significant difference in number of lifetime sex partners between HIV-infected (median 4, IQR 3-8) and HIV-uninfected women (median 3, IQR 1.5-4), p = .0001. HPV detection is shown in Table 1. **Conclusions:** Oncogenic HPV types, including types preventable by vaccination were prevalent in Kenyan women. HIV-infected women were more likely to have detection of HPV 16, other oncogenic HPV types, and multiple types in spite of ART. In this longitudinal study, other factors will be included such as behaviors, the effect of HIV viral load, CD4 count, and details of ART.

HPV detection in 115 HIV-infected and 104 HIV-uninfected women.

HPV Types	HIV Infected	HIV Uninfected	P value
Any HPV (%)	59.1	35.6	.0005
HR-HPV[1] (%)	47.0	27.9	.0037
LR-HPV[2](%)	32.2	17.3	.0113
HPV 16 (%)	10.4	2.9	.0272
Nine-valent HR-HPV vaccine types[3](%)	26.1	17.3	.1168
HR-HPV not covered by nine-valent vaccine[4](%)	32.2	15.4	.0038
Two or more HR-HPV types (%)	20.0	6.7	.0041
Number of HR-HPV types (mean)	1.3	0.6	.0001

[1]Oncogenic (High-Risk) HPV [2]Non-oncogenic (Low-Risk) HPV [3]HPV 16, 18, 31, 33, 45, 52, 58 [4]HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, IS39

5534 Poster Session (Board #261), Mon, 1:15 PM-4:45 PM

Dose dense neoadjuvant chemotherapy (NACT) with carboplatin-paclitaxel in locally advanced cervical cancer. *First Author: Domenica Lorusso, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*

Background: NACT followed by radical surgery is considered a valid therapeutic approach in locally advanced cervical cancer (LACC). The standard neoadjuvant treatment has not yet been identified. The most widely used regimen is the TIP (Cisplatin-Paclitaxel-Ifosfamide) combination which is effective but highly toxic. The aim of the study is to evaluate clinical (CR) and pathologic (PR) response to carboplatin-paclitaxel dose dense regimen as NACT in LACC. **Methods:** Consecutive patients with stage FIGO IB2-IIB were prospectively enrolled and treated with 3 cycles of neoadjuvant Carboplatin (AUC5) d1 and Paclitaxel (80 mg/m^2) d1, 8, 15 q21 chemotherapy. After 4 weeks from completion of NACT, patients were submitted to radical hysterectomy and pelvic lymphoadenectomy. Abdomino-pelvic MRI and gynaecological evaluation were performed at baseline and after 3 cycles in order to evaluate CR. PR was defined as follows: PR0: no residual disease, PR1: residual disease $\leq$ 3 mm stromal invasion, PR2: residual disease $>$ 3 mm. A two-stage optimal Simon design was applied in order to detect a 60% of PR0+PR1: if at least 7 responses were registered among the first 16 patients, the trial would continue the enrolment. **Results:** 67 patients were enrolled in 40 months. After the enrollment of the first 16 patients, at least 7 responses were detected, so the trial proceed to the second step of enrolment. 11 patients (16%) went out from the study because of allergic reaction to the first paclitaxel administration and were not evaluable. 4 of the 56 patients experienced stable or progression disease and did not underwent surgery. The only grade 3-4 registered toxicity was neutropoenia in 10.7% of patients. Patients characteristics and responses are reported in the table below. **Conclusions:** Combination of dose dense Carboplatin-paclitaxel resulted in encouraging clinical and pathologic responses and in a favourable toxicity profile. This scheme merits further evaluation in randomized clinical trials versus TIP.

Patients characteristics.	N°	%
FIGO STAGE:		
IB2	19	28
IIA	15	23
IIB	33	49
GRADING:		
G3	39	58
HISTOTYPE:		
SQUAMOUS	10	15
ADENOCARCINOMA	57	85
CLINICAL RESPONSE:		
CR	10	18
PR	42	75
SD	1	2
PD	3	5
PATHOLOGIC RESPONSE:		
PR0	14	27
PR1	10	19
PR2	28	54

5535 Poster Session (Board #262), Mon, 1:15 PM-4:45 PM

Evaluation of capecitabine in patients with platinum-pretreated advanced or recurrent cervical carcinoma: A retrospective study of the IRCCS National Cancer Institute of Milan. *First Author: Domenica Lorusso, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy*

Background: Cervical cancer is underrepresented in the gynecological clinical research. The objective of this retrospective study was to evaluate the activity and the safety of capecitabine in patients with platinum-pretreated recurrent cervical carcinoma. **Methods:** We performed a retrospective review of medical records from patients with advanced or recurrent cervical carcinoma pretreated with platinum-based therapy who received oral capecitabine at the Gynecological Units of the IRCCS National Cancer Institute of Milan (Italy). We used Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 to evaluate response to therapy and Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to evaluate adverse events. **Results:** From October 2013 to August 2017, we treated with oral capecitabine dose 29 patients with advanced or recurrence cervical carcinoma, already exposed to platinum. All patients receive a combination of carboplatin plus paclitaxel as first-line therapy for advanced/recurrent disease. At first capecitabine administration the median of previous treatments was 2 (range from 1 to 5). After three cycles of oral capecitabine the clinical benefit rate (CBR) was 62% with 41.3% of PR and 20.7% of SD. Grade 3 reported toxicity were 10% neutropenia and 3% hypertransaminasemia. CBR was 83.3% in adenocarcinomas versus 47% in squamous cell carcinomas. The most frequent grade 1 or 2 adverse events were fatigue (55%), hand-foot syndrome (38%) and diarrhea (24%). **Conclusions:** Our study suggests that oral capecitabine should be considered an active and safe treatment in patients with platinum-pretreated advanced or recurrent cervical carcinoma.

5536 Poster Session (Board #263), Mon, 1:15 PM-4:45 PM

A phase II evaluation of nivolumab, a fully human antibody against PD-1, in the treatment of persistent or recurrent cervical cancer. *First Author: Alessandro Santin, Yale University School of Medicine, New Haven, CT*

Background: Despite current treatments patients with persistent/recurrent cervical cancer (CC) after platinum-based chemotherapy have limited therapeutic options with a median survival limited to only ~7 months. Most of CC are infected with high-risk Human Papillomavirus (HPV) making these tumors potentially highly immunogenic. However, upregulation of the PD-1/PD-L1 pathway on CC or infiltrating immune cells may negatively regulate immunity and contribute to CC progression. We present the results of NRG-GY002, a 2-stage, phase II study with Nivolumab, an anti–PD-1 antibody, in patient with persistent or recurrent CC. **Methods:** Key eligibility criteria included persistent/recurrent CC, failure of prior systemic therapy and ECOG PS 0-1. Nivolumab 3 mg/kg was given every 2 wk for up to 46 doses over 92 wk or until disease progression, intolerable toxicity, death, or withdrawal of consent. Response was assessed every 8 wk for the first 6 mo and every 12 wk thereafter. The primary end point was objective tumor response by RECIST v1.1. **Results:** 26 pts with persistent/recurrent CC were enrolled (25 eligible and evaluable for response and toxicity); median age was 45 years old, 36.0% had an ECOG PS of 1, and 100% had received one prior systemic chemotherapy regimen for metastatic disease. As of February 5, 2018, all patients have been off study treatment; median follow-up for vital status was 18.7 months (range, 2 – 28.1). 21 (84%) pts experienced a treatment-related adverse event (TRAE), most of which were grade 1 and 2. Six (24 %) pts had grade 3 TRAEs, 1 of whom discontinued nivolumab (type I diabetes). No grade 5 TRAEs occurred, and grade 4 TRAEs occurred in 2 pts. There was 1 confirmed PR (4%; 90% CI, 0.4%-22.9%), duration of response 3.8 months. The proportion of patients with stable disease (SD) was 36% (9/25; 90% CI, 20.2%-54.4%); the median duration of SD was 5.7 months (range, 3.5-12.7). The estimated PFS and OS at 6 months was 16% and 78.4%, respectively. **Conclusions:** Single agent nivolumab exhibited low antitumor activity and an acceptable safety profile in pts with persistent or recurrent CC previously treated with platinum-based chemotherapy. (ClinicalTrials.gov NCT #02257528) Clinical trial information: NCT02257528.

5537 Poster Session (Board #264), Mon, 1:15 PM-4:45 PM

Evaluation of rucaparib in platinum-sensitive recurrent ovarian carcinoma (rOC) in patients (pts) with or without residual bulky disease at baseline in the ARIEL3 study. *First Author: Carol Aghajanian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In ARIEL3, pts were randomized 2:1 (oral rucaparib 600 mg or placebo). Rucaparib significantly improved progression-free survival (PFS) vs placebo in all primary analysis groups (Coleman et al. *Lancet*. 2017;390:1949-61). An exploratory subgroup analysis of ARIEL3 pts with or without bulky residual disease (> 2 cm per blinded independent central review [BICR]) at baseline is reported. **Methods:** Pts were assigned to 2 analysis subgroups: with or without bulky residual disease at baseline. PFS was assessed in 3 predefined cohorts: *BRCA* mutant; homologous recombination deficient (HRD) (*BRCA* mutant or *BRCA* wild type/high loss of heterozygosity); and intent-to-treat (ITT) population. **Results:** PFS data for each subgroup (visit cutoff date 15 Apr 2017) by status of bulky disease at baseline are summarized in the Table. Safety data were consistent with data reported previously. In the rucaparib arm, the most common grade ≥3 treatment-emergent adverse event in pts with and pts without bulky disease was anemia (20.0% and 18.5%, respectively). Clinical trial information: NCT01968213. **Conclusions:** Rucaparib improved PFS vs placebo in all 3 predefined cohorts for both pts with and without bulky residual disease. PFS benefit with rucaparib was largest in pts with *BRCA*-mutant rOC.

			PFS (investigator review)		PFS (BICR)	
			HR (95% CI)	Median PFS, mo; *P*value*	HR (95% CI)	Median PFS, mo; *P*value*
Cohort	**Rucaparib, n**	**Placebo, n**	**Rucaparib vs placebo**		**Rucaparib vs placebo**	
Bulky disease at baseline (per BICR)						
Yes						
***BRCA* mutant**	21	10	0.09 (0.02–0.37)	11.1 vs 2.8; *P*= 0.0002	0.13 (0.03–0.55)	17.1 vs 2.9; *P*= 0.0028
HRD	39	18	0.30 (0.13–0.69)	8.3 vs 2.8; *P*= 0.0030	0.58 (0.25–1.34)	8.3 vs 2.9; *P*= 0.1994
ITT	71	29	0.40 (0.24–0.69)	8.2 vs 2.9; *P*= 0.0007	0.46 (0.26–0.81)	8.3 vs 3.0; *P*= 0.0057
No						
***BRCA* mutant**	109	56	0.26 (0.17–0.40)	16.6 vs 5.6; *P*< 0.0001	0.22 (0.13–0.37)	26.8 vs 5.5; *P*< 0.0001
HRD	197	100	0.31 (0.23–0.43)	13.8 vs 5.5; *P*< 0.0001	0.32 (0.22–0.47)	24.7 vs 5.6; *P*< 0.0001
ITT	304	160	0.36 (0.29–0.46)	11.0 vs 5.4; *P*< 0.0001	0.34 (0.26–0.45)	16.2 vs 5.4; *P*< 0.0001

*Stratified log-rank *P* value.

5538 Poster Session (Board #265), Mon, 1:15 PM-4:45 PM

53BP1 as a predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. *First Author: Rachel M Hurley, Mayo Medical School, Rochester, MN*

Background: Poly(ADP-ribose)polymerase (PARP) inhibitors have shown substantial activity in homologous recombination (HR) deficient ovarian cancer and are undergoing testing in other HR-deficient tumors. For reasons that are poorly understood, not all patients with HRD cancers respond to these agents. Preclinical studies have demonstrated that changes in alternative DNA repair pathways affect PARP inhibitor (PARPi) sensitivity. As this has not previously been assessed in the clinical setting, we examined the relationship between HRD score, *BRCA1* and *BRCA2* mutation status, expression of NHEJ pathway repair proteins, and response of ovarian cancers treated with single agent PARPi. **Methods:** Archival biopsies from ovarian cancer patients undergoing treatment on a single-agent PARPi trial were stained for PARP1, RAD51, and multiple components of the nonhomologous end-joining (NHEJ) pathway, including 53BP1, KU70, KU80 and DNA-PK_{CS}. Assays were validated by showing that the IHC signal was markedly attenuated with gene knockout or highly effective siRNA. Histochemistry-(H-) scores were determined for each repair protein in each sample. HRD score was determined from tumor DNA. **Results:** Responses to the PARPi ABT-767 were observed exclusively in ovarian cancers with an HR-deficiency. In this HR-deficient subset, 7 of 18 patients (39%) had objective responses, however actual HRD score did not further correlate with change from baseline tumor volume ($r = 0.0499$; $p = 0.87$). Conversely, in the HR-deficient subset, 53BP1 H-score showed a strong correlation with change from baseline tumor volume ($r = -0.69$, $p = 0.004$), followed by KU80 ($r = -0.46$; $p = 0.08$). **Conclusions:** Differences in complementary repair pathways, particularly in the NHEJ pathway, correlate with PARPi response of HR-deficient ovarian carcinomas. Among HR-deficient ovarian carcinomas, 53BP1 H-score demonstrated a strong correlation with the percent change of tumor volume.

5539 Poster Session (Board #266), Mon, 1:15 PM-4:45 PM

The impact of health related quality of life (HRQoL) on short term survival of recurrent ovarian cancer patients: Analysis of pooled data from the North-Eastern German Society of Gynecological Oncology (NOGGO) meta data base. *First Author: Jalid Sehouli, AGO and Charité Campus Virchow-Klinikum, Berlin, Germany*

Background: The goal of this analysis is a predictive score (recurrent ovarian cancer survival score, NOGGO-ROCSurv score) using HRQoL and other risk factors to estimate the risk of 1-year mortality in recurrent ovarian cancer patients. **Methods:** The data of recurrent patients with baseline HRQoL assessment using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 were selected from the NOGGO data base. ROC analysis were used to evaluate the predictive value of the risk factors and to find cut off values. Multivariable stepwise logistic regression models for 1-year mortality were performed to identify risk factors and their weights for a risk score. **Results:** Out of 972 patients 808 (83.1%) had 1st, 145 (14.9%) 2nd, and 19 (2.0%) 3rd recurrence, most patients (814, 83.8%) with advanced tumor stage at first diagnosis, 918 (94.4%) with good performance status (PS). The median age was 61 years (range 25-84 years). 1-year survival rate was 67.1%. Nearly all HRQoL scales except cognitive functioning, sleep disturbance, financial difficulties and diarrhea showed predictive value for short term survival with an area under the curve (AUC) up to 62.6% for global quality of life (gQoL). The risk score included chemo therapy free interval (CTFI) < 1 year, PS > 1, gQoL < 25, fatigue > 70, Nausea > 25, age ≥ 75 years, appetite loss > 25 and pre-existing cardiovascular disease (ordered from most to least important). The AUC for the risk score was 0.744 (95% CI 0.708 – 0.780), and the high risk group showed a positive predictive value of 84.5%, a negative predictive value of 72.5%, a sensitivity of 22.3%, and a specificity of 98.0%. **Conclusions:** HRQoL combined with other risk factors is predictive for 1-year survival. This risk score may help decision making for therapy and may be useful for stratification in randomized trials. But the identified patient group under risk is only small. So an improvement of the score is reasonable and a validation necessary.

5540 Poster Session (Board #267), Mon, 1:15 PM-4:45 PM

Methylated circulating tumor DNA as a potential marker of PARP inhibitor efficiency in BRCA mutated ovarian cancer patients. *First Author: Karina Dahl Steffensen, Department of Oncology, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark*

Background: The liquid biopsy has proven to be an excellent material for analysis of different circulating tumor markers, among which mutated tumor DNA (ctDNA) ranks high. Cancer specific ctDNA methylation can be used to quantitate tumor DNA and is a promising new approach for monitoring changes in tumor burden in response to therapy. Homeobox genes (*HOX*) constitute a family of transcription factors that involved in regulating differentiation and are expressed in normal adult reproductive tissue and methylation of the *HOXA9* gene has been observed in 95% of patients with high grade serous ovarian carcinoma. Treatment with PARP inhibitors has demonstrated considerable benefit in ovarian cancer (OC) patients but stratification of patients for PARP inhibitor (PARPi) treatment by BRCA status has proved suboptimal. The primary aim of the present study was to investigate if methylated *HOXA9* already at baseline, before initiation of single agent PARPi treatment could predict treatment efficacy in OC patients with platinum resistant or intermediate resistant relapse. **Methods:** Plasma from OC patients were retrieved at baseline before initiation of daily oral single agent Veliparib as part of a phase II investigator initiated trial. DNA was purified from 4 ml plasma, bisulfite converted and analysed by droplet digital PCR with methylation specific assay for HOXA9 and Albumin as reference. The fractional abundance of methylated HOXA9 was calculated. CA125 was analysed according to international standard. **Results:** The phase II trial enrolled 32 patients of which 23 patients had methylated *HOXA9* at baseline. Patients with methylated *HOXA9* showed a worse progression-free survival ($p = 0.046$) compared to patients with non-methylated *HOXA9*. In multivariate analysis *HOXA9* showed borderline significance ($p = 0.056$, HR 2.53 (95%CI: [0.98-6.54]) when correcting for age, performance status and platinum sensitivity. Baseline CA125 was not a predictor of PFS. **Conclusions:** The data presented suggests circulating methylated *HOXA9* as a potential marker for prediction of efficacy of PARPi treatment. Clinical trial information: NCT01472783.

5541 Poster Session (Board #268), Mon, 1:15 PM-4:45 PM

Potential impact of dietary intervention/counseling on survival in ovarian cancer patients: Results from an observational study. *First Author: Jessica Michalak, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ovarian cancer is the fifth leading cause of cancer death in women, and survival rates remain largely unchanged within the past forty years. Previous research suggests that dietary intervention may impact cancer development, prognosis, and survival. The purpose of this study was to determine if dietary intervention was associated with improved survival rates in ovarian cancer patients. **Methods:** A total of 183 women were enrolled in the cohort study at MD Anderson. Clinical data collected on a cohort of patients who received the dietary intervention including counseling and supplementation were compared to a cohort of contemporary controls and summarized using descriptive statistics. Survival was computed from the time of admission to time of death or loss to follow-up. The method of Kaplan-Meier was used to provide overall survival estimates at select points in time, and the Log-rank test was used to compare survival distributions between cohorts. **Results:** Estimates of overall survival for intervention (49) and control (125) patients were: 95.9% and 66.8% at 5-years; 87.1% and 34.0% at 10-years; and 76.7% and 22.9% at 15-years, respectively (Log-rank test P-value $< .001$). Control patients had over four times the risk of death relative to patients receiving intervention after adjusting for age at admission. **Conclusions:** Dietary intervention/counseling with supplementation may positively impact survival in women diagnosed with ovarian cancer. Although our findings inspire interest, a weakness was the study's observational nature and the strong potential for confounding. A prospective, appropriately powered randomized clinical trial is warranted to validate these results.

5542 Poster Session (Board #269), Mon, 1:15 PM-4:45 PM

A first-in-human study of monoclonal antibody GM102 in patients with anti-Mullerian-hormone-receptor II (AMHRII) positive gynecological cancers. *First Author: Alexandra Leary, Gustave Roussy Cancer Campus, Villejuif, France*

Background: AMH and its membrane receptor AMHRII induce regression of Müllerian ducts in the male embryo. AMHRII is constitutively expressed in ovarian granulosa tumors (GCT) and re-expressed in ~70% of gynecological tumors. GM102, a low-fucose IgG1 antibody, binds AMHRII and acts through macrophage engagement via CD16 high affinity binding, resulting in enhanced tumor phagocytosis. **Methods:** In the completed escalation part, AMHRII-positive ovarian, cervical and endometrial cancer patients (pts), with measurable disease, Performance Status ≤ 1 and adequate organ function, received GM102 1 to 20mg/kg every 2 weeks (q2w) then 7 and 10mg/kg weekly (qw) in 8 successive cohorts. Expansion phase will include granulosa, epithelial ovarian and cervical cancers. The objective was to determine a recommended dose (RP2D) from safety, pharmacokinetics, pharmacodynamics (PD) and GM102 anti-tumor activity (RECIST) and change in tumor growth rate (TGR = % change in tumor volume/month pre-treatment vs. after 2 cycles). PD included circulating immune cells (CIC) (ICOS, CD14, CD16, CD64, CD69) and in paired biopsies, macrophage (CD68, CD163, CD16) and T cell (CD3, CD4, CD8, FoxP3, Granzyme B) markers. **Results:** 27 pts with AMHRII+ gynecological tumors (including 4 GCTs) received 1 to 21 GM102 infusions. Terminal half-life was 130-200hrs. No dose limiting toxicity was observed. Treatment-emergent toxicities were mostly grade 1-2 (including rash, influenza-like symptom, 1 pt each). One pt had grade 3 anorexia and weight loss. 8/17 (47%) evaluable pts exhibited a decrease in TGR [45%-169%] under GM102. Among 4 GCT pts, 2 had a partial response and inhibin B decreased in 3. In CIC, T cell, monocyte and neutrophil activation was observed, and circulating CD16+ monocytes decreased suggesting possible recruitment to tumor site. In paired biopsies, CD16 expression increased in macrophages as well as Granzyme B suggesting GM102-induced cellular cytotoxicity. **Conclusions:** GM102 was well tolerated at all doses and schedules. RP2D includes 7mg/kg qw and 15mg/kg q2w. The encouraging PD and anti-tumor activity warrants further development of GM102, especially in the rare subtype of GCT. Clinical trial information: NCT02978755.

5543 Poster Session (Board #270), Mon, 1:15 PM-4:45 PM

Role of primary surgery for persistent residual disease after more than 5 cycles of chemotherapy for primary advanced ovarian cancer. *First Author: Philipp Harter, Kliniken Essen Mitte, Essen, Germany*

Background: The standard of care in patients with advanced ovarian cancer is upfront surgery followed by chemotherapy. An interval debulking after 3 chemotherapy cycles might be an alternative in selected patients. However, some patients attend a referral center after having received 5 or more cycles of neoadjuvant chemotherapy with persistent disease. So far, the role of a "delayed" interval surgery is poorly defined. **Methods:** Retrospective analysis of the KEM hospital database 2011-2017 of patients with newly diagnosed advanced epithelial ovarian cancer and delayed cytoreductive surgery for persistent disease after a minimum of 5 cycles of chemotherapy. **Results:** 39 patients underwent delayed interval debulking. 92.3% had a serous high grade ovarian cancer. The median number of pre-OP cycles was 6 (range 5-8). Intra-operatively, the median Peritoneal Cancer Index was 11. 53.8% underwent a bowel resection (5.1% had a protective stoma) and the median surgical complexity score was 7 (2-16). The median duration of surgery was 285 minutes (range 80-510), complete resection was achieved in 84.6%. The rate of severe complications (Clavien Dindo grade 3 or 4) was 23.1%; we observed no post-operative mortality. The median number of chemotherapy cycles after surgery was 2 (range 0-4). 15 (38.5%) patients received bevacizumab before cytoreductive surgery and 16 (41.0%) patients received maintenance therapy with bevacizumab post-operatively. The median PFS and OS in patients with complete resection was 17.2 and 49 months in contrast to only 6.4 and 14 months in patients with incomplete resection. **Conclusions:** Delayed interval surgery might be restricted to selected pts in whom the probability for achieving a complete resection is high. Patients in whom a complete resection could not be achieved show a very poor prognosis and it is likely that they rather experience harm than any benefit from surgery.

5544 Poster Session (Board #271), Mon, 1:15 PM-4:45 PM

Identification of outcome-correlated serum cytokine and chemokine clusters in ovarian clear cell carcinoma. *First Author: Akira Yabuno, Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan*

Background: With the progress of immune-oncology, the immunological background of epithelial ovarian carcinoma (EOC) is gradually becoming understood. However, most of the studies have been focused on the local tumor-immune microenvironment, and the systemic immunological background in patients with EOC has not been well studied. Serum cytokines and chemokine networks may reflect the complex systemic immunological interactions in cancer patients. Studying groups of cytokines and their networks may help in improving immunotherapy for EOC patients. **Methods:** A total of 178 cases of EOC were analyzed in this study, including 73 high-grade serous (HGSC), 66 clear cell (CCC) and 39 endometrioid (EMC) subtype cases. Suspension cytokine arrays, which enable measurement of the levels of 27 cytokines and chemokines, were performed with the patients' sera taken before the primary surgery. Levels of all cytokines were log (x+1) transformed and normalized. Associations between each cytokine and clinocopathological factor were analyzed in all EOC patients using multivariate linear regression models. Cluster analyses were performed for all EOC and each histotype. **Results:** In the multivariate analyses, eleven of 27 cytokines were correlated with histotypes. In contrast, no correlations were found between each cytokine and FIGO stage. Cluster analysis of all EOC patients revealed distinct cytokine profiles in HGSC and CCC, but not in EMC. Cluster analyses in each histotype revealed 2 cytokine clusters in both HGSC and CCC. Interestingly, 22 of 27 cytokines (81.5%) were commonly clustered in HGSC and CCC. Cluster 1 included IL-2, 6, 8, 15, chemokines and angiogenic factors, whereas Cluster 2 included IL-4, 5, 9, 10, 13, TNFalpha and G-CSF. We classified the tumors into 4 subgroups based on a high or low level for each cluster in both HGSC and CCC, and this cluster-based classification demonstrated significantly different progression-free and overall survivals for CCC patients ($p = 0.00097$ and $p = 0.017$). **Conclusions:** Serum-based cytokine clusters determine the histotypes of EOC and their prognosis in patients with CCC. Further study of cytokine networks may provide new strategies for cancer immunotherapy.

5545 Poster Session (Board #272), Mon, 1:15 PM-4:45 PM

Exploratory analysis of percentage of genomic loss of heterozygosity (LOH) in patients with platinum-sensitive recurrent ovarian carcinoma (rOC) in ARIEL3. *First Author: Ana Oaknin, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: In ARIEL3, rucaparib significantly improved progression-free survival (PFS) vs placebo in all randomized patients, including patients with *BRCA*-mutant, *BRCA* wild-type/high-LOH (prespecified as ≥16% genomic LOH), or *BRCA* wild-type/low-LOH (< 16% genomic LOH) rOC (Coleman et al. *Lancet*. 2017;390:1949-61). This exploratory analysis evaluated the optimal cutoff for percentage of (%) genomic LOH in *BRCA* wild-type rOC in ARIEL3. **Methods:** Genomic LOH of archival tumor tissue DNA was centrally assessed using Foundation Medicine's next-generation sequencing-based assay (Cambridge, MA, USA). Treatment effect for investigator-assessed PFS (invPFS) was analyzed in *BRCA* wild-type rOC for the prespecified cutoff (16%) and across a range of cutoffs for % genomic LOH (5%–30%). Hazard ratios (HRs) were estimated using a stratified Cox proportional hazards model. Prognostic and predictive utility of % genomic LOH was assessed by comparing invPFS between and within the treatment arms. **Results:** In ARIEL3, 564 patients were randomized. Of the 368 patients with *BRCA* wild-type associated rOC, LOH was calculable for 319. Rucaparib significantly improved invPFS vs placebo between the 5% and 23% cutoffs for % genomic LOH. Using the prespecified cutoff (16%), the HR (rucaparib vs placebo) was 0.44 (95% confidence interval [CI], 0.29–0.66; $P< 0.0001$) for patients with high-LOH rOC. To further assess the % genomic LOH cutoff, we compared patients with high- vs low-LOH rOC within the rucaparib arm and found a statistically significant benefit for invPFS at the prespecified cutoff of 16% (HR, 0.70; 95% CI, 0.50–0.97; $P= 0.0338$). In the placebo arm, no statistically significant benefit was observed for invPFS in patients with high- vs low-LOH rOC at any cutoff tested. **Conclusions:** Rucaparib improved invPFS vs placebo across the range of cutoffs tested for % genomic LOH, including the prespecified cutoff of 16% for high LOH. The observance of significant differences between patients with high- vs low-LOH rOC in the rucaparib but not placebo arm suggests that genomic LOH is a predictive but likely not prognostic biomarker. Clinical trial information: NCT01968213.

5546 Poster Session (Board #273), Mon, 1:15 PM-4:45 PM

Effect of hypertension (HTN) on progression-free survival (PFS) in patients (pts) receiving front-line bevacizumab (BEV) for primary advanced ovarian cancer (OC) in the NOGGO single-arm OTILIA study: A post hoc analysis in 808 pts. *First Author: Robert Armbrust, Campus Charité Mitte, Charité Centrum 17, Klinik f. Geburtsmedizin, Berlin, Germany*

Background: The efficacy and safety of front-line BEV-containing therapy for OC were demonstrated in two phase III trials. At the 3rd interim analysis of OTILIA (NCT01697488) evaluating front-line BEV in German clinical practice, median PFS was 21.3 months. The potential association between HTN and PFS was explored in the present analysis. **Methods:** Pts with newly diagnosed FIGO stage IIIB–IV OC received the EU-approved BEV-containing regimen. In exploratory analyses, outcomes were analyzed according to the presence or not of HTN at baseline (BL). Cox regression models in each subgroup explored the effect on PFS of HTN developing (no HTN subgroup) or worsening (pre-existing HTN subgroup) during treatment in a time-dependent manner. **Results:** Of 808 evaluable pts, 406 had BL HTN and 402 did not. Pts in the HTN subgroup were generally older (median 71.8 vs 61.8 years in the subgroup without HTN) with a higher BMI (median 25.7 vs 23.1 kg/m^2) and more likely to have diabetes (16% vs 5%). Median BEV duration was similar in the two subgroups (13.5 vs 13.3 months, respectively). As of 31 Jan 2017, PFS events had been recorded in 364 pts (45%). Median PFS was 21.3 months in both subgroups. HTN worsened in 291 (72%) of 406 pts with pre-existing HTN and developed in 132 (33%) of 402 pts without BL HTN. Cox regression analysis suggested an association between onset of HTN and PFS in pts without BL HTN (hazard ratio [HR] 0.69, 95% CI 0.50–0.96) but not between worsening of HTN and PFS in those with pre-existing HTN (HR 1.18, 95% CI 0.82–1.70). Residual tumor burden was associated with worse PFS in both subgroups (HR 2.04; 95% CI 1.39–3.00 in pts without BL HTN; HR 2.42, 95% CI 1.56–3.74 in pts with pre-existing HTN). **Conclusions:** These exploratory analyses suggest no detrimental effect of HTN on PFS in BEV-treated pts. Based on these observations, in pts with HTN and ongoing clinical benefit, it seems reasonable to continue BEV therapy if HTN is managed appropriately. As this was an exploratory interim analysis, the observed more favorable PFS in pts with HTN developing during BEV should be validated in further prospective trials. Clinical trial information: NCT01697488.

5547 Poster Session (Board #274), Mon, 1:15 PM-4:45 PM

Tumor regression grading after neoadjuvant chemotherapy predicts long-term outcome of stage IIIC epithelial ovarian cancer. *First Author: Mingyi Zhou, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, China*

Background: Prognostic value of tumor regression grading (TRG) after neoadjuvant chemotherapy (NAC) in patients with FIGO stage IIIC epithelial ovarian cancer (EOC) is controversial. **Methods:** A total of 55 stage IIIC EOC patients who underwent interval debulking surgery (IDS) after NAC at the Department of Gynecology of Liaoning Cancer Hospital and Institute between January 2003 and September 2016 and had full information were involved this retrospective study. All the pathological sections were individually reviewed by two pathologists. TRG was determined by the ratio of viable tumor versus fibrosis, ranging from TRG 0 when no viable tumor, to TRG 5 when fibrosis was absent. TRG 1 was defined as regression more than 75%, TRG 2 was defined as regression more than 50% but less than 75%, TRG 3 was defined as regression more than 25% but less than 50%, and TRG 4 was defined as regression less than 25%. Patients were stratified into TRG 0-1-2 group and TRG 3-4-5 group according to cut-off values calculated through receiver operating characteristic (ROC) curves. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier method. Univariate analyses were performed using log-rank tests. Multivariate analyses were performed using Cox regression analysis to assess the prognostic factors of TRG, which were expressed as hazard ratios (HRs). **Results:** Univariate and multivariate analyses suggested that TRG and residual disease (RD) were independent predictive factors of PFS, and TRG, RD and CA125 change were independent predictive factors of OS. TRG was a better prognostic factor compared with CA125 value change after NAC (area under curves [AUC] of the ROC of TRG 0.93 versus AUC of the ROC of CA125 change 0.69). The median PFS of the patients in TRG 0-1-2 group was 14.0 months longer than TRG 3-4-5 group (26.0 months versus 12.0 months, HR 2.19, 95% confidence interval [CI] 1.17-4.07, $P = 0.014$). The median OS of the patients in TRG 0-1-2 group was 28.6 months longer than TRG 3-4-5 group (50.4 months versus 21.8 months, HR 3.10, 95%CI 1.49-6.42, $P = 0.002$). **Conclusions:** TRG after NAC was an independent prognostic factor of patients with FIGO stage IIIC EOC.

5548 Poster Session (Board #275), Mon, 1:15 PM-4:45 PM

Incidence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients (pts) with a germline (g) *BRCA* mutation (m) and platinum-sensitive relapsed ovarian cancer (PSR OC) receiving maintenance olaparib in SOLO2: Impact of prior lines of platinum therapy. *First Author: Jacob Korach, Sheba Medical Center, Tel Aviv University, Tel Hashomer, Israel*

Background: Olaparib has been investigated and subsequently approved as maintenance treatment after response to platinum-based chemotherapy in pts with relapsed OC. A relationship between increasing dose and duration of platinum therapy and an increased risk of MDS/AML has been reported (Travis *et al. N Engl J Med* 1999). Events of MDS/AML have been reported in pts treated with olaparib, but a causal relationship has not been established. The results of a *post hoc* analysis evaluating the incidence of MDS/AML by prior lines of platinum therapy in pts with g*BCRA*m PSR OC receiving maintenance olaparib or placebo in the Phase III SOLO2 trial (ENGOT Ov-21; NCT01874353; Pujade-Lauraine *et al. Lancet Oncol* 2017) are reported here. **Methods:** The safety analysis set comprised 195 pts who received olaparib tablets (300 mg twice daily) and 99 pts who received placebo. The median duration of follow-up in the olaparib and placebo groups (pts censored at time of primary analysis) was 25.3 and 25.1 months, respectively. **Results:** The overall incidence of MDS/AML was similar in the olaparib and placebo groups (2.1% vs 4.0%; Table). With both olaparib and placebo, the incidence of MDS/AML appeared to increase with an increasing number of lines of prior platinum therapy. This trend did not appear to be driven by pt age. This trend was also observed in a larger pooled analysis of olaparib clinical studies. Clinical trial information: NCT01874353. **Conclusions:** Olaparib did not increase the risk of MDS/AML vs placebo in SOLO2. Rather, a trend was seen for a higher incidence of MDS/AML with an increasing number of prior lines of platinum therapy. A limitation of this analysis is the small number of events that occurred in each group; however, results of a separate, larger pooled analysis of trial data support these findings.

MDS/AML incidence and pt age by number of prior lines of platinum therapy.

	MDS/AML incidence, n/N (%)		Median pt age, years	
	Olaparib	Placebo	Olaparib	Placebo
2	1/110 (0.9)	2/62 (3.2)	56.0	55.0
3	1/60 (1.7)	1/20 (5.0)	56.5	58.5
≥4	2/25 (8.0)	1/17 (5.9)	57.0	61.0
Overall	4/195 (2.1)	4/99 (4.0)	56.0	56.0

5549 Poster Session (Board #276), Mon, 1:15 PM-4:45 PM

Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-resistant ovarian cancer: Maturing safety and activity profile from the FORWARD II phase 1b study. *First Author: David M. O'Malley, The Ohio State University College of Medicine, Columbus, OH*

Background: Mirvetuximab soravtansine is an ADC, comprising a FRα-binding antibody linked to the tubulin-disrupting maytansinoid DM4, currently being evaluated in combination with bevacizumab as part of an ongoing Phase 1b trial (FORWARD II; NCT02606305) in pts with platinum-resistant ovarian cancer. **Methods:** Pts were administered mirvetuximab soravtansine (6 mg/kg; adjusted ideal body weight) in combination with bevacizumab (15 mg/kg) on Day 1 of a 21-day cycle. Responses were assessed according to RECIST 1.1 and adverse events (AEs) evaluated by CTCAE v4.0. **Results:** To date, a total of 51 pts have received combination therapy at this dose level: 11 in dose escalation; 40 during the expansion stage. Pts had a median age of 64 years and received a median of 3 prior lines of systemic therapy (range 1-8); 51% and 29% of pts had received prior therapy with bevacizumab or a PARP inhibitor, respectively. The four most commonly reported AEs were nausea, fatigue, diarrhea, and blurred vision (45-57% of pts), which were primarily grade 1 or 2. The most frequent grade 3 AE was hypertension (8 pts - 16%). For the efficacy evaluable population (49 pts), objective tumor responses were observed in 19 pts for a confirmed overall response rate (ORR) of 39% and a median progression-free survival (mPFS) interval of 9.5 months (95% CI, 4.6, -). In a subset analysis of pts (n = 20) with ≤ 3 prior therapies and medium to high FRα levels (i.e., ≥ 50% of cells with ≥ 2+ staining intensity) the ORR was 55% with mPFS not yet reached, with a median follow-up of 5.7 months (range 1.3-11.7). Updated results will be presented. **Conclusions:** The mirvetuximab soravtansine-bevacizumab combination continues to display a manageable safety profile in pts with platinum-resistant ovarian cancer. The encouraging efficacy results justify further exploration of this novel therapeutic combination in this difficult to treat population. Clinical trial information: NCT02606305.

5550 Poster Session (Board #277), Mon, 1:15 PM-4:45 PM

Prediction of post-operative residual disease in advanced-stage ovarian cancer (AOC) using whole transcriptome expression: An exploratory analysis of the AGO-OVAR 11 (ICON7) trial. *First Author: Florian Heitz, Department of Gynecologic Oncology, Kliniken Essen-Mitte, Essen, Germany*

Background: Complete resection (CR) at primary debulking surgery is the single most important prognostic factor in AOC. It has been demonstrated, that suboptimal debulking (residual disease > 1cm) might be associated with TCGA molecular subtypes and de novo generated gene expression (GE) signatures. The aim of this study was to validate previous findings and to investigate the impact whole transcriptome GE analyses might have on postoperative residual tumor prediction in a phase III ovarian cancer frontline trial. **Methods:** Core biopsies from formalin fixed paraffin embedded tumor tissue of FIGO stage IIIC/IV AGO-OVAR 11/ICON7 pts were used to generate whole-genome DASL GE data. TCGA molecular subtype and two previously published GE debulking signatures (7 genes and 11 genes) were correlated with size of residual disease (CR vs. any residual disease). Logistic Regression (LR), support vector machine with polynomial kernel, and random forest were used as classifiers. We built models with all GE features as well as gene selected with HITON-PC, a method that select the markov blanket of the outcome. **Results:** 283 pts met inclusion criteria, of those 114 (40.3%) had complete resection. Previous reported debulking signatures using 7 and 11 genes respectively did not predict residual disease in this cohort. Best Area under the Curve (AUC) for 7 gene signature was generated using LR 0.50 ± 0.05, while 11 gene signature had an AUC of 0.53 ± 0.04. Similarly, TCGA molecular subtypes (AUC = 0.56 ± 0.04), an independent de novo developed signature (AUC = 0.51 ± 0.04) and the total gene expression data set using all 21,000 genes (AUC = 0.55 ± 0.03) were not able to predict residual disease status. **Conclusions:** In contrast to previous findings, we were not able to predict residual disease using GE in tumor samples from the AGO-OVAR11/ICON7 phase III trial. A standardized radical surgical approach resulting in a higher frequency of complete resection might allow detection of biologic factors responsible for sub-optimal debulking. The ongoing AGO-OVAR TRUST trial might be able to address this important clinical question.

5551 Poster Session (Board #278), Mon, 1:15 PM-4:45 PM

METRO-BIBF: Phase II, randomised, placebo controlled, multicentre, trial of low dose (metronomic) cyclophosphamide (MCy) with or without nintedanib in relapsed ovarian cancer (ROC). *First Author: Marcia Hall, Mount Vernon Cancer Centre, Middlesex, United Kingdom*

Background: ROC patients (pts), heavily pretreated with IV chemotherapy (CT) are a heterogenous group, median OS 3-9 mo. Oral MCy is well tolerated, avoids IV CT and has been shown to have clinical benefit. MCy has anti-angiogenic properties, inhibiting growth of tumour, endothelial and host vasculature. Augmentation with bevacizumab showed encouraging results in single arm studies. METRO-BIBF evaluates a novel combination of MCy with either placebo (P) or nintedanib (N)- oral inhibitor VEG/PDG/FGFR tyrosine kinases. **Methods:** Eligible pts received ≥2 lines of CT; platinum-resistant/intolerant, ECOG PS 0-2, life-expectancy of > 6 weeks. MCy (100mg/d) was given continuously with either N or P, to progression / toxicity. No prior TKI permitted; pts stratified for prior bevacizumab. Priamry aim to increase median OS by 2 mo. PFS, toxicity and QoL also measured. **Results:** 117 pts were randomised 08/14 – 10/16, median age 64, 87% HGS ROC, 39% pts ≥ 5 lines prior CT. Dose of N/P was reduced from 200 to 150 mg bd after planned review of N/P/MCy in first 46 pts. 96 patients have died. N had no effect on OS (HR 1.08, p = 0.72). Table shows OS/PFS by arm. Combining MCy pts from both arms, median OS was 6.4 mo and 26 patients (23%) took MCy for ≥ 6 mo. Pts without prior bev treatment (69%) stayed longer on MCy than pts with prior bev (31%) (mean diff: 53 days, p < 0.01). Grade 3-4 toxicity as expected in 64.4% pts on N/MCy vs. 54.5% pts on P/MCy; more N/MCy pts had neutropenia and diarrhoea. Two treatment-related deaths: 1 bowel perforation, possibly disease-progression (N), 1 liver failure (P). QoL did not differ between arms. **Conclusions:** Adding N to MCy did not improve OS/PFS. But in this large study of MCy in heavily pre-treated ROC, almost one quarter remained on therapy for > 6 months, suggesting either more indolent disease and/or MCy has longer-term cytostatic or immunological benefits requiring further investigation. Clinical trial information: NCT01610869.

	Placebo (N = 55*) *3 pts did not start M/Cy	Nintedanib (N = 59)
Median OS (95% CI) mo	6.4 (5.0-10.1)	6.8 (4.5-9.5)
OS: 6 mo	50.9%	55%
OS: 12 mo	31.3%	20%
Median PFS (95% CI) mo	2.7 (2.5-4.7)	2.9 (2.7-4.6)
PFS: 6 mo	22.8%	29.6%
PFS: 12 mo	5.7%	5.9%

5552 Poster Session (Board #279), Mon, 1:15 PM-4:45 PM

Facilitated referral pathway for genetic testing at the time of ovarian cancer diagnosis: Uptake of genetic assessment and testing and impact on patient-reported stress, anxiety and depression. *First Author: Sarah S. Lee, New York University Langone Medical Center, New York, NY*

Background: To determine if a patient-centered, facilitated genetics referral pathway whereby all women with newly-diagnosed ovarian cancer are proactively contacted by a genetics navigator (GN) for genetic assessment (GA) increases rates of GA and genetic testing (GT) uptake without increased patient-reported stress, anxiety or depression **Methods:** Patients with epithelial ovarian cancer were referred for GA by their gynecologic oncologist within six weeks of diagnosis. Patients were contacted by a GN and offered an appointment for GA and GT within six weeks of contact. English-speaking patients completed quality of life (QoL) instruments (Impact of Events Scale, State-Trait Anxiety Questionnaire, Hospital Anxiety and Depression Scale) immediately pre-and post-GA and 6-9 months later. Primary outcome was feasibility of this pathway as defined by presentation for GA or declining GA within 6 weeks of contact by a GN. **Results:** From 10/2015-12/2017, 88 patients were enrolled. Seventy-one (81%) patients had GA and 62 (70%, 87% of those who had GA) underwent GT. Median time from diagnosis to GA was 28 days (range 9-75). Among patient who underwent GT, 11 (18%) had a pathogenic mutation (BRCA1-6, BRCA2-4, MSH2-1) and 25 (40%) had a variant of uncertain significance. Forty-one patients completed QoL assessments which demonstrated mild to moderate stress, normal to clinically significant anxiety and borderline levels of depression. QoL assessments were not associated with the GT result and with no significant changes in stress, anxiety or depression when comparing QoL measurements for each patient obtained pre/post-GA and 6-9 months later. **Conclusions:** A facilitated referral to genetic counselors at time of ovarian cancer diagnosis is effective and efficient, resulting in GA in 81% of patients within 4 weeks of diagnosis, GT in 70% of patients and discovery of pathogenic mutations in 18% of those tested, and does not demonstrate a psychologic toll. Concern about emotional distress should not deter clinicians from early genetics referral as GT in this population can yield important prognostic and therapeutic information.

5553 Poster Session (Board #280), Mon, 1:15 PM-4:45 PM

A phase I study of concomitant galinpepimut-s (GPS) in combination with nivolumab (nivo) in patients (pts) with WT1+ ovarian cancer (OC) in second or third remission. *First Author: Roisin Eilish O'Cearbhaill, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: WT1 is highly expressed in serous ovarian cancer. GPS is WT1-targeting heteroclitic peptide tetravalent non-HLA-restricted vaccine, and has shown promising phase 2 activity in AML, mesothelioma and myeloma. Efficacy of GPS may be enhanced through checkpoint blockade, providing a rationale for combining it with anti-PD1 antibody, nivo. We conducted a phase I study to evaluate the safety and immunogenicity of the combination in WT1+ OC in remission. **Methods:** Pts with WT1+ OC in $\geq 2^{nd}$ remission were enrolled from 06/16-07/2017, and received GPS (800 mcg) x 6 total doses mixed with adjuvant (0.5 ml) and 70 mcg GM-CSF (all s.c. in extremities) and nivo 3 mg/kg IV q2wks over 12 weeks. DLTs were assessed using CTCAE criteria, with detection of $>$ 2/10 DLTs deeming the combination unsafe. Treatment was continued until disease progression or toxicity. Immune responses (IgG & IgM WT1 antibody, T cell assays) induced by the combination were evaluated. The 1-year progression-free survival (PFS) rate, defined as the interval from start of preceding chemo to date of progression or death, is an exploratory objective. **Results:** n=11; Median age 61 yrs (41-76). 7 pts in 2^{nd} and 4 pts in 3^{rd} remission. 1 DLT (gr 3 myositis with myocarditis post GPS and nivo #2). Most common AEs were Gr $\leq$2 fatigue and injection site reactions. Immune Response Results: n=9; Serum levels of antigen-specific IgG (against both individual WT1 peptides in GPS and the full-length WT1) significantly increased in 86% of evaluable pts between study wks 6-27. Antigen-specific T cell responses to individual WT1 peptides were observed between 6-15 wks, primarily CD4 and to a smaller extent, CD8 T cells. 1yr PFS rate was 64% in the ITT analysis (7/11) and 70% (7/10) in pts who had $>$ 2 GPS/nivo doses. **Conclusions:** Administration of GPS in combination with nivo was safe, well tolerated and induced high frequency of T- and B-cell immune responses, warranting further evaluation. The 1yr PFS rate compares favorably to historic rates of approximately 50% in comparable populations. Additional cohorts are planned to receive the current combination along with vaccination against additional tumor-associated antigens. Clinical trial information: NCT02737787.

5554 Poster Session (Board #281), Mon, 1:15 PM-4:45 PM

A phase I dose-escalation of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) carboplatin for the frontline treatment of advanced ovarian cancer. *First Author: Leslie M. Randall, University of California, Irvine, Orange, CA*

Background: Hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of frontline ovarian cancer surgery has shown preliminary overall survival benefit, but selection of chemotherapy agent and dose is mostly arbitrary. **Methods:** For this prospective study, women with peritoneal carcinomatosis of suspected ovarian, tubal, or peritoneal origin with optimal (R1 or R0) primary or interval debulking were eligible. Those with non-gynecologic primary, suboptimal surgery, or intraoperative complications were excluded. Dose for a pre-planned sample size (n = 30) was escalated according to a Bayesian continual reassessment schedule. The simulated maximum tolerated dose (MTD) estimate was 970 mg/m^2. Closed-technique HIPEC was administered at 41^{o}C for 60 minutes. Serum and perfusate samples were collected at time 0 and every 15 minutes for PK. Adverse events (AEs) were assessed every other day until discharge and weekly for 30 days according to NCI CTCAE v4.03. **Results:** We enrolled 52 subjects to reach n = 30 (attrition rate 42% for non-gynecologic primary or suboptimal surgery). Median age was 63 (range 33-78) with 15 Caucasian, 6 Hispanic, 7 Asian, and 2 other. Any AE was observed in 26 (87%) of subjects with 15 (50%) experiencing grade 3 or greater AEs. The most common grade 1-2 AEs were anemia (40%) and nausea (13.3%). Grade 3 AEs included anemia (10%), pancreatic leak (3.3%), wound dehiscence (3.3%), and sub diaphragmatic abscess (3.3%). One patient had grade 4 neutropenia and thrombocytopenia and grade 5 *C. difficile* colitis and sepsis; this was the only patient death. The post-trial MTD was 1115 mg/m^2. PK analysis is ongoing. **Conclusions:** HIPEC with carboplatin was well tolerated at the protocol-specified doses in this cohort. The majority of AEs were attributable to surgery. Intraoperative protocol assignment is associated with a significant attrition rate that should be accounted for in sample size calculations and reported in clinical trials of HIPEC therapy. Clinical trial information: NCT02199171.

5555 Poster Session (Board #282), Mon, 1:15 PM-4:45 PM

Inter and intra-observer variability with the assessment of RECIST in ovarian cancer. *First Author: Michelle K. Wilson, Auckland City Hospital, Auckland, New Zealand*

Background: Measurement of response with RECIST is central to the interpretation of trial outcomes and relies upon accurate and reproducible unidimensional tumor measurements. This study assessed intra and inter-observer variability with assessment and selection of target lesions for RECIST in patients with ovarian cancer. **Methods:** Eight international radiologists measured 30 lesions at 2 discrete time points. Lesion measurements between radiologists were compared to assess inter-observer variability. Percentage difference between lesions was calculated. Measurements of the same lesion at two time points by each radiologist were used to assess intra-observer variability. Radiologists were also asked to select 2 target lesions for RECIST. Reproducibility of lesion selection based on site (peritoneal vs nodal vs visceral) was calculated. **Results:** 80 lesions were measured with a median size of 2.6cm (range 0.8-9.5cm). Seventy-one lesions (89%) were 1.5cm or larger. Assessments at two time points were performed by 7 radiologists. Inter-observer assessment of a single lesion varied on average by 22% (range 5 to 68%). Measurements differed by $\geq$20% in 28% of visceral, 79% of nodal and 60% of peritoneal lesions. When measured by the same radiologist only 10% of lesions differed by $\geq$20%. Intra-observer measurements were less likely to vary by $\geq$20% (10 vs 54%; $p < 0.0001$). Radiologists were more likely to measure the same lesion with visceral (7/7 lesions; 100%; $p = 0.01$) and nodal (9/10; 90%; $p = 0.01$) lesions versus peritoneal lesions (5/14; 36%). When selecting 2 lesions for RECIST, the largest lesion was most consistently chosen (35/38 target lesions; 92%). When this was repeated, 5 of 7 radiologists (71%) chose the same lesions each time. **Conclusions:** RECIST underpins trial outcomes yet significant variability in tumor measurements was found in this study. These results suggest RECIST assessments by the same radiologist should improve consistency. Peritoneal lesions are a key site of disease progression in ovarian cancer yet these were the most inconsistent to select and had significant inter-observer variability in measurements. These factors need consideration as we strive to improve response assessment in clinical trials.

5556 Poster Session (Board #283), Mon, 1:15 PM-4:45 PM

Characterization and predictors of long term ($\geq$ 10 years) survivors in NRG/GOG randomized clinical trials of intraperitoneal and intravenous chemotherapy in stage III ovarian cancer patients. *First Author: Michael Friedlander, Department of Medical Oncology, Prince of Wales Hospital, Sydney, New South Wales, Australia*

Background: ~25% of patients with stage III OC are reported to be alive $\geq$ 10 years after diagnosis in registry studies[1]. Some have long term disease-free survival (LTDFS) without recurrence and others have recurrent active disease but the proportions of each is unclear. We propose to determine the proportion, characteristics, and predictors of long term survival in patients with stage III ovarian cancer (OC) enrolled in clinical trials who are $\geq$ 10 years LTDFS . **Methods:** Data from 3 NRG/GOG trials (104, 114, and 172) which enrolled patients to intraperitoneal (IP) vs. intravenous (IV) chemotherapy were analysed. Demographics and clinic-pathologic characteristics of patients living $\geq$ 10 years were tabulated. Using a landmark approach at 10 years, Cox regression survival analysis was performed to evaluate independent prognostic factors that predict LTDFS. **Results:** Of 1,229 stage III OC patients, 18.8% (232/1229) were alive $\geq$ 10 years. Of these, 13.7% (n = 168) had LTDFS $\geq$ 10 years and 5.2% (n = 64) had recurrent disease. Compared to the overall study group, the LTDFS $\geq$10 years patient had a median age of 54.8 vs. 57.2 years ($p < 0.001$), gross residual disease after primary surgery 42.3% vs. 45.8% ($p = 0.027$); serous cell type 62.5% vs. 68.4%; endometrioid 14.3% vs. 9.4% ($p = 0.035$), well differentiated cancers 12.5% vs. 8.5% ($p < 0.001$), respectively. Of the LTDFS patients, 45.2% were treated with IP and 54.8% with IV chemotherapy ($p = 0.3$). Age (HR = 1.077; 95% CI = 1.03–1.12; $p < 0.001$) was the only independent prognostic factor for LTDFS $\geq$10 years on multivariate Cox analysis. **Conclusions:** Approximately 14% of stage III ovarian cancer patients were in LTDFS at $\geq$10 years and an additional 5% were alive with recurrent disease. Younger age at diagnosis was the only independent prognostic factor for LTDFS $\geq$10 years. Further work is needed to understand characteristics and predictors of exceptional responders and whether they could be identified at initial diagnosis. [1] Baldwin et al Obstetrics & Gynecology: 2012: 120; 3: 612–618

5558 Poster Session (Board #285), Mon, 1:15 PM-4:45 PM

Predictive factors for prolonged response to olaparib as maintenance therapy in ovarian cancer patients with *BRCA* mutations. *First Author: Sana Intidhar Labidi-Galy, Hopitaux Universitaires de Geneve, Geneve, Switzerland*

Background: To investigate clinical factors predictive for prolonged progression-free survival (PFS) in ovarian cancer (OC) patients carrying *BRCA* mutations and receiving olaparib as a maintenance therapy. **Methods:** Multicentric (7 cancer centers) international (France and Switzerland) retrospective study of OC patients having germline or somatic mutations of *BRCA1/BRCA2* genes and treated with olaparib as maintenance therapy after platinum-based chemotherapy. **Results:** One hundred and fifteen patients were included. Median age was 60 years. There were 92 *BRCA1* carriers, 22 *BRCA2* carriers and one patient had double mutation of *BRCA1* and *BRCA2* genes. Ninety-two percent had serous carcinomas. Six patients had somatic mutations (all *BRCA1*) and 109 had germline mutations. Median follow-up was 9.8 months. Ninety percent of the patients were platinum-sensitive: 24% had platinum-free interval (PFI) at 6-12 months and 65% had PFI $>$ 12 months. Responses to platinum-based chemotherapy before olaparib as maintenance therapy were: SD (15.7%), PR (52.2%) and CR (32.2%). In multivariate analysis, factors predictive for prolonged PFS under olaparib were: CR (HR = 0.13; 95%CI 0.06-0.28; $p< 10^{-3}$), PFI $>$ 12 months (HR = 0.43; 95%CI 0.26-0.73; p= 0.002) and *BRCA2* mutations (HR = 0.42; 95%CI 0.24-0.94; p= 0.033). **Conclusions:** Complete response to platinum before olaparib, PFI $>$ 12 months, and *BRCA2* mutations are predictive for prolonged PFS in *BRCA* carriers who received olaparib as maintenance therapy.

5559 Poster Session (Board #286), Mon, 1:15 PM-4:45 PM

Cost-effectiveness of niraparib versus routine surveillance, olaparib, and rucaparib for the maintenance treatment of adult patients with ovarian cancer in the United States. *First Author: Mark Fisher, FIECON, St Albans, United Kingdom*

Background: To estimate the cost-effectiveness of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, compared with routine surveillance (RS), olaparib and rucaparib for the maintenance treatment of patients with recurrent ovarian cancer. **Methods:** A decision-analytic model estimated the cost per quality-adjusted life-year gained for niraparib versus RS, olaparib and rucaparib from a US payer perspective. Recurrent ovarian cancer patients with or without germline *BRCA* mutation, who were responsive to their last platinum-based chemotherapy regimen, entered the model (non-g*BRCA*mut, g*BRCA*mut). The model had three health states; progression-free disease, progressed disease and dead. For non-g*BRCA*mut and g*BRCA*mut, mean progression-free survival (PFS) was estimated for niraparib and RS, and rucaparib using parametric survival distributions based on ENGOT-OV16/NOVA (Niraparib Phase III trial) and ARIEL3 (Rucaparib Phase III trial), respectively. For non-g*BRCA*mut, olaparib PFS was estimated from Study 19 (Olaparib Phase II trial). For g*BRCA*mut, a cost-minimisation analysis was conducted versus olaparib. Due to immature overall survival (OS) data in ENGOT-OV16/NOVA and ARIEL3, mean OS benefit was estimated as double the mean PFS benefit for niraparib, olaparib and rucaparib versus RS. Costs included; drug, chemotherapy, monitoring, adverse events, and terminal care. EQ-5D captured quality-of-life. A 3% annual discount rate was used. **Results:** Treatment with niraparib increased costs and QALYs versus RS, with an incremental cost-effectiveness ratio of \$94,186 and \$58,804, for non-g*BRCA*mut and g*BRCA*mut. Niraparib had lower costs and higher QALYs compared to olaparib and rucaparib in both populations, with a cost difference of -\$57,575 and -\$60,400 versus olaparib, and a cost difference of -\$117,916 and -\$261,950 versus rucaparib for non-g*BRCA*mut and g*BRCA*mut. **Conclusions:** These estimates indicate that niraparib was cost-effective compared to olaparib and rucaparib. Additionally, the cost-effectiveness ratio falls within an acceptable range versus RS. Mature OS data is required to validate these results.

5560 Poster Session (Board #287), Mon, 1:15 PM-4:45 PM

Nanoparticle micellar formulation of paclitaxel in combination with carboplatin for women with recurrent platinum sensitive ovarian cancer (OAS07-OVA): Overall survival results of a phase 3 randomized trial. *First Author: Nina Heldring, Oasmia Pharmaceutical AB, Uppsala, Sweden*

Background: The primary objective in the pivotal trial OAS-07OVA was reached and it was demonstrated that Paclical, a nanoparticle micellar formulation of paclitaxel (Oasmia Pharmaceutical AB) is non-inferior to Cremophor-EL Paclitaxel in terms of progression free survival (PFS) in the treatment of recurrent platinum-sensitive ovarian, fallopian tube or peritoneal carcinoma. Paclical is given as 1-h infusion without standard use of premedication. The follow-up analyses presented here includes overall survival (OS) and subgroups of PFS and OS. **Methods:** In this open 1:1 randomized 2-armed phase 3 study, 789 patients were included 2009 - 2012 in 81 centers. Non-inferiority in terms of OS was included as a secondary objective, anddefined as the time between date of randomization and death. Following the end of study, information of the death of participating patients was collected on a special form until August 2016. The upper non-inferiority limit of the one-sided confidence interval of the hazard ratio of the two treatment arms was set to 1.185. **Results:** Non-inferiority of OS was showed as the hazard ratio estimated based on a Cox proportional hazards model stratified by CA125 and relapse was 0.95 (95% CI: 0.78; 1.16) in the PP population. The median overall survival time was 25.7 months in the Paclical arm and 24.8 months in the Taxol arm. Non-inferiority of OS was also seen in patients experiencing their first relapse, and patients with serous adenocarcinoma at diagnosis. In addition, sensitivity analyses as well as subgroup analyses showed a consistent tendency of favor for Paclical in terms of PFS. **Conclusions:** Paclical is non-inferior to Taxol with respect to OS and PFS for patients with recurrent platinum-sensitive ovarian cancer. Even though the pivotal study was not designed to show superiority, subgroup analyses show a consistent tendency of favor for Paclical in terms of OS and PFS indicating a benefit for the Paclical group. Clinical trial information: NCT00989131, Eudra CT: 2008-002668-32 Clinical trial information: 2008-002668-32.

5561 Poster Session (Board #288), Mon, 1:15 PM-4:45 PM

Tumor molecular profiling to differentiate extreme responses to first-line platinum-based chemotherapy in suboptimally debulked serous ovarian cancer patients. *First Author: Johanne I Weberpals, Ottawa Hospital Research Institute, Ottawa, ON, Canada*

Background: Patients with advanced high grade serous ovarian cancer (SOC) who undergo a suboptimal debulking primary surgery typically have adverse clinical outcomes. However, a spectrum of sensitivity to first line platinum-based chemotherapy is observed but poorly understood. In this study, we perform molecular characterization of two groups of responders (extreme versus poor) to first line carboplatin/taxol chemotherapy in suboptimally debulked SOC patients. **Methods:** Suboptimally debulked SOC patients with advanced disease (stage III-IV) were grouped by response to first-line chemotherapy and clinicopathologic data collected. Extreme platinum-sensitive (PS) responders had a PFI (progression-free interval) $>$ 12 months (mo) and platinum-resistant (PR) responders had a PFI $<$ 6mo. Tissue specimens were used to interrogate the molecular features of both PS and PR cohorts using whole exome and transcriptome sequencing. Sequence alignment and variant calling were performed using GATK and annotation was performed using Variant Effect Predictor for assessment of non-synonymous tumor mutation burden (TMB) and discovery of novel mutational signatures to predict platinum response. **Results:** There were 39 patient samples analyzed from primary surgery (PS group = 20; PR group = 19). Median PFI for PS and PR patient cohorts was 30 mo and 3 mo ($p < 0.001$), respectively. In all tumors, in addition to BRCA and TP53 mutations, additional oncogenic mutations were noted in genes associated with PI3K/AKT/mTOR signaling and in epigenetic regulation. The PS samples were characterized by mutations in BRCA1/2 and the PR samples by mutations in MGA. Compared to tumors in the PR cohort, PS tumors had a significantly higher non-synonymous mutation rate using TMP analysis ($p < 0.05$) with a trend towards increased immune response. Additional bioinformatics analysis is ongoing and will include copy number variation analysis, immune inference using ESTIMATE and Gene Set Enrichment Analysis. **Conclusions:** Contracting a mutational signature is feasible from patient tumors at primary surgery and helps to elucidate extreme responses to platinum-based chemotherapy.

5562 Poster Session (Board #289), Mon, 1:15 PM-4:45 PM

Integrated molecular analysis of Asian ovarian cancer: Gene expression and whole exome sequencing analyses from the iPocc Translational Research study (TriPocc). *First Author: Ruby Huang, Cancer Science Institute of Singapore, National University of Singapore, Singapore*

Background: iPocc is a randomized, multicenter international study comparing the efficacy of first line intravenous (IV) dose-dense paclitaxel and intraperitoneal (IP) carboplatin with standard IV dose-dense paclitaxel and carboplatin in women with epithelial ovarian, fallopian tube or primary peritoneal cancer. TriPocc is the translational research protocol evaluating the molecular and predictive biomarkers for differences in treatment outcome. **Methods:** Fresh frozen (FF) biopsies (N = 123) collected during surgeries from participating institutions in Japan and Singapore were included into TriPocc. Briefly, DNA and RNA were extracted from FF biopsies and paired germline DNA were extracted from the peripheral blood mononuclear cells (PBMC). Whole-transcriptome profiling (WTP) was done by Affymetrix Human Transcriptome Array (HTA) 2.0 (N = 120) for gene expression molecular subtypes (GEMS). Whole-exome sequencing (WES) was done by Nextera Rapid Capture Custom Enrichment Kit for library preparation followed by Illumina NextSeq 500 for paired somatic and germline sequencing (N = 116). The Broad Institute Genome Analysis Tool Kit (GATK) V3.7 was used for variant calling. **Results:** High grade serous carcinoma (HGSC) was the most frequent histotype (N = 72; 60%), followed by endometrioid (N = 18; 15%) and clear cell carcinoma (N = 16; 13.3%). Mes was the dominant GEMS (N = 43; 35.8%), followed by Epi-B (N = 29; 24.2%), Stem-A (N = 27; 22.5%), Stem-B (N = 17; 14.2%), and Epi-A (N = 4; 3.3%). Unique mutations were discovered in HGSC. Top significant mutations identified (q-value lower than 1xE-9) included *ITGA4, UCN3, COL4A3, ACP2, SEH1L, AGL, FAM26F, OR5H15, EXO1, TEKT3, ZNF720, IFI44L, MERTK, TP53, DHX57, TTC31,* which were not reported previously in the TCGA cohort. BRCA1/2 mutations (26.1% of all samples) were found in 35.2% of HGSC and 13.5% of non-HGSC, which is higher than previously reported. **Conclusions:** The integrated genomic analysis from TriPocc has enabled the discovery of potentially novel molecular alterations in Asian ovarian cancers. The predictive value of these molecular alterations will be assessed once the iPocc outcome data are mature.

5563 Poster Session (Board #290), Mon, 1:15 PM-4:45 PM

Locus-specific loss of heterozygosity (LOH) in *BRCA1/2* mutated (mBRCA) ovarian tumors from the SOLO2 (NCT01874353) and Study 19 (NCT00753545) clinical trials. *First Author: Kirsten Timms, Myriad Genetics, Salt Lake City, UT*

Background: The PARP inhibitor olaparib is approved in the US for patients with mBRCA (germline) advanced ovarian cancer, and in the EU for platinum-sensitive relapsed mBRCA (germline or somatic) ovarian cancer. A recent study reported retention of a normal allele in 7% of germline *BRCA1* mutant ovarian tumors and 16% of germline *BRCA2* ovarian tumors, and suggested that absence of locus-specific LOH may be a biomarker of primary resistance to DNA damaging agents (Maxwell KN et al, Nature Commun. 2017;22:319). **Methods:** mBRCA tumors were identified from two trials with patients with platinum sensitive relapsed ovarian cancer: SOLO2 (NCT01874353), Study 19 (NCT00753545). Analysis was performed on tissue obtained at the time of diagnosis. LOH status was assigned using a genomic instability algorithm, and confirmed via human review. Both processes evaluated relative read count and allele dosage data from 54,000 independent SNPs. **Results:** 210 mBRCA tumors (144 *BRCA1*, 66 *BRCA2*) were identified in the SOLO2 cohort. 103 mBRCA (70 *BRCA1*, 33 *BRCA2*) were identified in the study 19 cohort. There was lack of locus-specific LOH observed in 1 *BRCA2* mutant in each trial. There was no statistically significant difference in the frequency of locus-specific LOH between the two cohorts. The frequencies of locus-specific LOH in the combined SOLO2 and Study 19 cohort were statistically significantly different to that reported by Maxwell et al (Table) for *BRCA1*, *BRCA2*, and combined *BRCA1/2* mutants (p = 0.001, 0.01, 0.00002, respectively). **Conclusions:** Locus-specific LOH in mBRCA tumors from the SOLO2 and Study19 cohorts was almost universal; however it is possible that selection for platinum sensitivity enriched for tumors with loss of both alleles. These data support the use of germline or tumor *BRCA1/2* testing as a means of identifying patients likely to respond to olaparib treatment in platinum-sensitive ovarian cancer. Further analysis of this phenomenon in additional cohorts will be presented. Clinical trial information: SOLO2 (NCT01874353), Study 19 (NCT00753545).

	Maxwell et al			SOLO2+Study 19		
LOH Status	***BRCA1***	***BRCA2***	***BRCA1/2***	***BRCA1***	***BRCA2***	***BRCA1/2***
Yes	48	27	75	214	97	311
No	4	5	9	0	2	2
Total	52	32	84	214	99	313
% non-LOH	7.7	15.6	10.7	0	2	0.6

5564 Poster Session (Board #291), Mon, 1:15 PM-4:45 PM

Assessing delay and barriers to risk-reducing surgery in women with BRCA mutations. *First Author: Anne Olsen, NYU School of Medicine, New York, NY*

Background: The NCCN recommends risk-reducing salpingo-oophorectomy (RRSO) for women with BRCA mutations by age 35-40 or upon completion of childbearing. We previously reported that RRSO was being performed at age 43-44; and age 46-47 when fertility considerations were excluded. Since these ages are past the NCCN guidelines, our objective was to elucidate the timing between genetic testing (GT) and risk-reducing surgery (RRS) and reasons for delay. **Methods:** We conducted a retrospective chart review to identify women with BRCA mutations who underwent RRSO between 2012-2017. We analyzed demographics, date of GT and RRS and reasons for delay in RRS. **Results:** We identified 187 patients with mutations who underwent RRS: 93 with *BRCA1* and 94 with *BRCA2*. Median age at RRS was 44 (28-77); 43 (31-77) and 45 (28-71), for *BRCA1* and *BRCA2*, respectively. The median time between GT and RRS was 9 (1-171) months (m). Fifty-six percent of patients (n = 105) had a documented reason for delay in RRS: 39 (37%) for future fertility; 25 (24%) for breast cancer (BC) treatment; 14 (13%) due to fear of surgical menopause; 10 (10%) to coordinate with simultaneous breast surgery; 17 (16%) miscellaneous. The median time of delay from mutation diagnosis to RRS among groups was: fertility, 29 (3-171) m; BC, 9 (2-36) m; menopause, 12 (4-76) m; and surgical coordination, 8 (4-13) m. Median age at RRS among groups was: fertility, 39 (31-46) years (y); BC, 45 (28-70) y; menopause, 42 (32-44) y; and surgical coordination, 52 (37-71) y. In patients undergoing RRS after diagnosis of BC, 30 of 36 (83%) had a family history that qualified them for earlier genetic testing by NCCN guidelines. Two of these BC patients had ovarian cancer at the time of RRS. **Conclusions:** Overall, patients underwent RRS within a year of mutation diagnosis. Patients comprised two distinct groups: those with fertility or menopause concerns who underwent RRS at 39-42 y, close to the NCCN recommended age; and those with BC who underwent RRS at 45-52 y. Over 80% of patients in the BC group qualified for earlier genetic screening. Obtaining a family history, referral for GT, and earlier diagnosis of mutations, prior to development of BC, will be an important step to better comply with NCCN guidelines and prevent ovarian cancer.

5565 Poster Session (Board #292), Mon, 1:15 PM-4:45 PM

PF-06647020 (PF-7020), an antibody-drug conjugate (ADC) targeting protein tyrosine kinase 7 (PTK7), in patients (pts) with advanced solid tumors: Results of a phase I dose escalation and expansion study. *First Author: Jasgit C. Sachdev, Scottsdale Healthcare, Paradise Valley, AZ*

Background: PF-7020 is an ADC comprising of a humanized monoclonal antibody against PTK7, a cleavable valine-citrulline linker and auristatin payload that is being investigated in an ongoing Phase I clinical trial in pts with advanced solid tumors resistant to standard of care (SoC). Here we report safety results and clinical activity of PF-7020. **Methods:** Eligible patients received PF-7020 intravenously once every three weeks (Q3W) in doses ranging from 0.2 - 3.7 mg/kg (mpk) in sequential dose escalation cohorts. Dose limiting toxicity (DLT) evaluation period was 21 days (cycle 1). Dose expansion cohorts of pts with advanced ovarian cancer (OVCA), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC) were treated with PF-7020 at recommended phase 2 dose (RP2D). PTK7 expression was assessed by immunohistochemistry. Adverse events (AEs) were assessed by CTCAE v4.03 and best objective response per RECIST v1.1. **Results:** As of 24 OCT 2017, 112 pts were treated with PF-7020 in dose escalation and expansion cohorts. The pharmacokinetic exposure of PF-7020 increased in a dose related manner, with a terminal half-life of 3 days at 2.8 mpk. 2 DLTs (Grade (Gr) 3 headache, Gr3 fatigue) were observed in the 3.7 mpk cohort, and a RP2D of 2.8 mpk was established. Toxicities were manageable, most AEs limited to Gr1 or 2 (no Gr5). Common treatment-related AEs were nausea, alopecia, fatigue, headache, neutropenia, and vomiting. Antitumor activity irrespective of PTK7 expression is summarized below and further enriched in PTK7 medium/high pts (not shown). **Conclusions:** Promising antitumor activity and manageable safety profile of PF-7020 were observed in pts with advanced OVCA, NSCLC and TNBC resistant to SoC. Further investigation of PF-7020 is ongoing. Clinical trial information: NCT02222922.

	Median Prior		Pts by Dose (mpk)				ORR (%)		mDOR (mo)	mPFS (mo)
Tumor	**Lines Therapy**	**Total Pts**	**1.25**	**2.1**	**2.8**	**3.7**	**(CR/PR)**	**DCR (%)**	**(min - max)**	**95% CI**
OVCA	5	44	0	1	42	1	27 (2/10)	73	4.6 (1.7 16.2)	2.9 (2.3; 5.6)
NSCLC	3	25	2	1	22	0	16 (0/4)	56	5.8 (2.8 10.1)	2.9 (1.4; 6.1)
TNBC	4	29	0	2	27	0	21 (0/6)	48	3.6 (1.1 10.4)	1.7 (1.4; 4.3)

DCR = disease control rate; mDOR = median duration of response

5566 Poster Session (Board #293), Mon, 1:15 PM-4:45 PM

Inhibition of the Wnt/β-catenin pathway to promote T-cell immunity and survival in a syngeneic mouse model of ovarian cancer. *First Author: David W Doo, University of Alabama at Birmingham, Birmingham, AL*

Background: The Wnt/β-catenin pathway downregulates protective immunity mediated by intra-tumoral CD8+T cells, resulting in immune exclusion across cancer types. WNT974 inhibits the enzyme porcupine, which controls Wnt ligand secretion. Our objective was to evaluate the effects of Wnt inhibition on tumor growth, immune response, and survival in a syngeneic mouse model of ovarian cancer (OVCA). **Methods:** C57BL/6 mice were injected subcutaneously (SC) or intraperitoneally (IP) with 7 x 10^6 ID8 mouse OVCA cells. After 28 days, WNT974 or vehicle control was administered by oral gavage for up to 28 days. SC tumors were measured with calipers and tumors were harvested for NanoString gene expression profiling. Mice with IP tumors were kept to evaluate survival, or sacrificed after 14 days of treatment and omental tumor weights and ascites volume were measured. Flow cytometry was used to evaluate the immune response in IP tumors. **Results:** In the SC model, treatment with WNT974 reduced tumor size compared to vehicle control at day 60 (22.4 vs. 41.0 mm^2, p = 0.0001). A gene signature of T cell infiltration was upregulated in SC tumors of WNT974-treated mice (p = 0.038). In the IP model, ascites volume (0.06 vs. 5.95 mL, p = 0.019) and number of ascites cells (2.60 x 10^7 vs. 7.45 x 10^7 cells, p = 0.019) were decreased after treatment with 14 days of WNT974. Analysis of the omental tumors revealed an increased ratio of CD8+ T cells to T regulatory cells in the WNT974-treated mice (2.90 vs. 1.67, p = 0.024), as well as an increased number of dendritic cells (23,613 vs. 8,332 cells, p = 0.045). A higher frequency of CD8+ T cells were found to express granzyme B (91.8 vs. 26.6%, $p < 0.0001$) and TNF-α (31.1 vs. 0.84%, $p < 0.0001$) after treatment with WNT974. Survival was significantly improved in the WNT974-treated group (p = 0.007). **Conclusions:** Using a syngeneic OVCA mouse model, treatment of ID8 tumor-bearing mice with WNT974 decreased tumor growth and ascites and prolonged survival. This effect coincided with an upregulated anti-tumor immune response, suggesting that the Wnt/β-catenin pathway may be an important immunomodulatory target in ovarian cancer.

5567 Poster Session (Board #294), Mon, 1:15 PM-4:45 PM

Phase II results of GANNET53: A European multicenter phase I/randomized II trial of the Hsp90 inhibitor Ganetespib (G) combined with weekly Paclitaxel (P) in women with high-grade serous, high-grade endometrioid, or undifferentiated, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer. *First Author: Nicole Concin, Medical University of Innsbruck, Innsbruck, Austria*

Background: Stabilized mutant p53 protein (mutp53) is a novel target in ovarian cancer. Mutp53 proteins depend on folding support by the Hsp90 chaperone. Hsp90 blockade induces degradation of mutp53, resulting in anti-tumor cytotoxicity and increased sensitivity to chemotherapeutics. The GANNET53 trial (EUDRACT 2013-003868-31, FP7 project funded by the European Union) tests the combination of Ganetespib (G) with Paclitaxel (P) in platinum-resistant epithelial ovarian cancer (PROC) patients (pts). **Methods:** Eligible pts had PROC, ≤ 4 prior chemotherapy lines, high-grade histology, disease measurable according to RECIST 1.1 or assessable according to GCIG CA-125 criteria. Pts were randomized in a 2:1 manner to receive weekly P (80 mg/m^2) + G (150 mg/m^2) or weekly P alone. Treatment was given i.v. on days 1, 8, 15 in a 28 day cycle until disease progression. Primary endpoint was PFS, secondary endpoints were OS, ORR, PFS2, safety, PRO and PK. **Results:** A total of 133 pts (median age 61 years, range 40-81) were enrolled. Median follow-up was 10.0 months in the ITT population. The study was prematurely closed for active recruitment due to unsecured drug supply with G (initially planned 222 pts). In the ITT population, median PFS was 3.5 and 5.3 months for P+G and P, respectively (p = 0.16; HR 1.3, 95%CI: 0.897-1.895). OS was 11.0 and 14.9 months, respectively (p = 0.13; HR 1.4, 95%CI: 0.902-2.171). The most frequent related gr 1/2 AEs in the P+G arm were typical transient (1-2 days) diarrhea (79% of pts), anemia (46%), nausea (41%), and peripheral neuropathy (36%), and in the P arm anemia (51%), peripheral neuropathy (47%), nausea (40%) and diarrhea (26%). Most frequent related > gr 2 AEs in the P+G arm were neutrophil count decrease (12% of pts), diarrhea (11%), and anemia (8%) and in the P arm anemia (9%), neutrophil count decrease (9%) and diarrhea (5%). ORR, PFSII and detailed safety data and analyses in PP population will be presented. **Conclusions:** The addition of G to weekly P did not improve survival in PROC patients. Clinical trial information: EUDRACT 2013-003868-31.

5568 Poster Session (Board #295), Mon, 1:15 PM-4:45 PM

Comparing the impact of dose reductions and delays on ovarian cancer patient outcomes with three-weekly versus dose dense carboplatin and paclitaxel regimens in the national prospective OPAL cohort. *First Author: Tharani Sivakumaran, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: To determine if chemotherapy dose reductions and delays in the adjuvant setting impact ovarian cancer pt outcomes. Secondary objective is comparing deliverability of three weekly and dose dense chemotherapy. **Methods:** OPAL is a national prospective study involving 958 pts with newly diagnosed epithelial ovarian (or peritoneal, fallopian tube) cancer. All pts who commenced 3 weekly Carboplatin (AUC 5/6) and Paclitaxel 175mg/m^2 (3CP) or Carboplatin (AUC 5/6) and weekly Paclitaxel 80mg/m^2(CddP) were identified from the OPAL study database. Information regarding patient demographics, treatment doses, adverse effects and clinico-pathological characteristics had been collated from medical records were identified. **Results:** Five hundred and fifty-two pts were identified from the database with 262 commencing 3CP and 290 commencing CddP. The median age at diagnosis was 62 yrs (range 21-79). The most common pathology was serous (74%) with most high grade (77%). Six cycles of chemotherapy were completed by 200 (76%) and 128 (44%) pts ($p < 0.001$) in the 3CP and CddP groups respectively. There was at least one treatment delay in 125 (48%) and 143 (49%) pts in the 3CP and CddP groups respectively. The 3CP and CddP groups had 46 (18%) and 91 (31%) pts respectively requiring at least a 15% dose reduction for Carboplatin; and 47 (18%) and 94 (32%) patients for Paclitaxel respectively. Severe haematological toxicity was experienced in 8% and 16% of pts in the 3CP and CddP group respectively and 7% experienced severe neurological toxicity in both groups. Mean relative dose intensities of Carboplatin was 93% and 85% for the 3CP and CddP group respectively; and for Paclitaxel was 86.5% and 75.5%. The median progression free survival (mPFS) was 23.3 mo vs 20.1 mo for 3CP and CddP groups (p = 0.0012). The mPFS in 3CP was 23.7 mo vs 26.5 mo in the dose reduction and no dose reduction group respectively; and for CddP group was 20.1 mo vs 20.4 mo. **Conclusions:** Dose reductions did not have an impact on mPFS. CddP had more treatment delays, dose reductions, haematological toxicities and lower completion rates than the 3CP group.

5569 Poster Session (Board #296), Mon, 1:15 PM-4:45 PM

Gene expression profiling using Nanostring technology to predict surgical outcome in advanced primary high grade serous ovarian cancer (HGSOC) patients (pts). Study of the Tumor Bank Ovarian Cancer (TOC). *First Author: Elena Ioana Braicu, Charité Universitätsmedizin Berlin, Department of Gynaecology, European Competence Center for Ovarian Cancer, Charité Campus Virchow-Klinikum, Berlin, Germany*

Background: Ovarian cancer has the highest mortality rates among gynecological cancer. Residual tumor mass after primary debulking surgery (PDS) is one of the most important prognostic factors. There are no accurate predictive tools to identify pts who won't benefit from upfront surgery. Aim was to discover and validate a debulking signature to predict surgical outcome in advanced HGSOC. **Methods:** Using *in silico* data analysis of publicly available data, we developed a 200 gene signature to differentiate between optimal vs. suboptimal debulked pts. Optimal debulking was defined as no macroscopical residual mass after PDS. The mRNA expression levels of the top 25% genes were validated in an independent cohort of 246 HGSOC pts, using Nanostring nCounter Analysis System. Only advanced stage, chemonaive HGSOC pts were included in the study. FFPEs and clinical data were provided by TOC (www.toc-network.de). Residual mass and clinical-histological parameters were documented prospectively. Surgery was performed by an experienced gynecological oncologist, between 2002-2013. The validation was performed using unsupervised hierarchical clustering (distance metric:1-correlation, complete linkage). Pts stratification in the two main clusters was assessed by Pearson's Chi-squared test with Yates' continuity correction. **Results:** 152 (61.7%) pts presented no residual mass after PDS. Median age at diagnosis was 59 years. The own generated data showed 29 differentially expressed genes between suboptimal and optimal debulked pts (Mann-Whitney U-test, $p < 0.05$). MYCN, PTCH1, MMP11, GREM1, PMEPA1, FABP4, ASPN and TGFB3 were the top differentially expressed genes ($p < 0.05$ and abs(log2FoldChange) > 0.5) between the two cohorts. Unsupervised hierarchical clustering of all measured genes, the 29 genes and the 8 top genes, showed significant phenotypical separation (p = 0.04, p = 0.00011 and p = 0.00022, respectively). **Conclusions:** Our debulking signature predicts macroscopical residual mass after PDS in advanced HGSOC. This will more likely allow pts selection for primary vs. interval debulking surgery.

5570 Poster Session (Board #297), Mon, 1:15 PM-4:45 PM

Differences in survival between Caucasians and Asians. *First Author: John K. Chan, Palo Alto Medical Foundation, San Francisco, CA*

Background: To compare the difference in the presentation and survival of Asian subgroups and whites with epithelial ovarian cancer. **Methods:** Data were extracted from the National Cancer Database between 2004-2013. Chi-squared tests, Kaplan-Meier methods, and Cox-proportional hazard models were used for statistical analyses. **Results:** Of the 81,355 women, 78,531 (96.5%) were White and 2,824 (3.5%) were Asians. Of Asians, 495 (23.5%) were Chinese, 487 (23.1%) Indian/Pakistani, 476 (22.6%) Filipino, 207 (11%) Vietnamese, 224 (10.6%) Japanese, and 219 (10.4%) Korean. Compared to Whites, Asians were younger (54 vs. 61 years: $p < 0.001$) had more early stage disease (47.8% vs. 35.0%; $p < 0.001$), non-serous histology (56.7% vs. 44.5%; $p < 0.001$), and better survival (63.9% vs. 50.6%; $p < 0.001$). Of the Asians, Korean and Vietnamese were younger at 53 years compared to Chinese, Indian/Pakistani, Filipino, and Japanese (54, 54, 55, and 59 years) Vietnamese presented with 38.2% of stage I disease compared to 37.8%, 28.8%, 36.6%, 33.8%, and 34.8% in Chinese, Indian/Pakistani, Filipino, Korean, and Japanese. The 5 years disease specific survivals for Vietnamese, Chinese, Indian/Pakistani, Korean, Filipino, and Japanese were 74%, 67.6%, 67.5%, 60.3%, 59.3%, and 53.4%, respectively ($p < 0.001$). On multivariate analysis, Chinese (HR: 0.78, 95%CI: 0.65-0.95, $p = 0.01$), Vietnamese (HR: 0.64, 95%CI: 0.47-0.87, $p = 0.005$), Indian/Pakistani (HR: 0.70, 95%CI: 0.57-0.85, $p < 0.001$) race predicted for better survival compared to whites. In addition. younger age at diagnosis (HR: 1.03, 95%CI: 1.027-1.029, $p < 0.001$), advanced stage of disease (HR: 1.98, 95%CI: 1.95-2.01), and endometrioid cell type (HR:0.72, 95%CI: 0.69-0.75, $0 < 0.001$) predicted for survival. **Conclusions:** Our data suggest that asians presented at a younger age, had more early stage disease with better survival compared to whites. More specifically, the subgroups of Chinese, Vietnamese and Indian/Pakistani have better survival compared to whites.

5571 Poster Session (Board #298), Mon, 1:15 PM-4:45 PM

Phase Ib study of anti-mesothelin antibody drug conjugate anetumab ravtansine in combination with pegylated liposomal doxorubicin in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer. *First Author: Iurie Bulat, ARENSIA Exploratory Medicine Research Unit, Institute of Oncology, Chisinau, The Republic of Moldova*

Background: Anetumab ravtansine (AR) comprises a novel fully human anti-mesothelin IgG1 antibody conjugated to the maytansinoid tubulin inhibitor DM4. A phase Ib dose escalation was conducted in patients with platinum-resistant ovarian cancer to assess overall safety, pharmacokinetics (PK) and clinical activity. **Methods:** Eligible pts with histologically confirmed, locally invasive or metastatic platinum-resistant ovarian cancer, and ECOG performance status ≤ 1 were enrolled. Pegylated liposomal doxorubicin (PLD) at 30 mg/m^{2}IV every 21 days (q3w) was administered with AR in two IV dosing schedules: 5.5 or 6.5 mg/kg q3w in 9 pts (Part I dose escalation) and at 6.5 mg/kg q3w in 12 patients (Part II expansion cohort). Tumor response was assessed based on RECIST v1.1 q6w C1-C9 and q12w thereafter. Determination of mesothelin expression in archival or fresh biopsy tumor samples by IHC (SP74, Ventana) was highly encouraged. PK of AR and PLD was performed. **Results:** A total of 21 pts were evaluable in Part I and II: mean age 61.5 yrs (range 42-77), PS 0/1 66.7%/33.3%, median prior lines of therapy 3 (range 1-10). The maximally tolerated dose (MTD) in combination was AR at 6.5 mg/kg and PLD at 30 mg/m^2 q3w. Adverse events (AEs) were similar to previously reported AEs for of each agent as monotherapy, including reversible corneal disorders, neutropenia, liver function test increases and gastrointestinal disorders. Drug-related (DR) serious AEs were low (2 pts, 9.5%). Most common grade 3-4 AEs were neutrophil count decreased (5, 23.8%) and platelet count decreased (2, 9.5%). A total of 11 pts (52%) had confirmed partial responses (PR) and 7 (33%) had stable disease for a disease control rate of 86%. Six pts (29%) had a durable PR (> 250 days). No PK interaction was observed. **Conclusions:** AR in combination with PLD showed preliminary efficacy with durable PRs in pts with platinum-resistant ovarian cancer. The safety profile was manageable. Further study of this combination is warranted. Clinical trial information: NCT02751918.

5572 Poster Session (Board #299), Mon, 1:15 PM-4:45 PM

Toxicity profile of patients with gynecological cancers (Gyne) enrolled in phase I trials. *First Author: Yeh Chen Lee, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Gyne patients enrolled in Phase I trials may be at increased risk of certain toxicities given their extent of abdominal disease and prior treatments (surgery, chemo and radiotherapy). This study aims to assess the toxicity profile of patients with and without gyne cancers enrolled in Phase I trials. **Methods:** A retrospective review of the National Cancer Institute Phase I database was conducted with trials enrolling at least 1 gyne patient over a 16-year period (1995-2015). Eligible patients required complete data collection from baseline to end of trial participation. Adverse events (AEs) were categorized by CTCAE. Each AE was counted one time and analyzed based on highest grade and drug attribution. **Results:** 4,269 eligible patients enrolled in 150 Phase I trials were identified and divided into 3 groups: 1) females with gyne cancer (n = 685); 2) females with non-gyne cancer (n = 1698); 3) males (n = 1886). Median age in each group was 56 *vs* 56 *vs* 60 years, respectively. Mean total AEs reported during treatment was highest for females with gyne cancer [mean (standard error of mean [SEM]): 17.1 (0.4) *vs* 14.7 (0.2) *vs* 13.5 (0.2)], despite being similar at baseline [mean (SEM): 7.0 (0.2) *vs* 7.4 (0.1) *vs* 7.0 (0.1)]. Differences were predominantly due to greater abdominal-related AEs, infection and myelosuppression in females with gyne cancer. Drug-related AEs were also highest for females with gyne cancer [mean (SEM): 8.3 (0.2) *vs* 6.9 (0.1) *vs* 6.2 (0.1)]. Grade 3-5 AEs were similar [mean (SEM): 2.3 (0.1) *vs* 2.3 (0.1) *vs* 2.1 (0.1)]. Discontinuations due to AEs were similar (9% vs 9% vs 10%) and deaths during treatment were higher in males (2% vs 2% vs 4%). Regarding study outcomes, females with gyne cancer remained on treatment marginally longer (4.3 *vs* 3.3 *vs* 3.1 cycles) and achieved higher objective response rates (11% *vs* 6% *vs* 3%). **Conclusions:** Gyne patients enrolled in Phase I trials experienced greater abdominal-related AEs and infection, thus warranting specific consideration. However, grade 3-5 AEs and discontinuations were similar in all groups, suggesting that toxicities were low-grade and did not compromise outcomes.

5573 Poster Session (Board #300), Mon, 1:15 PM-4:45 PM

Determinants of severe chronic fatigue among epithelial ovarian cancer survivors: A GINECO VIVROVAIRE study. *First Author: Florence Joly, GINECO and Regional Centre Control Against Cancer Francois Baclesse, Caen, France*

Background: Vivrovaire was a large case-control study comparing patients reported outcomes (PROs) between 318 Epithelial Ovarian Cancer Survivors (EOCS) without relapse ≥ 3 years after 1st line treatment and age matched controls. Severe chronic fatigue (SCF), the main end point, (26% of EOCS) was one of the most frequent reported late side effects (Joly et al, abstr 940PD, ESMO 2017). The aim of this exploratory study was to assess determinants of SCF among EOCS. **Methods:** EOCS were recruited in 27 centers. Patients filled-in PROs questionnaires: quality of life, neurotoxicity and fatigue (FACT-G, FACT-O, FACT/GOG-Ntx, FACT-F), anxiety/depression (HADS), sleep disturbance (ISI) and physical activity (IPAQ). SCF was defined as FACT-F score < 37. Variables associated with SCF ($p < 0.01$) were included in a multivariate logistic regression. **Results:** EOCS were: Median age 65[20-86] years, high level of education (52%), FIGO stage I/II (50%), III/IV (48%). Histologic subtypes were: serous 49%, endometrioid 15%, clear-cell 8%, mucinous 4%. BRCA1/2 mutations: n = 23 (15%). 98% of EOCS had surgery and 99% received platinum and taxane chemotherapy, associated with antiangiogenic agent (13%). Median follow-up was 5[2-24] years. Current treatments included psychotropic (12%) and pain medications (3%). 26% of EOCS reported SCF, 63% poor quality of sleep, 53% and 22% anxiety/depression, and 27% neurotoxicity. Only 18% of EOCS had high physical activity. Results of univariate and multivariate analysis appear in table. **Conclusions:** Depression, persistence of neurotoxicity, and sleep disturbance are the main determinants of SCF among EOCS. These symptoms should be early detected and treated.

	Univariate associations with SCF			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
Comorbidities*[a]	2.6	1.4-5	**.003**			
Psychotropic and pain medications[a]	7.4	3.5-16	**< .0001**			
Physical activity (vs High)						
Low	3.8	1.6-8.7	**.001**			
Moderate	1.3	0.6-3.2	**.517**			
Anxiety[a]	5.9	3-11	**< .0001**			
Depression[a]	20.7	10-42	**< .0001**	17.5	7.8-39	**< 0.0001**
Neurotoxicity[a]	0.8	0.8-0.9	**< .0001**	6.4	3-13.6	**< 0.0001**
Sleep disturbance[a]	6.6	3-14	**< .0001**	3.5	1.4-8.3	**0.005**

**= Diabetes, Thyroid and heart diseases, Depressive syndrome, Obesity a : yes vs no*

5574 Poster Session (Board #301), Mon, 1:15 PM-4:45 PM

First results of a prospective national controlled study: Prophylactic Radical Fimbriectomy (NCT01608074), in women with a hereditary familial risk of breast/ovarian cancer—Tolerance and pathological findings. *First Author: Eric Leblanc, Centre Oscar Lambret, Lille, France*

Background: Risk-reducing salpingo-oophorectomy is the gold standard to prevent the development of a pelvic high grade serous carcinoma (HGSC) in women at risk of breast/ovarian cancer. However, some are reluctant to perform this surgery due to significant related adverse effects. Most of HGSCs stem from the distal fimbrial part of fallopian tubes. Thus we suggested a new prophylactic procedure called radical fimbriectomy (RF), which consists of the resection of both tubes along with the fimbrio-ovarian junction (attached ovarian fragment), completed at 50 years-old or menopause by a bilateral oophorectomy. We present the first results of this operation focused on perioperative morbidity and pathological observations. **Methods:** BRCA1/2 carriers or any women with a documented familial risk of breast/ovarian cancer were first counseled to perform a classical laparoscopic RRSO. If they denied, they were offered to enter the RF controlled study. All pathological specimens were examined using the SEE-FIM protocol. Intra- and 30-day post-operative events and pathological data were recorded according to protocol. **Results:** From January 2012 to June 2014, 121 laparoscopic RF were performed. Intraoperative complications were: 1 laparo-conversion for adhesions and 2 grade I procedural hemorrhages. 20 patients (16.5%) complained of Clavien grade I, and 2 (1.7%) grade II adverse effects. Pathologically, we found one (0.8%) invasive HGSC, two (1.7%) Serous Tubal Intraepithelial Carcinoma (STIC), one (0.8%) Serous Tubal Intraepithelial Lesion (STIL) and 21 (17.7%) p53 signatures. All lesions were located at the fimbria, except the HGSC found at a tubal isthmus. **Conclusions:** In this cohort, 2.5% of patients had a diagnostic of occult tubal neoplasia, as observed in the literature. Tubal examination by a trained pathologist, using SEE-FIM protocol, is necessary to detect precancerous lesions. A longer time is still necessary to report the efficacy of RF in terms of cancer prevention. Meanwhile, we can conclude that RF is safe, well tolerated and effective in term of occult neoplasia detection. Clinical trial information: NCT01608074.

5575 Poster Session (Board #302), Mon, 1:15 PM-4:45 PM

LION-PAW: Lymphadenectomy in ovarian neoplasm-pleasure ability of women—Prospective substudy of the randomized multicenter LION study. *First Author: Annette Hasenburg, University of Mainz, Mainz, Germany*

Background: There is limited information regarding the impact of radical surgery including pelvic and para-aortic lymphadenectomy (LNE) and subsequent chemotherapy on sexuality in patients (pts.) with advanced ovarian cancer (AOC). We addressed this question within the prospectively randomized LION trial, evaluating the role of LNE in AOC. **Methods:** The Sexual Activity Questionnaire (SAQ) was used to assess sexual function in terms of its subscales activity, pleasure, and discomfort. Additionally we added the "orgasm" subscale from the Female Sexual Function Index. The questionnaire was administered together with the EORTC QLQ-C30 questionnaire at baseline before surgery, after 6, 12 and 24 months. Primary endpoint was changes in sexual function. **Results:** 495 pts. received the questionnaires. 254 pts. responded at baseline (55 sexually active, 182 sexually inactive,17 data not available (na)), 55 at 6 months, 139 at 12 and 81 at 24 months (22 active, 56 inactive, 3 data na). Median age was 60.5 years (range 21.4 – 75.8 yrs.). Discomfort evaluated as dryness of the vagina and pain during sexual intercourse was significantly worse at 12 months compared to baseline ($p < 0.001$), however, the surgical variable LNE did not show any impact on this. In contrast, the orgasm subscale showed diverging results with a deterioration from baseline to 12 months in the LNE group, but slightly improving in the no-LNE group. This difference was significant ($p = 0.02$). None of the other subscales showed significant differences between arms at any time point. **Conclusions:** A significant difference in pts. with or without LNE after 12 months regarding the ability to get an orgasm was observed in sexually active patients with AOC. This domain should be addressed when sexually active pts. are informed about the potential sequelae of systematic LNE. However, the majority of pts. in this LION substudy were sexually inactive and furthermore the compliance to respond to the sexuality questionnaire was limited. Clinical trial information: NCT00712218.

5576 Poster Session (Board #303), Mon, 1:15 PM-4:45 PM

Progression free survival (PFS) as a surrogate endpoint for overall survival (OS) in first-line advanced ovarian cancer (AOC) therapy: A Gynecologic Cancer InterGroup individual (GCIG) patient-level (IPD) analysis of multiple randomized trials. *First Author: Xavier Paoletti, Gustave Roussy Institute, Villejuif, France*

Background: OS is considered the gold standard endpoint for controlled clinical trials but it requires extended follow-up (median OS > 40 months for first line therapy) and large sample sizes. Our objective was to evaluate whether PFS based on CA125 measurements confirmed by radiological exam or on combined GCIG criteria is a surrogate endpoint for OS in AOC. **Methods:** Using the meta-analytic approach on trials published after 2000, correlations between PFS and OS at the individual level, and between treatment effects on PFS and on OS at the trial level, were estimated using Kendall' tau and copula bivariate (R^2_{Copula}) models respectively. Criteria for PFS surrogacy required $R^2_{Copula} \geq 0.80$. **Results:** We analyzed IPD from 8,973 patients enrolled in 15 randomized first line trials of standard (n = 7), intensification (n = 5) and maintenance (n = 3) chemotherapies or targeted treatments. No heterogeneity in the treatment effects across trials was detected. High correlations were found at the individual level (tau = 0.69) but low correlation at the trial level ($R^2_{Copula} = 0.03$). Sub-group analyses led to similar results. **Conclusions:** This large IPD meta-analysis did not establish PFS as a surrogate endpoint for OS in first line treatment of AOC, but the analysis was limited by the narrow range of treatment effects observed and post study treatment. Additional trials are being collected that will enable us to refine the sub-groups analyses. Table of results

Endpoint / Trial type	Trials N (pts)	tau[a]	R^2_{Copula}
Overall	15 (8973)	0.69	0.03
CA125 confirmed by radiological exam	9 (5126)	0.67	0.16
GCIG criteria	4 (2548)	0.7	0.14
Carbo-Tax as control	9 (5807)	0.72	0.05
Standard or intensification	12 (7703)	0.71	0.10
Maintenance	3 (1270)	0.64	0.14

[a]tau and R^2 values range from 0 (no association) to 1 (perfect correlation).

5577 Poster Session (Board #304), Mon, 1:15 PM-4:45 PM

Phase 1b study of oncolytic vaccinia virus GL-ONC1 in recurrent ovarian cancer (ROC). *First Author: Robert W. Holloway, Gynecologic Oncology Program, Florida Hospital Cancer Institute, Orlando, FL*

Background: Immunotherapy can trigger immune activation including tumor-infiltrating CD8+ T cells, leading to antitumor response and survival benefits. Immunotherapeutic GL-ONC1 (modified vaccinia virus) causes oncolysis, immune activation and durable anti-cancer memory. **Methods:** Intraperitoneal infusion of GL-ONC1 monotherapy was given at higher repeated doses compared to a previous Ph1 trial in patients (pts) with platinum refractory/resistant disease. Primary endpoint: adverse events; Secondary endpoints: anti-tumor response by RECIST1.1 & survival. Eleven heavily pretreated pts with end-stage ROC were enrolled: 3-4 prior lines (n = 3), ≥ 5 lines (n = 8), ECOG 0 (n = 7) or 1 (n = 4), ascites/pleural effusion (n = 9) & progressive disease (PD) at baseline (n = 10). There were two dose cohorts: 3×10^9 (n = 6) or 1×10^{10} (n = 5) plaque forming units/day on 2 consecutive days. **Results:** (1) Adverse reactions included Grade 1-2 chills (n = 7), nausea (7), fever (6), abdominal pain/distention (4), & vomiting (3). There were no differences in toxicity for the two dose levels. (2) GL-ONC1 colonized and replicated in the tumor, as indicated by a virus-encoded glucuronidase assay. (3) Clearance of tumor cells in ascites with induction of lymphocyte infiltration was shown in 5 pts with ascites. (4) Reduction of circulating tumor cells (CTC) was identified in 6/8 (75%) pts who had baseline CTC, ranging 1-42 per 7.5 mL blood. (5) Enhanced infiltration of CD8+ T cells into tumor tissue was demonstrated by repeat biopsy. (6) Disease Control Rate (DCR = partial response (PR) + stable disease (SD) ≥ 15 weeks) was 6/11 (55%). (7) Extended progression-free survival (PFS) of 23, 35, 59 (with confirmed PR) & 71 weeks were observed in 4 pts, respectively. (8) A tumor-specific T cell response was absent at baseline but confirmed at Week-30 in the PR patient by IFN-γ ELISPOT assay. (9) More than doubling of PFS compared to the last chemotherapy regimen was recognized in 4/11 (36%) pts. **Conclusions:** Promising safety data, anti-tumor activity, and immune activation mechanisms were documented in this Ph1b trial, and a Ph2 trial (VIRO-15) is currently enrolling. Future studies combining GL-ONC1 and other immune therapies and/or chemotherapy are under consideration. Clinical trial information: NCT02759588.

5578 Poster Session (Board #305), Mon, 1:15 PM-4:45 PM

Platinum based chemotherapy selects for PDGFRα dependent angiogenesis. *First Author: Nuala McCabe, Almac Diagnostics, Craigavon, United Kingdom*

Background: Patients with High Grade Serous Ovarian Cancer (HGSOC) initially respond to SOC platinum based treatment but most will eventually relapse with platinum resistant disease. Angiogenesis is known to be an integral pathological feature of HGSOC and anti-angiogenic agents have been trialed in this population, but have failed to demonstrate a significant impact on overall survival (OS). Here, we asked if platinum resistance could be associated with an improved response to anti-angiogenic therapies. **Methods:** A meta-analysis of 14 phase II and III clinical trials in EOC were used to investigate the association between platinum resistance and response to anti-angiogenic agents. In addition we analysed gene expression in 12 matched pre-and post-chemotherapy samples. Novel cisplatin-resistant HGSOC cell lines and novel ascites-derived primary cell lines from HGSOC patients with known outcomes following platinum-based chemotherapy were developed to investigate the relationship between angiogenesis and platinum resistance. **Results:** The meta-analysis revealed an OS benefit for anti-angiogenics in platinum-resistant disease ($p = 0.029$), whilst platinum-sensitive disease derived only PFS benefit ($p = < 0.0001$). In the matched pairs of patient samples, post-platinum samples had a higher micro-vessel density (MVD) relative to their paired treatment-naïve sample ($p = 0.0001$). Additionally, an *in vivo* angiogenesis matrigel plug assay demonstrated that cisplatin-resistant EOC cell lines were associated with an increase in MVD ($p = < 0.0001$). MVD was reduced in the platinum-resistant cells following treatment with bevacizumab ($p = 0.001$). Ascites-derived cells established from platinum-resistant patients demonstrated overexpression of VEGF-A through increased PDGFRa and PDGFRb expression. **Conclusions:** We have demonstrated that previous platinum therapy for EOC is associated with an increase in tumour PDGFα and VEGF-A expression, correlating with a response to anti-angiogenic therapies. This data suggests that platinum therapy resistance may inform the selection of EOC patients for novel anti-angiogenic therapies in future clinical trials.

5579 Poster Session (Board #306), Mon, 1:15 PM-4:45 PM

Paired somatic and germline genetic testing for ovarian cancer patients: Observations, benefits and implications for treatment. *First Author: Daniel Chen, Ambry Genetics, Aliso Viejo, CA*

Background: Germline and somatic genetic testing have traditionally been offered separately; however, the clinical applications of these tests are now converging with continued FDA approval of targeted therapies for both germline and somatic mutation carriers. This study aims to describe the findings of a paired testing (germline and somatic) approach among ovarian cancer (OC) patients. **Methods:** Study participants consisted of 95 consecutive OC patients undergoing paired testing at a clinical diagnostic laboratory. Eleven OC predisposition genes in the homologous recombination (HR) repair pathway were targeted by capture-based NGS: *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MRE11A, NBN, PALB2, RAD51C,* and *RAD51D*. Paired analysis of sequence data from both tumor (minimum of 20% neoplastic cellularity) and blood specimens was performed to differentiate variants of somatic vs. germline origin. Customized NGS pipelines and/or microarray were used to detect gene copy number variants. Additional test results included hypermethylation analysis of *BRCA1* and *RAD51C* promoter regions by methylation-specific PCR, when available. **Results:** In total, 41 patients (43.2%) were eligible for PARP-inhibitor therapy based on the presence of a germline (n = 3, 7.3%), somatic (n = 34, 82.9%) or germline and somatic (n = 4, 9.8%) *BRCA1* or *BRCA2* pathogenic mutation. Of 38 (40.0%) patients with somatic alterations, 3 (7.9%) had sequencing mutations, 32 (84.2%) had whole gene deletions of *BRCA1* and/or *BRCA2*, and 3 (7.9%) had both alteration types. Somatic whole gene deletions of *BRCA1* or *BRCA2* were often accompanied by gains or losses of other genes in the tumor. Twenty-nine patients (30.5%) were germline and tumor *BRCA1/2*-negative, but tested positive for germline or somatic pathogenic mutations in other HR genes or tumor promoter methylation in *BRCA1* or *RAD51C*. **Conclusions:** Our findings highlight the benefits of paired testing over germline and/or somatic testing alone, such as concurrent confirmation of germline mutations and maximizing detection of patients who would benefit from therapy. Further research is needed to determine the impact of paired testing on healthcare costs and patient outcomes.

5580 Poster Session (Board #307), Mon, 1:15 PM-4:45 PM

Phase I study of carboplatin (C), pegylated liposomal doxorubicin (PLD) and everolimus (E) in platinum-sensitive epithelial ovarian, Fallopian tube or primary peritoneal cancer in first relapse (NCT01281514). *First Author: Lainie P. Martin, Fox Chase Cancer Center, Philadelphia, PA*

Background: The PI3K/AKT/ mTOR pathway may play an important role in chemotherapy resistance in ovarian cancer. (E) is an orally administered mTOR inhibitor approved for multiple indications. This Phase I trial evaluated the feasibility of combining E with C and PLD in women with recurrent, platinum sensitive ovarian cancer. **Methods:** Patients were administered C AUC 5 with PLD 30 mg/m2 on 28 day cycles, and escalating doses of E, starting at 2.5 mg/day. Planned Phase I doses of E were 2.5 mg/d, 5 mg/d, 7.5 mg/d and 10 mg/d. The study used a modified TITE-CRM design with a requirement that cohort 1 complete 6 cycles of chemotherapy with E at 2.5 mg/d prior to dose escalation. The primary endpoint was safety and tolerability. **Results:** 21 patients were treated on study. There was a DLT of rash at dose level(DL) 1, 2.5 mg/d; patient discontinued treatment on trial after cycle 1. 5 additional patients completed 6 cycles at DL1 without DLT. 3 patients completed 6 cycles of treatment at DL3, 7.5 mg/d, but 2 experienced DLT and required dose reduction. 12 patients were enrolled at DL2; no DLTs were seen at DL2. 7 patients completed 6 cycles without dose modification. 1 patient required dose modification of E for thrombocytopenia. 2 patients stopped treatment early due to disease progression. 2 patients experienced hypersensitivity reactions to Doxil, and failed desensitization. They were permitted to remain on study with C and E, but were considered inevaluable. DLTs included rash,(n = 1 at DL1), headache (n = 1 at DL3) and thrombocytopenia (n = 1 at DL3). The most common AEs included neutropenia, anemia, stomatitis, rash, nausea, vomiting, diarrhea and constipation (42-90%). Grade 3 AEs included neutropenia (n = 3), thrombocytopenia (n = 2), stomatitis (n = 1), rash (n = 1) and PE/DVT (n = 2). The MTD of E in combination with C and PLD was determined to be 5 mg/d. 3 patients experienced a CR and 11 patients experienced a PR, for a RR of 67%. 3 patients experienced stable disease and 3 experienced disease progression. **Conclusions:** C with PLD and E at 5 mg/day is tolerable with intriguing activity in women with platinum sensitive relapsed ovarian cancer. Clinical trial information: NCT01281514.

5581 Poster Session (Board #308), Mon, 1:15 PM-4:45 PM

Clear cell ovarian cancer (CCOC): 115 patient (pt) series showing access to experimental therapy may improve response rates in recurrent disease. *First Author: Michael-John Devlin, University College London Hospitals, London, United Kingdom*

Background: 10 year survival for ovarian cancer (OC) in the UK has improved from 18% (1971) to a predicted survival of 35% (2011). Historical data show pts with advanced CCOC have worse survival compared to other histological subtypes of epithelial OC. We sought to determine treatment type and outcome of CCOC pts at 2 UK gynaecological cancer centres. **Methods:** Medical records of pts with CCOC treated between 2002 and 2017 were reviewed. Data collected comprised pt and tumour characteristics, treatment and outcome. **Results:** 115 pts, median age 56 (29-86) years (y) with CCOC were identified: stage (S) I (62), II (16), III (23), IV (8) and unknown (6). 91 pts had pure CCOC and 24 had mixed histopathology: endometrioid (83%), serous (12%), other (5%). Endometriosis co-existed in 43 (37%) pts; 34 pure CCOC, 8 mixed endometrioid. BRCA mutations were present in 4/19 tested and MMR loss in 2/8 tested. 21/23 pts with a thromboembolic event and 9/10 pts with hypercalcaemia (2.72-3.63mmol/L) had advanced or recurrent disease. 19 pts had a prior or synchronous malignancy, most commonly endometrial (8) or breast (6). Primary refractoriness to first line treatment occurred in S I (3%), III (13%) and IV (100%) CCOC with median overall survival (OS) of 224 days (d). Recurrence rates were 22% (S I), 38% (S II) and 61% (S III). Molecular targeted agents (MTA) were used in 29 treatments; bevacizumab (45%), nintedanib (17.5%), PARP combination (10%), PI3K/mTOR inhibitor (10%), other novel agent (17.5%).33pts had 2nd line treatment with overall response rate (ORR) of 30% and progression free survival (PFS) 258d. 12/33pts treated with a regimen containing a MTA had PFS 358d vs 228d for those without. ORR in the 3rd line was 14% with PFS 185d. The OS rate at 1y was 98% (S I), 100% (S II), 86% (S III) and 0% (S IV) and at 5y was 81% (S I), 50% (S II) and 23.5% (S III). **Conclusions:** Late stage CCOC has a phenotype distinct to early stage with a propensity to be treatment resistant, recur, have paraneoplastic manifestations and poor survival. The 2nd line ORR of 30% in our cohort is higher than expected and may reflect increased MTA use. 21% and 25% pt had a BRCA variant or MSI loss suggesting benefit of testing CCOC.

5582 Poster Session (Board #309), Mon, 1:15 PM-4:45 PM

Efficacy and immune modulation of the tumor microenvironment with the combination of the PARP inhibitor rucaparib and CD122-biased agonist NKTR-214. *First Author: Andrew Simmons, Clovis Oncology, San Francisco, CA*

Background: NKTR-214 is a biased agonist of the IL2Rbg (CD122) pathway that activates and mobilizes CD8 T and NK cells into the tumor microenvironment. The PARP inhibitor rucaparib has demonstrated activity in *BRCA* mutant deficient tumors through synthetic lethality. We hypothesized that PARP inhibition in a *BRCA* syngeneic model would lead to immunogenic cell death and synergize with NKTR-214 through antigen priming and enhanced activation of newly infiltrated intratumoral T and NK cells. **Methods:** Mice (n = 10/group) were inoculated with the murine ovarian tumor cells (BR5FVB1) harboring genetic alterations (TP53-/-, BRCA1-/-, myc and Akt) frequently present in human ovarian carcinomas. Tumors were grown to 125 mm^3 prior to treatment with vehicle, rucaparib (150 mg/kg BID x 28 days), NKTR-214 (0.8 mg/kg q9d x 3), or the combination and tumor volumes were measured. Immune modulation was evaluated by IHC and gene expression. **Results:** Treatment with the combination resulted in 88.5% tumor growth inhibition (day 22; $p < 0.0001$), and tumors were monitored for regrowth after 28 days of dosing. Tumor volume nadir was 94.5 mm^3 on day 38 for rucaparib treated animals and progressed to > 1000 mm^3 by day 59. In contrast, 50% of mice treated with NKTR-214 and rucaparib combination were tumor free on day 113, suggesting development of immune memory. The combination of NKTR-214 and anti-PD1 in the same model did not provide tumor-free mice. An increase in infiltrating T cells, NK cells, dendritic cells, and neutrophils, as well as the induction of interferon-gamma induced chemokines was observed with the combination of rucaparib and NKTR-214 by expression profiling. IHC staining also showed significant increases in CD3, CD4 and CD8 T cells with the combination ($p < 0.05$). **Conclusions:** The novel combination of NKTR-214 plus rucaparib results in durable complete responses in a genetically-relevant ovarian tumor model. Profiling of tumors suggested the activity of this combination is through antigen priming of infiltrating memory T cells, increased NK cell numbers, and enhanced cytotoxicity of immune infiltrates into the tumor.

5583 Poster Session (Board #310), Mon, 1:15 PM-4:45 PM

A gene expression prognostic signature for overall survival in patients with high-grade serous ovarian cancer. *First Author: Joshua Millstein, Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Median survival for high-grade serous ovarian cancer (HGSOC) patients is 3-4 years with a wide range of outcomes. Gene expression patterns have been reported to be predictive of outcome, but results have been inconsistent. The aim of this study was to assess the predictive utility of genes previously associated with outcome and to develop a clinically useful predictor for overall survival (OS). **Methods:** We identified 200 genes associated with prognosis from a meta-analysis of previously published gene expression profiling studies in HGSOC and selected an additional 313 candidate genes. Expression in formalin fixed paraffin embedded (FFPE) HGSOC tumor tissue was measured with Nanostring for 3770 women with known OS. Regression-based and machine learning methods were used to develop a prognostic signature for OS. These approaches included stepwise regression, elastic net penalized regression, random survival forests, and component-wise gradient boosting. Models were trained and tested on approximately 2/3 of the data and the best performing model was evaluated on the remaining 1/3. **Results:** In single gene Cox models for OS adjusted for age and stage, there were 275 significant associations (false discovery rate (FDR) < 0.05). The two most significant genes were *TAP1* ($p = 2.2e\text{-}17$; hazard ratio (HR) = 0.84 (0.81, 0.87)) and *ZFHX4* ($p = 1.3e\text{-}15$; HR = 1.19 (1.14, 1.25)). Elastic net yielded the best performing signature in the training data, and in the validation data it was substantially more prognostic than any individual gene (HR = 2.42 (2.09, 2.81), scaled to 1SD). The area-under-the-curve (AUC) for the signature combined with age and stage for 5yr OS was 0.74, substantially larger than the AUC for age and stage alone (0.62). **Conclusions:** These data confirm previously reported or hypothesized associations between gene expression in HGSOC tumor tissue and overall survival. Our signature could be useful in designing clinical trials for patients who are destined to have poor survival, thereby delivering new agents to the patients who are in the most urgent need. Identification of genes associated with the outcome also provides the opportunity to develop targeted therapeutic approaches.

5584 Poster Session (Board #311), Mon, 1:15 PM-4:45 PM

Phase III randomized trial of maintenance pegylated liposomal doxorubicin (PLD) / carboplatin versus without in patients with advanced ovarian cancer: An Asian Gynecologic Oncology Group study. *First Author: Chyong-Huey Lai, Department of OB/GYN, Chang Gung Memorial Hospital, Taoyuan, Taiwan*

Background: An Asian Gynecologic Oncology Group (AGOG) phase III randomized trial was conducted to determine whether maintenance chemotherapy after complete remission could improve progression-free survival (PFS) in FIGO stages III/IV ovarian cancer. **Methods:** Between June 2007 and September 2014, 45 patients were enrolled and randomized (1:1) with stratification factor of residual tumor and stage. One patient was found ineligible shortly after registration and randomization and was excluded without treatment. Twenty-three patients were randomized to arm A (4-weekly carboplatin AUC4 and liposomal doxorubicin 30 mg/m^2) for six cycles and 21 patients were randomized to arm B (observation). The primary endpoint was PFS. Overall survival (OS) was calculated as secondary end-point. **Results:** Enrollment was slow, therefore a decision of closing accrual was made by the AGOG Board meeting when 7+ years had lapsed. We ended the study after the last enrolled patient had completed 3-year follow-up. With a median follow-up of 80.1 months, 30 patients experienced cancer progression (14 [60.9%] for arm A and 16 [76.2%] for arm B). The median PFS was significantly better in arm A (38.9 months) than arm B (9.2 months) (log-rank p = 0.038), and the median OS was marginal better in arm A (not applicable, > 50 % of patients were alive at study end) than arm B (42.8 months) (log-rank p = 0.117). Overall rates of grade 3/4 adverse events were 60.9 % for arm A and 0.0 % for arm B ($p < 0.001$). Grade 3/4 including neutropenia were more frequent in arm A than arm B with 30.4% and 0.0%, respectively (p = 0.0094). **Conclusions:** Despite limitation in small sample size, it suggests that maintenance chemotherapy after complete remission could be beneficial significantly improving PFS in stages III/IV ovarian cancer. Clinical trial information: ACTRN12607000329460.

5585 Poster Session (Board #312), Mon, 1:15 PM-4:45 PM

Histone deacetylase inhibition alters tumor phenotype and stimulates a productive anti-tumor immune response in preclinical models of ovarian cancer. *First Author: Tyler McCaw, University of Alabama, Birmingham, Birmingham, AL*

Background: Ovarian cancer remains the most deadly gynecologic malignancy. Chemotherapy and surgical reduction are initially effective but most patients relapse with chemoresistant disease. Immunotherapy is currently being evaluated in multiple clinical trials as a treatment modality for ovarian cancer, but response rates as a single agent have been disappointing. Because an altered epigenetic framework contributes to malignant transformation and immune escape in ovarian cancer, our objective was to evaluate whether histone deacetylase (HDAC) inhibition could reorient the suppressive tumor microenvironment and stimulate a productive anti-tumor immune response. **Methods:** Syngeneic ovarian cancer cells (ID8 or ID8 p53-/-) were injected into the peritoneal cavity of C57BL/6 mice and treated daily with 20mg/kg entinostat or vehicle, starting on day 21. First, we assayed transcript-level changes in gene expression of whole tumor lysates using the NanoString PanCancer Immune Profiling Panel. Next, we used flow cytometry to assess the number and function of T cells in the tumor and ascites. **Results:** HDAC inhibition increased expression of genes associated with T and NK cell infiltration, cytolytic functions, major histocompatibility class I and class II, as well as other genes associated with immune recognition. In addition, entinostat significantly reduced the number and suppressive capacity of regulatory T cells in both the tumor and ascites. Notably, HDAC inhibition led to infiltration of higher quality CD8 cytotoxic T cells with superior effector functions. These CD8 T cells expressed lower levels of the exhaustion-associated transcription factor Eomes, suggesting they will remain highly functional for a longer amount of time and are less susceptible to exhaustion. **Conclusions:** Our results suggest entinostat could dramatically increase tumor immunogenicity and help turn a "cold" (non-inflamed) tumor into a "hot" (T cell inflamed) tumor, while potentiating anti-tumor T cell functions. Thus, inclusion of HDAC inhibition may increase the frequency of patients responding to checkpoint blockade and/or other immunotherapies.

5586 Poster Session (Board #313), Mon, 1:15 PM-4:45 PM

Genomic profiling of lymph node metastases in endometrial cancer and association with volume of metastasis. *First Author: Stephanie Sullivan, University of North Carolina, Chapel Hill, NC*

Background: Lymph node (LN) metastasis and genomic profiles are important prognostic factors in endometrial cancer (EC). However, the prognostic significance of the volume of metastatic disease found in sentinel lymph node (SLN) specimens is unknown. We sought to determine if particular genomic mutations were associated with LN metastasis and volume of LN metastasis. **Methods:** Surgically staged women with EC at a single institution were enrolled in a genetic sequencing institutional protocol. Relevant targets were enriched by a custom designed Agilent SureSelect hybrid capture enrichment library using standard protocols. A subset of the EC population underwent SLN biopsy with completion lymphadenectomy and hysterectomy as part of the FIRES study. SLN specimens underwent ultrastaging to detect low volume disease such as isolated tumor cells (ITCs). **Results:** 345 patients with EC completed surgical staging and tumor sequencing between 3/2007 and 9/2016; median age 63 yrs and median BMI 34.2 kg/m^2. 55 patients (16.0%) were LN positive (LN+) while 290 (84.0%) were LN negative (LN-). The LN+ group were less likely to have endometrioid histology than the LN- group (54.5% vs 77.2%) and more likely to have grade 3 disease (65.5% vs 33.1%) ($p < 0.001$ for both). LN+ patients were more likely than LN- patients to have p53 mutations (44.4% vs 27.0%, $p = 0.02$), and less likely to have PTEN mutations (38.9% vs 59.1%, $p = 0.01$). Polyclonality of PIK3CA mutations (defined as > 2 mutations in the same tumor) was only observed in the LN- patients ($p = 0.08$). 44 patients had a staging with SLN biopsy. Of these, 8 (18.2%) had ITC's as their only metastatic disease. All ITC patients with p53 mutations were of non-endometrioid histology (3/8). PTEN (80.0%) and PIK3CA (60.0%) mutations were observed in the endometroid ECs. No patients with ITCs had a recurrence. **Conclusions:** Primary tumors associated with LN metastases have both genomic mutations and histologic features consistent with more aggressive disease. In patients with low volume (ITC's) metastases, genomic mutations aligned with histology. More work is needed to better define the relationship between genomic mutations, histology, metastatic volume and prognosis.

5587 Poster Session (Board #314), Mon, 1:15 PM-4:45 PM

Adjuvant therapy may decrease disparities in outcomes for black endometrial cancer patients. *First Author: Fan Zhu, Presence St. Joseph Hospital, Chicago, IL*

Background: Prior literature reports worse survival in Black (B) endometrial cancer patients compared to White (W) counterparts. This study compares outcomes between B and W patients after accounting for clinicopathologic (CP) factors and treatment. **Methods:** From 2006-2014, 305 (169 B and 136 W) patients with endometrial cancer treated at a single hospital were identified. CP features, treatment, and outcome data were collected. 201 (117 B and 84 W) with surgery and follow up were included in analysis. KM curves and log-rank test were performed to compare survival. Multivariable analysis (MVA) with Cox model was fitted for outcomes accounted for patient features, tumor details and treatment. To assess the stability of parameters and significance, an imputation analysis was performed. **Results:** Analysis showed that B and W patients had similar BMI, Charlson Comobidity Index (CCI), smoking history, stage, depth of invasion, and nodal involvement. B patients were older ($P < 0.06$) and had more non-endometrioid histology ($P < 0.005$) and lymphovascular invasion (LVI) ($P < 0.05$). Radiotherapy (RT) was used in 43% B and 30 % W ($P = 0.069$), and chemotherapy in 38% B and 27% W ($P = 0.08$), respectively. On MVA, non-endometrioid histology (HR = 10; $P < 0.05$), smoking (HR = 4.18; $P < 0.05$) and higher CCI (HR = 1.39; $P < 0.05$) were associated with worse OS. Race was not a predictor of OS. G3 endometrioid histology (HR = 16.14; $P < 0.05$), non-endometrioid histology (HR = 22.78; $P < 0.005$), smoking (HR = 3.32; $P < 0.05$) and higher CCI (HR = 1.41; $P < 0.05$) portended worse DFS. Early-stage improved DFS (HR = 0.16; $P < 0.005$). The 5-yr OS for B and W were 37% (SE 0.08) and 44% (SE 0.13) ($p = 0.164$) and the 2-yr DFS for B and W were 77% (SE 0.05) and 91% (SE 0.04), respectively ($p = 0.215$). For patients with known recurrence (N = 35), smoking (HR = 11; $P < 0.005$) and higher CCI (HR = 1.45; $P < 0.05$) portended worse OS; EBRT (HR = 0.07; $P < 0.05$) and W race (HR = 0.123; $P < 0.05$) predicted longer time to recurrence. **Conclusions:** While high risk CP features were associated with worse outcomes as expected, the more high risk features in B patients did not lead to worse outcomes. One explanation for this could be adjuvant therapy, which was implemented at least similarly between races in this study.

5588 Poster Session (Board #315), Mon, 1:15 PM-4:45 PM

Differences in survival outcomes in advanced endometrial cancer due to variation in adjuvant therapy and histology. *First Author: Emily Meichun Ko, University of Pennsylvania, Philadelphia, PA*

Background: To determine the impact on overall survival (OS) of the sequence-order of adjuvant radiation (RT) and chemotherapy (CT) on different advanced endometrial cancer (EC) histologies. **Methods:** Stage 3 endometrioid (EAC), serous (SER), clear cell (CC), and carcinosarcoma (CS) patients who underwent primary surgical staging from 1999-2011 were identified in SEER-Medicare. Sequence, timing, and modality of RT and CT were analyzed using Kaplan-Meier estimates, log rank tests, and multivariable cox modeling. Treatment groups with $n < 10$ were excluded in cox modeling. **Results:** Of 2375 cases identified (1537 EAC, 485 SER, 96 CC, 257 CS), 31.3% received no AT. The remainder received RT or CT alone, concurrent RT-CT, serial or sandwich modalities (table 1). OS differed by receipt of AT overall as well as within each histologic subtype (log rank $p < 0.05$, all). After adjusting for age, race, substage, region, and histology, all patients receiving AT except for concurrent RT-CT followed by CT, had improved OS over no treatment (all $p < 0.05$). However, differences by histology were seen. For EAC the sandwich arm had the greatest reduction in death (72%), whereas for SER and CC the concurrent RT-CT arms fared best. For CS receipt of any CT improved OS, whereas above RT alone did not. (Table1). **Conclusions:** OS for advanced EC significantly differs by histology and mode of adjuvant therapy. Future studies should evaluate whether sandwich therapy for EAC, concurrent RT-CT for SER and CC, and CT alone for CS may most effectively improve OS.

Adjuvant therapy: adjusted HR for OS.

Type of AT	(%)	All histology	EAC	SER	CC	CS
None	31.3	ref	ref	ref	ref	ref
RT	26.2	0.80 (0.71, 0.91)	0.78 (0.67, 0.92)	0.96 (0.67, 1.36)	0.90 (0.45, 1.81)	0.73 (0.49, 1.09)
CT	24.8	0.60 (0.52, 0.70)	0.60 (0.48, 0.74)	0.69 (0.53, 0.90)	0.60 (0.26, 1.36)	**0.45 (0.30, 0.67)**
Concur RT-CT	9.5	0.51 (0.41, 0.64)	0.60 (0.45, 0.79)	**0.43 (0.26, 0.69)**	**0.29 (0.10, 0.82)**	**0.50 (0.29, 0.87)**
Serial CT- RT	4.4	0.52 (0.38, 0.72)	0.56 (0.37, 0.84)	0.68 (0.38, 1.22)		
Serial RT-CT	1.6	0.60 (0.39, 0.93)	0.55 (0.32, 0.95)			
Sandwich	1.3	0.53 (0.31, 0.90)	**0.28 (0.12, 0.69)**			
Concur RT-CT, then CT	0.6	0.69 (0.32, 1.46)				

5589 Poster Session (Board #316), Mon, 1:15 PM-4:45 PM

Analysis of patient-reported outcomes (PROs) for GOG-258, a randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel (Cis-RT+CP) vs. carboplatin and paclitaxel (CP) for optimally debulked, locally advanced endometrial carcinoma: A Gynecologic Oncology Group/NRG study. *First Author: Ursula A. Matulonis, Dana-Farber Cancer Institute, Boston, MA*

Background: Protocol GOG-258 randomized Cis-RT+CP or CP for 6 cycles to patients (pts) with stage III/IVA endometrial carcinoma (Matei et al, ASCO 2017). Recurrence-free survival was the primary endpoint and was not increased by addition of RT. PRO analyses evaluated the impact of treatment (tx) on quality of life (QOL) during tx and up to 1 year. **Methods:** PROs were assessed at baseline prior to tx, 6 weeks (wks) after starting tx (corresponding to 1-wk post completion of RT (Cis-RT+CP) or prior to cycle 3 (CP)), and 18 and 70 wks after tx start. The analysis used FACT-En TOI, FACT/GOG-neuropathy (Ntx) subscale, and FACT-C items C3, C5 combined with En1, O1, O3, Cx6 in TOI of FACT-En for gastrointestinal (GI) symptoms (exploratory). **Results:** Questionnaire compliance was 95% at baseline, 90% at 6 wks, 87% at 18 wks, and 78% at 70 wks after tx start. Pts (332 on Cis-RT +CP and 349 on CP) with valid baseline and ≥ 1 follow-up PRO assessments were evaluable for analysis. After adjusting age and baseline scores, pts receiving Cis-RT+CP reported 5.2 points (97.5% CI: 2.7~7.8; adjusted $p < 0.001$) lower TOI scores on average at 18 wks (end of tx) compared to CP. The tx difference remained statistically significant at 70 wks (3.4 points lower on Cis-RT+CP group; 97.5% CI: 0.7~6.2; adjusted $p = 0.022$); none exceeded the 6 point difference pre-set as "clinically meaningful." Pts in both groups reported increased chemo-induced Ntx symptoms since tx start, but pts on CP reported 2.0 points lower (worse Ntx symptoms) (97.5% CI: 1.4~2.6; adjusted p-value < 0.001) in the Ntx subscale score at 6 wks (post 2 cycles of chemo) than those receiving RT. Pts on Cis-RT+CP reported significantly worse GI symptoms compared to CP arm pts at all assessments. **Conclusions:** The Cis-RT+CP group experienced overall worse QOL and GI toxicity; both groups reported neuropathy which did not return to baseline by 1 year. PRO differences observed with Cis-RT+CP and CP may influence choice of treatment for locally advanced endometrial cancer. Clinical trial information: NCT00942357.

5590 Poster Session (Board #317), Mon, 1:15 PM-4:45 PM

Assessment of activating estrogen receptor 1 (*ESR1*) mutations in gynecologic malignancies. *First Author: Stephanie Gaillard, Duke Cancer Institute, Durham, MD*

Background: Endocrine therapy is often considered to treat hormone-responsive gynecologic (gyn) malignancies. Mutations in *ESR1* leading to constitutive transcriptional activity have been reported in estrogen receptor positive (ER+) breast cancers and may contribute to acquired resistance to endocrine therapy. Using comprehensive genomic profiling (CGP) we assessed the frequency of *ESR1* activating genomic alterations (GA) in gyn malignancies. **Methods:** DNA from FFPE tumor tissue obtained during routine clinical care for 9645 gyn malignancies (ovary, fallopian tube, uterus, cervix, vagina, vulvar, and placenta) was analyzed for all classes of GA [base substitutions (muts), indels, rearrangements, and amplifications] in *ESR1* by hybrid capture, next generation sequencing. **Results:** 295 ESR1 GA were identified in 285 (3.0%) cases; 10 cases contained 2 ESR1 GA each. *wtESR1* amplifications were identified in 80 (0.8%) cases and *mutESR1* were present in 86 (0.9%) cases. *mutESR1* were more common in uterine compared to other cancers (2.0% vs $< 1\%$, $p < 0.001$). *mutESR1* were also enriched in carcinomas with endometrioid histology: 4.2% in uterine endometrioid vs 0.2% in uterine serous carcinomas ($p < 0.001$) and 3.5% in ovarian endometrioid compared to 0.3% in ovarian serous carcinomas ($p < 0.001$). The Y537S, D538G, L536P, and S463P mut comprised 35%, 17%, 13%, and 12%, respectively, of all *mutESR1*. Clinical data for multiple gyn malignancy patients demonstrate that *mutESR1* may be a *de novo* or acquired endocrine resistance mechanism. Low-grade serous ovarian cancer (LGSOC) samples obtained at diagnosis and after recurrence in a patient treated with letrozole demonstrated an acquired mutESR1 Y537S. Another LGSOC patient had a *mutESR1* Y537N at diagnosis and has attained prolonged clinical benefit (> 4 years) with fulvestrant. **Conclusions:** *ESR1* GA are present at a low frequency in gyn malignancies, are enriched in endometrioid histologic subtypes, and may occur either de novo or as a resistance mechanism to prior endocrine therapy. CGP identified clinically relevant *ESR1* GA that may be useful in directing therapy of gyn malignancies.

5591 Poster Session (Board #318), Mon, 1:15 PM-4:45 PM

A 12 multigene NGS panel to characterize molecular biotypes in endometrial cancer. *First Author: Ignacio Romero, Instituto Valenciano de Oncología (IVO), Valencia, Spain*

Background: The Cancer Genome Atlas (TCGA) study for endometrial carcinomas (EC) defined four prognostic molecular biotypes based on *POLE* status, Microsatellite instability (MSI) and Copy Number (CN) analysis. The aim of this study was to develop a prognostic EC molecular classifier, based on the analysis of a small multi-gene NGS panel, as a tool that supports the therapeutic decision making for EC patients. **Methods:** Serous (S) and endometrioid (E) EC (stages I, II and III from FIGO 2009) were identified from a prospective EC database of 187 patients. DNA from FFPE blocks was obtained and sequenced following the NGS TruSeq Custom Amplicon low input (Illumina) protocol interrogating a 12 multi-gene panel, including: *POLE, PTEN, TP53, ARID1A, ARID5B, FBXW7, PPP2R1A, CTCF, CTNNB1, RPL22, PIKRCA y PIK3R1*. MSI analysis was carried out using eight specific microsatellite markers. Random Forest classification algorithm (RFA) including the NGS results of the 12-gene panel, histology, stage and grade was developed from TCGA EC data. Validation was performed in our independent cohort of EC cases. **Results:** A total of 96 cases (13 S and 83 E) fulfilled histology, stage and DNA quality assessment criteria for the analysis. Most of the cases were Stage I (77); stage II and III being 2 and 17 respectively. Median age at diagnosis was 62 years (36-87) with a median follow-up of 33 months (2– 88). A RFA to classify patients in the four EC molecular biotypes was developed using a training set from TCGA EC dataset. The accuracy of this RFA (99 %) was confirmed in an independent set of the TCGA cohort, and then independently validated in our series with the following results by biotype: POLE, 17/96 (17.7 %); MSI-H, 15/96 (15.6 %); CN High (CNH), 22/96 (22.9 %); and CN Low (CNL), 42/96 (43.7 %). Progression-free and Overall survival analysis revealed that POLE and CNH biotypes constitute the best and worst prognostic groups respectively (PFS, $p = 0.038$; OS, $p = 0.029$). **Conclusions:** We have defined a prognostic model to classify EC molecular biotypes on the basis of the analysis of a 12 multi-gene NGS panel; which could be easily implemented as molecular diagnostic tool.

5592 Poster Session (Board #319), Mon, 1:15 PM-4:45 PM

Patterns of care and survival outcomes of stage IIIA endometrial cancer: An analysis of the National Cancer Database. *First Author: Sherry Yan, Department of Radiation Oncology, NYU Langone Health, New York, NY*

Background: Stage IIIA endometrial cancer with serosal or adnexal involvement has a better prognosis than other advanced uterine cancers and likely behaves differently compared to those with vaginal, parametrial or lymph node involvement. We performed a population-based analysis of Stage IIIA endometrial cancer from the National Cancer Database (NCDB) to evaluate survival outcomes by treatment regimens. **Methods:** Patients with FIGO stage IIIA endometrioid endometrial cancer treated with hysterectomy and bilateral oophorectomy and receiving adjuvant treatment between 2004 and 2014 were identified. Treatments evaluated include chemotherapy alone (CT), pelvic radiation ± brachytherapy (RT±BT), chemotherapy with brachytherapy (CT+BT), chemotherapy with pelvic radiation (CT+RT), or chemotherapy with pelvic radiation and brachytherapy (CT+RT+BT). Treatment trends over time were analyzed. Multivariate Cox proportional hazard models were developed to examine treatment outcomes. **Results:** Of 6,760 patients who met study criteria, 1842 (27.2%) received adjuvant CT; 2,732 (40.4%) received RT±BT; 702 (10.4%) received CT+BT; 871 (12.9%) received CT+RT; and 613 (9.1%) received CT+RT+BT. The practice of RT±BT declined from 56% to 16%, while CT alone rose from 18% to 36% and CT+BT rose from 4% to 14% over the study period ($p < 0.001$). Median follow-up was 69.0 months. Five-year overall survival was 83.7%, 69.7%, 73.6%, 63.6% and 78.0% for CT+BT, CT, CT+RT, RT±BT, and CT+RT+BT, respectively. Older age, black race, higher Charlson-Deyo comorbidity score, higher tumor grade, lymphovascular invasion, and having Medicare/uninsured were negative predictors of survival on multivariate analysis. CT+BT was significantly associated with improved survival over CT (HR 1.89, 95% CI 1.53-2.33; $p < 0.001$), CT+RT (HR 1.72, 95% CI 1.36-2.18; $p < 0.001$), RT±BT (HR 2.46, 95% CI 2.01-3.01; $p < 0.001$), and CT+RT+BT (HR 1.38, 95% CI 1.07-1.79; $p < 0.001$). **Conclusions:** While pattern of care shows an increase in use of adjuvant chemotherapy alone in Stage IIIA endometrial cancer, our findings demonstrate that chemotherapy should be combined with vaginal cuff brachytherapy to decrease mortality.

5593 Poster Session (Board #320), Mon, 1:15 PM-4:45 PM

Quality of life (QoL) in a phase III trial of pelvic external beam radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk, early stage endometrial carcinoma: An NRG Oncology/Gynecologic Oncology Group study. *First Author: Vivian Vongruenigen, Summa Health, Akron, OH*

Background: In GOG Study 249, VCB/C was not superior to PXRT in overall survival or treatment failure rate (Randall et al, ASTRO, 2017). Here we compare QoL, fatigue, neurotoxicity, and gastrointestinal (GI) symptoms between patients randomized to VCB/C versus PXRT, and examine the association between primary comorbid illness plus obesity on QoL. **Methods:** The Functional Assessment of Cancer Therapy (FACT) – Endometrial Trial Outcome Index (FACT-En TOI) for QoL, FACIT-Fatigue subscale, FACT/GOG-Neurotoxicity subscale, and 6 items from the FACT-En for gastrointestinal (GI) symptoms were measured at baseline, 4 and 11 weeks, 8 and 14 months post-enrollment. Treatment differences were assessed with a linear mixed model adjusting for pretreatment score, assessment time, and age at enrollment. **Results:** 540 of 601 eligible patients provided evaluable patient-reported assessments. QOL was not statistically significantly different between treatment arms. However, fatigue and neurotoxicity were significantly worse in the VCB/C group compared to the PXRT group ($p < 0.001$) especially at 11 weeks. Patients in the PXRT arm, however, reported significantly ($p < 0.001$) worse GI symptoms when compared with those in VCB/C. Patients with ≥3 comorbid illnesses reported 7.1 points lower (95% CI: 12.0~-2.3; $p = 0.004$) QOL scores than those with ≤ 2 comorbid illnesses, and 6.5 points lower (95% CI: 2.8~102; $p < 0.001$) fatigue scores than those with ≤1 comorbid illness. Although obesity status was not associated with the QOL score, patients with morbid obesity (BMI≥40) reported worse fatigue (4.1 points lower; 95% CI: 0.8~7.5; $p = 0.008$) than other patients. **Conclusions:** VCB/C was associated with substantially more fatigue and neuropathy; however, PXRT resulted in more GI symptoms. Absent any survival or disease control benefit of VCB/C over PXRT, PXRT remains an effective and appropriate treatment for this patient population. In addition, patients with three or more comorbidities at study entry are likely to have worse QoL and fatigue. Clinical trial information: NCT00807768.

5594 Poster Session (Board #321), Mon, 1:15 PM-4:45 PM

Efficacy and safety of nivolumab (Nivo) in patients (pts) with advanced or recurrent uterine cervical or corpus cancers. *First Author: Kosei Hasegawa, Saitama Medical University International Medical Center, Hidaka, Japan*

Background: Recent advances in immuno-oncology provide evidence for the efficacy of PD-1/PD-L1 blockade therapy for a variety of cancers. However, the clinical activity of Nivo, an anti-PD-1 monoclonal antibody, in the treatment of advanced/recurrent uterine cervical (CVC) and corpus cancers (CC) is not yet clear. **Methods:** Phase 2, multicenter, multicohort, open-label study evaluating the efficacy and safety of Nivo in pts with advanced/recurrent CVC or CC (JapicCTI-163212). Patients received Nivo 240 mg every 2 weeks until progression or unacceptable toxicity. Primary end point was overall response rate (ORR; complete or partial response [PR]); an ORR ≥19.2% was considered efficacious. Secondary end points included progression-free survival (PFS), overall survival (OS), and safety. PD-L1 immunohistochemical staining, microsatellite instability (MSI) testing, and HPV typing (CVC only) were evaluated for biomarker analysis. **Results:** A total of 20 CVC (14 squamous, 5 adenocarcinoma [AC], 1 adenosquamous) and 23 CC (15 endometroid AC, 6 other endometrial cancer, 2 carcinosarcoma) pts were enrolled. Most pts had ≥2 prior chemotherapy regimens (CVC 13/20; CC 14/23). ORR was 25% (5/20) and 23% (5/22 evaluable), median PFS was 5.6 and 3.4 months, 6-month OS was 84% and 73%, and 12-month OS (preliminary) was 73% and 49% in CVC and CC, respectively. One pt with CVC AC had PR. Most of the pts who responded had a durable response (4/5 CVC, 5/5 CC) at data cut-off (Aug 18, 2017). Drug-related adverse events were seen in 63% (Grade 3-4, 19%) of pts. There were no drug-related deaths. In CVC, ORR was higher in pts with PD-L1^{+} tumors (33%; 5/15) than in pts with PD-L1^{-} tumors (0%; 0/5) based on a PD-L1 expression level of ≥1%; HPV status did not affect ORR (33% in both HPV^{+} [3/9] and HPV^{-} [1/3]). In CC, ORRs were similar, regardless of PD-L1 status (PD-L1^{+}, 25% [2/8] vs PD-L1^{-}, 21% [3/14]). All CC pts with MSI-High (n = 2) had PRs that were durable; no pts with CVC had MSI-High. **Conclusions:** This study demonstrates that Nivo has acceptable toxicity with evidence of clinical activity (primary end point met) in pts with CVC and CC. PD-L1 expression in CVC and MSI-High in CC may predict the clinical activity of Nivo. Clinical trial information: JapicCTI-163212.

5595 Poster Session (Board #322), Mon, 1:15 PM-4:45 PM

Immune profile and outcomes of patients (pts) with gynecological malignancies (GYN) enrolled in early phases immunotherapy (IO) trials. *First Author: Victor Rodriguez Freixinos, Vall d'Hebron University Hospital, Barcelona, Spain*

Background: Immune checkpoint inhibitors have shown promising activity in multiple tumor types. However, there are no approved IO for GYN. **Methods:** We identified GYN pts treated with IO from 2014-2017 in phase I/II trials at Vall d´Hebron. Tumor infiltrating lymphocites *(TILs)*; PD-L1 expression by immunohistochemistry (IHC) (SP263 antibody); microsatellite instability (MSI) by IHC and Gynecological Immune Prognostic Index (GIPI) (baseline derived NLR (dNLR) (neutrophils/(leucocytes-neutrophils)) > 3 and LDH > upper limit of normal) were correlated with outcomes. **Results:** Sixty GYN cases (32 ovarian (OC); 8 endometrial(EC);15 cervical(CC) and 5 vulvar (VC)) were selected. Median number of metastatic sites and prior lines were 2 (1-4) and 2 (0-8) respectively. Median TILs was 10% (1%-90%); 10% of pts had high TILs (≥ 50%) and CC showed higher TILs (p = 0.007). PD-L1 > 1% was shown in 60% of pts (46% OC, 43% CC, and 11% EC). Single agent IO involved 47% of cases. Median follow-up was 69m. Overall response rate was 15%. Median progression-free survival (PFS) and clinical benefit rate (CBR) (complete/partial response or stable disease ≥ 6 months (m)) were 2.63m [95% CI 2.07-5.13] and 32% respectively, without differences in any subgroup (4 EC pts with CBR are ongoing). Two EC pts (14%) from the population with CBR had MSI. dNLR and > 3 metastatic sites correlated with worse PFS (p = 0.035 and p < 0.0007 respectively). PD-L1 expression as continuous variable (p = 0.017) but not TILs (p = 0.37) correlated with improved outcomes. PD-L1≥20% associated with longer mPFS (NR (95% CI 5.13-NA) vs. 2.47m (95% CI 1.9-3.77); HR = 0.08, p = 0.017). "Hyperprogression" (HPD) (≥40% tumor burden increase or ≥20% plus multiple new lesions) was shown in 23% of pts without differences in any subgroup. Poor GIPI group (2 factors (+)) had a trend for worse overall survival (4.43 vs. 18.23m; HR = 2.63 (95% CI 0.9-7.5), p = 0.07). **Conclusions:** Although IO drug development is slowly evolving in GYN, we found encouraging activity in a significant proportion of GYN pts. HPD is not a rare event in GYN. Further work is needed to better characterize pts at risk of HPD and optimize immune-related biomarkers, particularly PD-L1 assessment.

5596 Poster Session (Board #323), Mon, 1:15 PM-4:45 PM

Lenvatinib + pembrolizumab in patients with advanced endometrial cancer: Updated results. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (LEN) is an inhibitor of VEGFR 1−3, FGFR 1−4, and other kinases. Pembrolizumab (PEM) is an anti-PD-1 antibody. We report updated interim results from a phase 1b/2 study evaluating LEN + PEM in patients (pts) with advanced endometrial cancer (EC) (NCT02501096). **Methods:** In this multicenter, open-label study, pts with histologically confirmed EC irrespective of microsatellite instability (MSI) or mismatch repair (MMR) status and measurable disease per immune-related RECIST (irRECIST) received LEN (20 mg PO QD) plus PEM (200 mg IV Q3W). Tumor assessments were performed by investigators using irRECIST. The primary phase 2 endpoint was objective response rate at 24 weeks (ORR_{WK24}), calculated only for evaluable pts who had 24 weeks of follow up or discontinued treatment or died prior to 24 weeks. Secondary endpoints included ORR (full analysis set), progression-free survival (PFS), and duration of response (DOR). **Results:** At data cutoff of Aug 1 2017, 54 pts were enrolled [endometrioid: Gr 1 (7), Gr 2 (12), Gr 3 (5); serous (18); others (8); unknown (4)]. Three (6%) pts were MSI-high (MSI-H); 43 (80%) were non-MSI-H/proficient MMR (MMRp); 8 (15%) were not done/unknown. Median follow-up for PFS was 4.0 months (95% confidence interval [CI], 2.7–7.6). ORR_{WK24} was 50.0% (95% CI, 32.4–67.6), and all responses were confirmed. ORR was 36.7% (95% CI, 23.4–51.7), which reflects the short follow-up time for pts with later enrollment. Median DOR has not yet been reached (not estimable [NE], 95% CI, 4.1–NE) and median PFS was 10.1 months (95% CI, 5.3–NE). Of the 3 MSI-H pts, 1 achieved partial response, 1 had stable disease, and 1 had progressive disease. For non-MSI-H/MMRp pts, ORR_{WK24} was 50.0% (95% CI, 29.9–70.1). Grade 3 treatment-related adverse events (TRAEs) occurred in 32 (59%) pts; there were no Grade 4 TRAEs. 3 (6%) pts discontinued treatment due to a TRAE. The most common TRAEs were hypertension (59%), fatigue (50%), diarrhea (44%), hypothyroidism (35%), and stomatitis (33%). **Conclusions:** Combination LEN + PEM demonstrated encouraging activity in advanced EC regardless of MSI/MMR status, with no new safety signals identified. A randomized, international, 2-arm, phase 3 study in recurrent EC is planned. Clinical trial information: NCT02501096.

5597 Poster Session (Board #324), Mon, 1:15 PM-4:45 PM

Biomarker results and preclinical rationale for combination lenvatinib and pembrolizumab in advanced endometrial carcinoma. *First Author: Vicky Makker, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lenvatinib (LEN) is a multikinase inhibitor of VEGFR 1−3, FGFR 1−4, and other targets; pembrolizumab (PEM) is an anti–PD-1 antibody. We report biomarker analyses from a phase 1b/2 trial in advanced endometrial cancer (EC) and preclinical rationale for the activity of combination LEN + PEM. **Methods:** In an exploratory analysis, 41 candidate serum biomarkers for LEN and PEM were assessed using immunoassay panels in 38 patients with EC receiving LEN + PEM at baseline, cycle 1 day 15 (C1D15), and C2D1. Data cutoff: May 31, 2017. Tumor-associated macrophages (TAM) were assessed in mouse syngeneic tumor models by flow cytometry and immunohistochemistry. RNAseq transcriptomes of tumors from mice treated with LEN, anti–PD-1, or LEN + anti–PD-1 were subjected to weighted gene coexpression network analysis for pathway enrichment analyses. **Results:** At C1D15 and C2D1 of LEN + PEM, significant changes were seen in the levels of 16 and 18 of 41 biomarkers, respectively, including increased levels of interferon (IFN)-γ and IFN-γ–regulated chemokines (CXCL9, CXCL10, CXCL11; all $P < 0.05$). Of these, significant associations were found between increases in CXCL9 and CXCL10 levels and patients with compete, partial, or unconfirmed partial responses (all $P < 0.05$). Preclinical model experiments *in vivo* showed that LEN alone significantly depleted the TAM population in excised tumors ($P < 0.01$). Transcriptome analyses of tumors from mice treated with LEN + anti–PD-1 showed that genes specifically regulated by the combination were significantly enriched for genes involved in signaling pathways associated with immune modulation, including IFN signaling (FDR P as low as 1.50×10^{-9}). **Conclusions:** In patients with advanced EC, LEN + PEM was associated with changes in several biomarkers, including IFN-γ–regulated chemokines, some of which may be associated with clinical response. *In vivo* preclinical experiments suggest that LEN monotherapy may modulate tumor microenvironment by decreasing the local TAM population, whereas LEN + anti–PD-1 may act via a mechanism that includes the IFN signaling pathway. Overall, these findings provide preclinical rationale for the activity of combination LEN + PEM. Clinical trial information: NCT02501096.

5598 Poster Session (Board #325), Mon, 1:15 PM-4:45 PM

Preoperative olaparib in early-stage endometrial cancer (EC): A phase 0, window of opportunity trial to evaluate the PARP inhibition effect, targeting cell cycle-related proteins (POLEN study). *First Author: Ignacio Romero, Instituto Valenciano de Oncología (IVO), Valencia, Spain*

Background: Olaparib (AZD2281, KU-0059436) is a poly ADP ribose polymerase (PARP) inhibitor. Biomarkers that predict a response to olaparib in EC are not fully established. The aim of this study is to identify pharmacodynamic and pharmacogenetic biomarkers associated with a short term exposure to olaparib in type I primary EC surgical patients (pts). **Methods:** In this phase 0, multicenter, single arm, window of opportunity trial, women diagnosed with type I primary EC received olaparib tablets (oral 300mg/BID; 4 weeks) before surgery. Biological effects were evaluated by comparing the initial biopsy and the tumor tissue at surgery. The primary endpoints were the significant inhibition of cyclin D1, Ki67 and active caspase 3 activity. Secondary objectives included the correlation between PARP inhibition and cell proliferation, angiogenesis and tumor-tissue biomarkers. The predictive role of PTEN, PMS2 and MSH6 mutations were evaluated. We control multiple testing issues with a false discovery rate (FDR) of 10%. **Results:** From March 2016, 41 pts have been screened, 36 included, 23 treated and 19 could be studied in biomarker analysis. Median age was 63y (51-82); 100% were endometrioid and clinical stage was I (17, 89.5%) and stages II, III and IV (2, 10.5%). Median time of olaparib exposure was 21 days (13-32). Significant inhibition was declared for cyclin D1 ($p = 0.01$), but not for Ki67 and active caspase 3 immunostaining. Differences in PARP1 baseline and post-treatment immunostaining correlates (Rho > 0.45; $p < 0.05$) with differences in pre-post cyclin D1, Ki67, phosphohistone H3, p50, VEGF and HIF1α measures. However, only cyclin D1 (Rho = 0.771, $p < 0.001$) showed a significant correlation under FDR criterion. Genetic alterations did not show differences in pre-post treatment measures. The most common AEs were nauseas (31.6%), vomiting (21.1%) and fatigue (21.1%) grade 1 and 2. No surgery was delayed due to toxicity. **Conclusions:** The study has identified some potential biomarkers associated with olaparib exposure in cell proliferation/apoptosis pathways that might help select best candidates. Clinical trial information: NCT02506816.

5599 Poster Session (Board #326), Mon, 1:15 PM-4:45 PM

Variability in Medicare utilization and payment among gynecologic oncologists. *First Author: Stephanie Lim, Duke University School of Medicine, Durham, NC*

Background: The Medicare Provider Utilization and Payment Data: Physician and Other Supplier Public Use File (POSPUF) for 2015 is a publicly available file from the CMS that includes all direct payments to providers who care for fee-for-service Medicare recipients. The objective of this study was to analyze variability in gynecologic oncologists' Medicare utilization and reimbursements, with attention to differences based on provider gender and time spent in practice. **Methods:** The POSPUF 2015 was analyzed with respect to Gynecologic Oncology specialty providers. We used publicly available data to confirm gynecologic oncology subspecialty and to determine each provider's total number of years in gynecologic oncology practice. Evaluation, management, and procedure/surgery codes were analyzed; drug delivery codes were excluded due to variability in billing these by facility/hospital. **Results:** The POSPUF file included 824 gynecologic oncologist providers receiving a total of $28,772,739 in payments. The majority of providers practiced in large metropolitan areas (66%) or mid-sized metro areas (27%). While females composed 38.5% of gynecologic oncologists, they accounted for only 28.1% of Medicare reimbursements. The median Medicare reimbursement to a Gynecologic Oncologist was $24,828 (IQR $11,564, $45,412), but this was significantly different by gender; female $19,394 (IQR $10,913, $34,894) compared to male $29,395 (IQR $13,903, $52,941). Overall, female providers receive 30.4% of evaluation and management reimbursements and 22.5% of surgical reimbursements. During the first ten years in practice, women composed 47.0% of providers and accounted for 52.3% of the services reimbursed, compared to 36.25% of providers/26.6% of the reimbursed services (11-20 years in practice), and 18.11% of providers/16.4% of services ($>$ 20 years in practice). **Conclusions:** While male gynecologic oncologists receive higher median reimbursements than females, there is a trend toward equal services and reimbursements between genders among younger providers, suggesting a trend toward gender equity over time.

TPS5600 Poster Session (Board #327a), Mon, 1:15 PM-4:45 PM

GOG 3016/ENGOT-cx9: An open-label, multi-national, randomized, phase 3 trial of cemiplimab, an anti-PD-1, versus investigator's choice (IC) chemotherapy in ≥2 line recurrent or metastatic cervical cancer. *First Author: Krishnansu Sujata Tewari, The Division of Gynecologic Oncology at the University of California, Irvine, Orange, CA*

Background: Patients with recurrent and metastatic cervical carcinoma experience modest survival benefit with first-line platinum-based chemotherapy with or without bevacizumab. Those with platinum-refractory disease have a median survival of only 7 months. Cemiplimab, a human monoclonal anti-PD-1, has exhibited antitumor activity and an acceptable safety profile in a phase 1 trial of solid tumors including recurrent cervical cancer. **Methods:** GOG 3016/ENGOT-cx9 is an open-label, randomized (1:1), phase 3 trial of cemiplimab versus IC chemotherapy in women ≥18 years with platinum-refractory recurrent and/or metastatic cervical cancer that has progressed within 6 months of the last dose of platinum-containing chemotherapy (NCT03257267). Patients will be stratified for the primary efficacy analysis by histology and geographic region. Patients will receive cemiplimab every 3 weeks (Q3W) or IC chemotherapy, ie, pemetrexed 500 mg/m^2 Q3W; topotecan 1 mg/m^2 daily x5 days, every 21 days; irinotecan 100 mg/m^2 days 1, 8, 15, and 22, followed by 2 weeks rest, for a 42-day (6-week cycle); gemcitabine 1000 mg/m^2 days 1 and 8, every 21 days; or vinorelbine 30 mg/m^2 days 1 and 8, every 21 days. Treatments will be given IV for up to 96 weeks. The primary objective is overall survival (OS). Key secondary objectives include the assessment of overall response, progression-free survival, and the frequency and severity of adverse events. Stratification factors include prior bevacizumab, histology, and ECOG status. Assuming duration of study enrollment and follow-up of 20 months and 12 months, respectively, we calculated we would need to enroll approximately 436 patients, with 330 deaths expected, to provide the study with 90% power to detect a reduction in the risk of death of at least 20% with cemiplimab, with the 1-sided type 1 error rate limited to 2.5%. An independent data monitoring committee (IDMC) will monitor the data during the study conduct. Clinical trial information: NCT03257267.

TPS5601 Poster Session (Board #327b), Mon, 1:15 PM-4:45 PM

A single arm, phase 2, multicenter, international trial of tisotumab vedotin (HuMax-TF-ADC) in previously treated, recurrent or metastatic cervical cancer. *First Author: Robert L. Coleman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cervical cancer treatment options are limited for patients with recurrent and/or metastatic cervical cancer. Tisotumab vedotin (TV) is an antibody-drug conjugate (ADC) composed of a human antibody targeted to tissue factor (TF), a protease-cleavable linker and the potent microtubule-disrupting agent monomethyl auristatin E (MMAE). The phase 1/2 GEN701 trial (NCT02001623) initially enrolled 34 patients with recurrent or metastatic cervical cancer in the cervical expansion cohort. Treatment with intravenous TV at 2 mg/kg every 3 weeks resulted in an overall response rate of 32% (confirmed and unconfirmed responses) by investigator review per RECIST v1.1 as a part of preliminary analysis. Furthermore, TV was safe and tolerable with a safety profile generally consistent with other MMAE-based ADCs **Methods:** This is an international, multicenter, open-label, non-randomized phase 2 trial evaluating efficacy of TV in approximately 100 patients with recurrent and/or metastatic cervical cancer who have progressed on a standard 1st line therapy and who have not received more than 2 prior systemic treatment regimens for recurrent or metastatic disease. Response will be assessed every 6 weeks for the first 30 weeks, and then every 12 weeks thereafter. The primary objective is to assess the confirmed objective response rate (ORR) by an independent review committee (IRC) using RECIST v1.1. Secondary efficacy endpoints include: duration of response (DOR), ORR by investigator review, time to response (TTR), progression free survival (PFS), overall survival (OS), and safety and tolerability. For the ORR analyses, a 2-sided 95% exact confidence interval will be calculated using the Clopper-Pearson method. PFA and OS will be analyzed using the Kaplan-Meier method. Adverse events (AEs) will be monitored and graded using CTCAE v5.0.

TPS5602 Poster Session (Board #328a), Mon, 1:15 PM-4:45 PM

SENTICOL III: International validation study of sentinel node biopsy in early cervical cancer: A GINECO, ENGOT and GCIG study. *First Author: Fabrice Lecuru, GINECO, Paris, France*

Background: Sentinel node biopsy (SLN) is an alternative to pelvic lymphadenectomy (PLN). The false negative rate is < 1%) when "MSKCC Algorithm" is fulfilled. The technique can detect isolated tumor cells (ITC) or micrometastases in 15 – 20 % of N0 patients, reveal SLN in unexpected areas in up 30% of cases and reduce short term lymphatic morbidity. However, the long-term prognosis of SLN negative patients is unknown. In 2014, the GCIG brainstorming on cervical cancer pointed out the need for a validation study, taking survival into account, giving birth to SENTICOL III. **Methods:** SENTICOL III is an international prospective multicenter randomized trial. We use a « co-primary » objective regarding Disease Free Survival (DFS) and Health Related Quality of Life. The hypothesis is that SLN biopsy alone provides similar DFS and better quality of life. Secondary objectives are outcome of patients with ITC and micrometastases, evaluation of mapping with indocyanine green (ICG), overall survival, recurrence free survival. A cost analysis will be undertaken and a tumor tissue bank will be established. Patients with an early stage cervical cancer defined as FIGO stage Ia1 with lymphovascular invasion to IIa1, maximum diameter ≤40mm on MRI and node negative on imaging will be eligible to participate. SLN biopsy will be performed using isotopic detection +/- blue dye or ICG. SLN of patients with an "optimal" mapping will be analyzed by frozen section. SLN negative patients will be randomized intraoperatively 1:1 to SLN only or SLN + PLN. All SLN will be submitted to ultrastaging (200 microns levels). All centers will follow a quality assurance program to ensure surgical competency and a standardized pathological evaluation 900 patients will be recruited in 3 years, with 4 years of follow-up. (3 years-disease free survival of 85%, with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373), a unilateral alpha error of 5%, and a power of 80%) The trial has started in France, and an international collaboration has been developed through GCIG and ENGOT. (NCT03386734). CHU Besançon is the sponsor for France Clinical trial information: ID-RCB : 2017-A00945-48.

TPS5603 Poster Session (Board #328b), Mon, 1:15 PM-4:45 PM

A randomized phase II/III trial of conventional paclitaxel and carboplatin (cTC) versus dose-dense paclitaxel and carboplatin (ddTC), with or without bevacizumab (Bmab), for stage IVb, recurrent, or persistent cervical cancer (CC): Japan Clinical Oncology Group study (JCOG1311). *First Author: Ryo Kitagawa, Department of Gynecology and Obstetrics, Tohoku Medical and Pharmaceutical University, Miyagi, Japan*

Background: Patients with metastatic or recurrent CC who are not amenable to curative treatment with surgery or radiation have a poor prognosis, and systemic chemotherapy is regarded as a standard treatment. Based on the JCOG0505, we considered tri-weekly cTC as the standard regimen. We subsequently focused on dose-dense, weekly administered paclitaxel, which was more effective than conventional administration for breast cancer and, in Japan, ovarian cancer. The efficacy and safety of ddTC have not been evaluated for CC. Therefore, we designed JCOG1311 to confirm the superiority of ddTC to cTC in metastatic or recurrent CC. However, Bmab was approved in Japan for treatment of metastatic or recurrent CC on May 2016. We amended the protocol to add the criteria by which patients would receive Bmab. **Methods:** Major eligibility criteria are stage IVB, persistent, or recurrent CC patients including SCC or adenocarcinoma histology. We enroll patients according to institution, PS, and platinum-free interval as adjustment factors, whether they receive carboplatin (AUC of 5) on day 1 plus either paclitaxel (175 mg/m^2) on day 1 (cTC), or paclitaxel (80 mg/m^2) on day 1, 8, 15 (ddTC). Both treatments are repeated every 3 weeks. They can receive Bmab (15 mg/kg) every 3 weeks if not contraindicated. 14 of planned 56 with measurable lesion receiving Bmab in phase II part, of which the primary endpoint is response rate (RR), have been enrolled until January 2018. If the RR of ddTC + Bmab arm is greater than that of cTC + Bmab arm plus 5%, the study will proceed to phase III part, which has OS as the primary endpoint. We hypothesize that the 2-year OS of ddTC arm will be greater than that of the cTC arm (i.e., ≥ 45% compared to 35%). According to the Schoenfeld and Richter method, the required sample size is total 420 patients, with one-sided α of 0.05 and β of 0.20 during 3.5 years of accrual and 2 years of follow-up. This trial is supported by the Japan Agency for Medical Research and Development. And, this trial was registered at the UMIN Clinical Trials Registry as UMIN000019191. Clinical trial information: 000019191.

TPS5604 Poster Session (Board #329a), Mon, 1:15 PM-4:45 PM

A phase 2, multicenter study to evaluate the efficacy and safety using autologous tumor infiltrating lymphocytes (LN-145) in patients with recurrent, metastatic, or persistent cervical carcinoma. *First Author: Amir A. Jazaeri, University of Virginia, Charlottesville, VA*

Background: Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has demonstrated efficacy in the treatment of immunogenic tumors with high mutation loads, such as melanoma, and virally-associated tumors, such as HPV-mediated cervical cancer. As outcomes for patients with recurrent, metastatic or persistent cervical cancer remain extremely poor, there is an enormous need for the development of novel immunotherapeutic approaches with curative potential such as ACT with TIL. **Methods:** Clinical trial C-145-04 (NCT03108495) is a prospective, phase 2 multicenter, open-label study evaluating the efficacy of a single autologous TIL infusion (LN-145) followed by IL-2 after a non-myeloablative lymphodepletion (NMA-LD) regimen in patients with recurrent, metastatic, or persistent cervical cancer who have failed at least one prior systemic therapy. Patients undergo surgical resection of a tumor from which TIL are extracted and expanded at a central GMP manufacturing facility that prepares a cryo-preserved TIL (LN-145) product for infusion. One week prior to LN-145 infusion, patients undergo NMA-LD consisting of cyclophosphamide (60 mg/kg) daily x 2 days followed by fludarabine (25 mg/m^2) daily x 5 days. LN-145 is infused 24 hours after NMA-LD and followed by up to 6 doses of IL-2 (600,000 IU/kg) every 8-12 hours. The primary endpoint is the objective response rate (ORR) per RECIST v1.1. Secondary endpoints include safety and efficacy parameters such as complete response, duration of response, disease control rate, progression free- and overall survival. In addition to the tumor resected, patients must have an additional measurable lesion for response assessment. Other major eligibility criteria include adequate bone marrow, liver, pulmonary, cardiac and renal function; ECOG performance status of 0 or 1. Clinical trial information: NCT03108495.

TPS5605 Poster Session (Board #329b), Mon, 1:15 PM-4:45 PM

EDMONd: A feasibility study of elemental diet as an alternative to parenteral nutrition for ovarian cancer patients with inoperable malignant bowel obstruction. *First Author: Agnieszka Michael, University of Surrey, Guildford, United Kingdom*

Background: Inoperable bowel obstruction (IBO) occurs in up to 50% of patients diagnosed with ovarian cancer. Nutrition support for patients with IBO is challenging. Parenteral feeding (PN) is the recommended route for patients with a prognosis of > 2 months, however there is little evidence that it improves quality of life and the cost of it is very high . If PN is not available patients are frequently discharged home from hospital with sips of clear fluids only. Management of inoperable bowel obstruction remains a major challenge and clear guidelines are needed. Elemental diet (ED) is a liquid diet that contains proteins in the form of amino acids, fats in the form of medium chain triglycerides, vitamins and trace minerals. EDs are almost completely absorbed in the upper small intestine **Methods:** The primary objective of the study is to establish if ED can be used as an alternative to home PN in patients with IBO by providing a 'proof of concept' of ED as an acceptable and useful feeding option. The secondary aim is to examine the impact of ED on quality of life. The primary endpoints of the study are taste acceptability (graded 1-5 on a purposely designed Elemental Diet data collection chart), incidence of vomiting and incidence of pain. The secondary endpoints include the number of women who can tolerate ED and can subsequently be treated with palliative chemotherapy (as per standard of care), the number of patients alive at the end of the study, quality of life and nutritional intake. This is a mixed-method single arm feasibility study of 34 patients diagnosed with IBO and who can tolerate 500ml of liquid. Patients are provided with ED and followed-up for 2 weeks. Patients' symptoms and quality of life are assessed using the Memorial Symptoms Assessment Scale (MSAS) and EORTC Quality of Life QLQ-C30 questionnaire. As this is a feasibility study to evaluate whether ED is an acceptable intervention for patients with IBO, recruiting 25 patients into the study will provide an answer to the question. As the prognosis is poor in this cohort we assumed 25% attrition rate 8 out of 34 patients have been recruited and the recruitment continues. Clinical trial information: ISRCTN16862540.

TPS5606 Poster Session (Board #330a), Mon, 1:15 PM-4:45 PM

OVARIO: The phase 2, single-arm, open-label study of maintenance therapy with niraparib + bevacizumab in patients with advanced ovarian cancer following response on frontline platinum-based chemotherapy. *First Author: Joanie M. Hope, Alaska Women's Cancer Care, Anchorage, AK*

Background: Niraparib (Zejula) a selective poly(ADP-ribose) polymerase (PARP) 1/2 inhibitor, significantly improved progression-free survival (PFS) as a single agent for patients with recurrent ovarian cancer (OC) relative to placebo in the ENGOT-OV16/NOVA trial, regardless of *BRCA* or HRD status. The ongoing AVANOVA trial (NCT02354131) has shown that niraparib can be safely combined with bevacizumab (bev). This combination is being explored in AVANOVA, as a strategy to increase tumor sensitivity to PARP inhibition. As an anti-angiogenic agent, bev can induce tumor hypoxia, leading to downregulation of *BRCA* and *RAD51,* which could sensitize tumors to PARP inhibition, and lead to apoptosis via contextual synthetic lethality. While *BRCA* and HRD status was insufficient to predict responders to niraparib in NOVA, a longer median PFS was observed for the cohorts with these biomarkers. In the phase 2 OVARIO study (NCT03326193), niraparib plus bev will be evaluated as a maintenance treatment in patients with advanced OC who have recovered from primary debulking surgery and have responded to frontline platinum-based chemotherapy with bev. **Methods:** Target enrollment is 90 patients, regardless of *BRCA or* HRD status, with stage 3b and 4 epithelial ovarian, fallopian tube, or peritoneal cancer. Patients must achieve complete response, partial response or no evidence of disease after the frontline platinum-based chemotherapy. The primary objective for OVARIO will be PFS at 18 months landmark. Secondary objectives include evaluation of PFS, overall survival, time to first subsequent therapy, and safety and tolerability. Exploratory objectives will be PFS at 6 and 12 months and patient-reported outcomes. The starting dose of niraparib will be based on the patient's baseline body weight and/or platelet count. Patients weighing $\geq$77 kg with a platelet count of $\geq$150,000/μL will receive 300 mg qd. Patients weighing $<$ 77 kg or with a platelet count of $<$ 150,000/μL will receive 200 mg qd. The bev dose will be 15 mg/kg q3w up to 15 months. Patients will be treated continuously until disease progression or unacceptable toxicity. Clinical trial information: NCT03326193.

TPS5607 Poster Session (Board #330b), Mon, 1:15 PM-4:45 PM

ATALANTE (ENGOT-ov29): A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab. *First Author: Jean Emmanuel Kurtz, GINECO, Strasbourg, France*

Background: The immunosuppressive environment is increased in Ovarian Cancer (OC) by the expression of T cell inhibitory receptors on tumor cells and immune cells. Targeting PD-1/PD-L1 pathway (an inhibitory immune pathway exploited by cancer) may restore CD8+ anticancer response from exhausted Tumor Infiltrating Lymphocytes (TILs). Bevacizumab (bev) is an anti-VEGF monoclonal antibody approved in the EU in first line or relapse for the treatment of advanced OC in combination with platinum-based chemotherapy (Cx) and in maintenance. VEGF has immunosuppressive properties, decreasing tumor access by TILs, increasing both PD-L1 expression on tumor cells and Treg activity. Hence there is evidence that anti-VEGF therapy and immunotherapy act synergistically. **Methods:** ATALANTE is a randomized (2:1), double blinded, phase III trial evaluating the efficacy and safety of adding the anti-PD-L1 monoclonal antibody atezolizumab (At) to Cx and bev in 405 OC patients (pts) in platinum-sensitive relapse. Main eligibility criteria include: ECOG $\leq$1, first or second platinum-sensitive relapse ($>$6 months), ECOG 0 or 1, normal organ function, absence of auto-immune disease or of chronic corticosteroid therapy. All patients must have a tumor biopsy at study entry for PD-L1 testing (stratification factor). Pts are treated with 6 cycles of platinum-based Cx (q3 or q4 weeks) plus bev + At (1200mg q3 weeks)/placebo followed by bev (15 mg/kg q3 weeks) plus At/placebo maintenance until progression or prohibitive toxicity. The primary endpoint is PFS based on RECIST v1.1 according to investigator assessment. The final PFS analysis will be performed when the number of predefined events is reached. The latest review by the Independent Data Monitoring Committee in July 2017 did not identify any safety issue and suggested that the trial can continue as planned. The study is currently recruiting internationally. Clinical trial information: NCT02891824.

TPS5608 Poster Session (Board #331a), Mon, 1:15 PM-4:45 PM

An open-label phase 1 trial of the safety and efficacy of daily subcutaneous SPL-108 injections when used in combination with paclitaxel in patients with platinum-resistant, CD44+, advanced ovarian epithelial cancer. *First Author: Eugenia Girda, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Ovarian cancer often presents in advanced stages and is treated with platinum-based chemotherapy. However, many patients develop platinum-resistant disease with either failing to achieve clinical response or progressing within 6 months after completion of treatment. Our laboratory has shown that CD44 contributes to the development of chemotherapeutic resistance, through MDR1-dependent/P-glycoprotein mediated efflux of chemotherapeutic agents. Targeting CD44 or related signaling pathways inhibits tumor growth and relapse, and increases sensitivity to cytotoxic agents. SPL-108 is an 8-amino-acid peptide derived from single chain urokinase plasminogen activator that binds to CD44. In vitro and in vivo experiments showed that SPL-108 has therapeutic activity in models of ovarian and other cancers. Phase I trials with SPL-108 in healthy volunteers demonstrated no systemic adverse events; phase Ib trials in women with gynecologic cancers showed self-limited, mild or moderate adverse events with several subjects showing stable disease. Phase II trials in ovarian cancer patients showed improved time to disease progression with no grade 4 toxicity, 6.5% had grade 3 all of which were constitutional. In the current trial, SPL-108 would be used in combination with paclitaxel in an attempt to reverse efflux-mediated resistance to chemotherapy. Due to positive safety profile of SPL-108, the goal is to achieve improved efficacy without enhanced toxicity. **Methods:** Open-label 2-arm phase I trial. Arm I includes 6-12 patients, with a 3+3 design with 2 cohorts. Cohort 1 will receive daily 150-mg SPL-108 SQ, cohort 2 will receive twice-daily 150-mg SPL108; both cohorts will have concurrent administration of weekly paclitaxel of 80 mg/m2, on Days 1,8,15 of a 28 day cycle. Safety will be assessed and subjects without dose-limited toxicity continue 6 cycles, unless disease progression or unacceptable toxicity occurs. Arm II is the Exploratory Expansion Phase: 12 subjects receive SPL-108 daily dose determined in the Arm I Safety phase with concurrent 80 mg/m2 paclitaxel. Clinical trial information: NCT03078400.

TPS5609 Poster Session (Board #331b), Mon, 1:15 PM-4:45 PM

Clinical trial in progress: A study of VB-111 combined with paclitaxel vs. paclitaxel for treatment of recurrent platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). *First Author: Richard T. Penson, Harvard Medical School, Boston, MA*

Background: Ofranergene obadenovec (VB-111) is a targeted anti-cancer gene therapy with a dual mechanism: an antiangiogenic broad effect and induction of a tumor directed viral immune response. Over 400 cancer patients have been treated with VB-111, with evidence of anti-tumor activity across three phase 2 studies and a favorable safety profile. A phase 2 trial in patients with platinum resistant ovarian cancer treated with VB-111 in combination with weekly paclitaxel was conducted. In a population with 50% platinum refractoriness and 52% prior antiangiogenics, CA-125 response was observed in 60% of patients with a dose response pattern and a significant increase in overall survival (OS) at therapeutic vs. low dose level (median 810 vs. 172 days, p = 0.042) as well as evidence of an immunotherapeutic effect. Based on these observations, a phase 3 study of VB-111 in combination with weekly paclitaxel in patients with recurrent platinum-resistant ovarian cancer was initiated (NCT03398655) in collaboration with The GOG Foundation, Inc. **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study of patients with platinum-resistant ovarian cancer, a deadly indication with significant unmet need. Patients with recurrent epithelial ovarian cancer, who have platinum-resistant and measurable disease (RECIST 1.1) previously treated with no more than 5 treatment lines are randomized 1:1 to receive VB-111 ($1x10^{13}$ VPs) combined with paclitaxel (80mg/m^2) or placebo combined with paclitaxel (80mg/m^2). Randomization is stratified by number of prior treatment lines and prior antiangiogenic therapy. Treatment beyond RECIST progression is allowed in the absence of significant deterioration. The primary endpoint is OS; secondary endpoints include objective response rate, progression free survival (both by RECIST 1.1), combined CA-125 and RECIST 1.1 response, and CA-125 response (GCIG). The sample size calculation of 350 patients (event driven) provides 88% power to detect a difference in survival at the two-sided 5% significance level using the logrank test. To date, 2 patients have been randomized. Clinical trial information: NCT03398655.

TPS5610 Poster Session (Board #332a), Mon, 1:15 PM-4:45 PM

A multicentric single-arm phase II clinical trial to evaluate safety and efficacy of the combination of olaparib and PLD for platinum resistant ovarian primary peritoneal carcinoma and fallopian tube cancer patients: The GEICO-1601 ROLANDO trial—A trial in resistant ovarian cancer with olaparib and pegylated liposomal doxorubicin. *First Author: Jose Alejandro Perez-Fidalgo, Hospital Clínico Universitario de Valencia; INCLIVA; Centro de Investigación Biomédica en Red de Oncología; CIBERONC-ISCIII; GEICAM Spanish Breast Cancer Group, Valencia, Spain*

Background: Olaparib is a PARP-inhibitor that has demonstrated efficacy in ovarian cancer in both platinum-sensitive and platinum-resistant relapse. *BRCA* mutations have been identified as an important predictive factor for response to olaparib, however in Study 19 progression free survival (PFS) was also improved in BRCA wildtype (*BRCA*wt) patients (1). A preclinical study showed synergism between doxorubicin and olaparib in 2D and 3D models of ovarian cancer (2). The combination of pegylated liposomal doxorubicin (PLD) 40 mg/m2 and olaparib 400 mg bid (capsule formulation) was considered tolerated and suitable in a phase I trial (3). **Methods:** This is a multicenter single arm phase II trial in women with platinum-resistant relapsed ovarian cancer. Patients receive Pegilated liposomal doxorubicin (PLD) 40 mg/m2 every 28 days and olaparib 300 mg bid tablets for 6 cycles followed by olaparib 300 mg bid maintenance until toxicity or disease progression. Primary endpoint is progression-free survival at 6 months (PFS6m). Secondary endpoints are PFS, overall-survival, response rate, quality of life, and growth modulation index. Key inclusion criteria are: 1) Serous or endometrioid ovarian cancer 2) Platinum-resistant relapse (between 28 days and 6 months after last platinum-containing chemotherapy (CT)) 3) Previous PLD is allowed if administered as part of a platinum-sensitive recurrence and $>$ 6 months before inclusion 4) *BRCA* mutant patients are eligible after only 1 previous CT line, 5) *BRCA*wt or unknown are eligible after at least 2 previous platinum sensitive lines 6) no more than 3 CT lines are allowed, 7) Hemoglobin $>$ 10 g/dl and 8) left ventricle ejection fraction $>$ 50%. Sample size calculation assumed that PFS6m 40% or higher would be of interest for further investigation; with 90% power and a 2-sided alpha error 0.05 the number of patients needed will be 32 patients. Enrolment was initiated in December 2017 and the first patient has been enrolled. Clinical trial information: NCT03161132.

TPS5611 Poster Session (Board #332b), Mon, 1:15 PM-4:45 PM

A phase Ib trial of pembrolizumab (Pembro) following adoptive cell therapy (ACT) in patients with platinum-resistant ovarian cancer; The ACTIVATE (Adoptive Cell Therapy InVigorated to Augment Tumor Eradication) trial. *First Author: Josee-Lyne Ethier, Cancer Centre of Southeastern Ontario, Kingston, ON, Canada*

Background: ACT is based on the in vitro expansion of T cells with anti-tumor activity, followed by transfer of large numbers of T cells back to the patient. T cells for ACT can be obtained from tumor-infiltrating lymphocytes (TILs), which represent a source of tumor-specific T cells. Evidence supports that epithelial ovarian carcinoma (OC) is immunogenic and has the potential to respond to immunotherapy. Pembro, a PD-1 monoclonal antibody, was shown to have activity in metastatic ovarian cancer with a response rate of 11.5% (Varga, ASCO 2015;33:5510). There is limited data regarding the efficacy of combining ACT with PD-1/PD-L1 inhibitors. However, ACT may synergize with checkpoint inhibitors to overcome immunosuppression within the tumor microenvironment, and dramatic clinical responses have been observed anecdotally. Based on these observations, a Phase 1b study of ACT followed by Pembro in advanced OC was initiated. **Methods:** This is a single-centre, non-randomized trial of Pembro following ACT using TILs in platinum-resistant OC. Key inclusion criteria include progression within 6 months of last platinum dose and tumor suitable for harvest. Patients undergo preparative lymphodepleting chemotherapy, followed by a single TIL infusion. Therapy with Pembro 200 mg q3 weeks is initiated once toxicities grade 2 or higher have resolved. The primary objective is safety, and the regimen will be deemed feasible if at least 80% of enrolled patients receive ACT with TILs and $\geq$2 doses of Pembro without unacceptable toxicity. Secondary objectives include evaluation of response rate, overall and progression free survival. The study will enroll 12 patients to determine whether the proportion of patients in whom the treatment regimen is tolerable, P, is less than or equal to 0.50 or is greater than or equal to 0.80. If the number of patients for whom treatment is feasible is 8 or more, the hypothesis that P $\leq$ 0.50 is rejected with a target error rate of 0.20. Enrollment is currently ongoing, with TIL preparation underway for 10 patients and plan to initiate treatment in 3 of these over the next 3 months. Clinical trial information: NCT03158935.

TPS5612 Poster Session (Board #333a), Mon, 1:15 PM-4:45 PM

PRO-105, a phase II open-label study of NUC-1031 in patients with platinum-resistant ovarian cancer. *First Author: Charlie Gourley, University of Edinburgh Cancer Research UK Centre, MRC IGMM, Edinburgh, United Kingdom*

Background: Patients with platinum-resistant ovarian cancer, following $\geq$3 lines of chemotherapy have limited treatment options. NUC-1031, a phosphoramidate transformation of gemcitabine, is designed to overcome the three key resistance mechanisms associated with gemcitabine: transport, activation and breakdown. By overcoming these resistance mechanisms, NUC-1031 achieves $>$ 200-times higher intracellular concentrations of the active anti-cancer metabolite, dFdCTP, compared to gemcitabine. NUC-1031 was well tolerated and demonstrated anti-tumor activity in ovarian cancer patients (Blagden *et al,* ASCO 2015; Blagden *et al,* ESMO 2017). Based on these data, a Phase II dose-confirming study was initiated to investigate NUC-1031 in patients with platinum-resistant ovarian cancer. **Methods:** PRO-105 is a randomized open-label, two-part clinical study designed to determine the optimal dose of NUC-1031 in patients with platinum-resistant ovarian cancer who have received $\geq$3 lines of chemotherapy. The primary endpoint is Objective Response Rate at the selected dose level (500 mg/m^2 or 750 mg/m^2), assessed by a blinded independent central reviewer. Secondary endpoints include duration of response, progression-free survival, overall survival, PK/PD and patient-reported outcomes. In Part I, up to 40 patients will be randomized to NUC-1031 at 500 mg/m^2 or 750 mg/m^2 on days 1, 8 and 15 of a 28-day cycle. Randomization is stratified for BRCA 1/2 mutation status and number of prior chemotherapy lines. One dose level will be selected for further evaluation in Part II based on safety, PK, dosing intensity and clinical activity. Enrollment will continue in Part II until 44 response evaluable patients are recruited at the selected dose. To date, 22 patients with platinum-resistant ovarian cancer have been randomized into Part I of the study, which is currently recruiting across 15 US and 8 UK sites. Clinical trial information: NCT03146663.

TPS5613 Poster Session (Board #333b), Mon, 1:15 PM-4:45 PM

Phase II study of neoadjuvant IGFBP-2 vaccination with neoadjuvant carboplatin and paclitaxel in advanced ovarian cancer. *First Author: William Rayford Gwin, University of Washington, Seattle, WA*

Background: Patients with advanced ovarian cancer not amenable to primary debulking surgery are candidates for neoadjuvant chemotherapy (NACT). Patients achieving a complete pathologic response (cPR) with NACT have superior overall survival; however, the rate of cPR is only 7.5%. In ovarian cancer, tumor infiltrating lymphocytes (TIL) are critically important in prognosis. Paclitaxel and carboplatin augment Type I immunity and decrease MDSCs and Tregs. A Phase I study of an IGFBP-2 vaccine designed to augment Type 1 immunity in Stage III/IV ovarian cancer patients was safe and induced IGFBP-2 specific immunity. Vaccination during the myeloid nadir after platinum/taxane chemotherapy has shown robust Th1 immune responses. We hypothesize that vaccination against IGFBP-2 during the myeloid nadir can synergize with NACT to improve the rate of cPR through Th1 immunity, antigen specific T cells, and TIL. **Methods:** *Trial Design*: Phase II single arm study of concurrent IGFBP-2 vaccination with carboplatin and paclitaxel. Patients receive NACT IV on day 1 of each 3 week cycle and receive the IGFBP-2 vaccination on day 14. Study treatment includes 3 vaccinations, evaluations at 1 week and 6 months post vaccine and yearly follow-up for 5 years. Toxicity is assessed at baseline and through end of study. Blood and tumor tissue will be collected for immunologic monitoring and evaluation. *Eligibility:* Patients with newly diagnosed advanced stage ovarian cancer who will receive NACT with subsequent planned cytoreductive surgery. *Specific aims*: (1) Determine the rate of pCR, (2) Determine the level of TIL in residual tumor (2) Determine whether IGFBP-2 induces IGFBP-2 specific T cells, (3) Explore if there is a predictive signature for pCR when IGFBP-2 vaccination is used with NACT. *Statistical Methods*: (1) The sample size of 38 will provide 80% power to detect a significant increase in pCR to 20% when compared to NACT alone, (2) Tumor tissue will be evaluated for TIL, (3) IGFBP-2 specific INF-g/IL-10 ratios by ELISPOT will be evaluated, (4) Whole exome sequencing will be performed to correlate expression profiles with response to vaccination. *Targeted Accrual:* 7 of the planned 38 patients have been enrolled. Clinical trial information: NCT03029611.

TPS5614 Poster Session (Board #334a), Mon, 1:15 PM-4:45 PM

INNOVATE-3: Phase 3 randomized, international study of tumor treating fields (200 kHz) concomitant with weekly paclitaxel for the treatment of platinum-resistant ovarian cancer. *First Author: Eilon David Kirson, Novocure, Haifa, Israel*

Background: Tumor Treating Fields (TTFields) are a non-invasive, regional antimitotic treatment modality FDA-approved for glioblastoma. TTFields act by disrupting mitotic spindle formation during metaphase. In multiple preclinical models of ovarian cancer, TTFields (200 kHz) reduced viability of cell lines via apoptosis. TTFields has demonstrated synergistic effects with taxanes *in vitro* and *in vivo*. The Phase 2 INNOVATE clinical study [NCT02244502] demonstrated the safety of TTFields combined with weekly paclitaxel in 31 PROC (platinum-resistant ovarian cancer) patients. Patients had a median of 4.1 prior chemotherapy regimens (range: 1-11). Most patients had CTCAE grade 1-2 TTFields-related dermatitis; 6.4% had grade 3 toxicity. Median progression-free survival was 8.9 months. The INNOVATE-3 is a phase 3 study in PROC of TTFields combined with weekly paclitaxel. **Methods:** Patients with PROC (progression per RECIST V1.1) within 6 months of last platinum therapy with a maximum of two lines following the diagnosis of PROC and maximum total of five prior lines of systemic therapy will be enrolled. Patients (ECOG score 0-1) will have no peripheral neuropathy. Patients with primary refractory disease (progression during first line therapy) will be excluded. Patients will be randomized in a ratio of 1:1 to receive either weekly paclitaxel alone or weekly paclitaxel in combination with TTFields (200 kHz). Weekly paclitaxel will be administered at standard starting of dose 80 mg/m^2 weekly for 8 weeks, and then on Days 1, 8, and 15 for each subsequent 28-day cycle. TTFields will be applied in the experimental arm for at least 18 hours/day on average, and maybe continued as long as there is no progression in the abdominal or pelvic regions ("in-field region") per RECIST V1.1. Clinical follow up will be performed q4w, with radiological follow up (CT or MRI scans of the abdomen and chest) q8w. The primary endpoint will be overall survival. Main secondary endpoints include progression-free survival, objective response rate, severity and frequency of adverse events and quality of life based on EORTC QLQ-C30 with the QLQ-OV28 questionnaire.

TPS5615 Poster Session (Board #334b), Mon, 1:15 PM-4:45 PM

STATEC: A randomised trial of non-selective versus selective adjuvant therapy in high risk apparent stage 1 endometrial cancer. *First Author: Tim Mould, University College London Hospital, London, United Kingdom*

Background: The benefit of lymphadenectomy on survival in stage 1 endometrial cancer remains uncertain. STATEC is a surgical trial designed to evaluate the use of nodal status after lymph node dissection to tailor adjuvant treatment in patients with high risk apparent stage I endometrial cancer. **Methods:** DESIGN: Randomised (1:1), controlled, two-arm, phase III, multicentre, international, non-inferiority trial. ELIGIBILITY: High risk apparent FIGO stage I endometrial cancer on diagnostic endometrial sampling OR hysterectomy. If randomisation occurs after hysterectomy and BSO: FIGO grade 3 endometrioid or mucinous carcinoma, high grade serous, clear cell, undifferentiated or dedifferentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma. STRATIFICATION: participating site, histology, lymphovascular space invasion, timing of hysterectomy and bilateral salpingo-oophorectomy (BSO). TREATMENT: Arm 1: Hysterectomy and BSO, plus intraoperative bilateral pelvic and para-aortic lymph node dissection + adjuvant therapy if node positive or stage III. Arm 2: Hysterectomy and BSO+ adjuvant therapy based on stage and uterine factors. ENDPOINTS: Overall survival (primary), disease-free, endometrial cancer-event free and endometrial cancer-specific survival, pelvic and extra-pelvic relapse-free survival, cost-effectiveness, surgical adverse events, quality of life and performance of sentinel lymph node assessment (secondary). QUALITY ASSURANCE: surgical specimen processing and microscopy to local specialist gynaecological oncology site pathologists, central pathology (10% of UK patients) and surgical imaging of all Arm 1 patients. Recruitment: 4 years, with 5 years follow up. STATISTICS**:** Using the exponential parameter of 0.0040, allowable hazard ratio of 1.272, a sample size of 2000 (500 deaths) will provide 85% power, and 5% two-sided statistical significance. With 80% power, the minimum sample size is 1720 patients (430 deaths). CURRENT ENROLMENT (as of February 2018): STATEC is open in the UK, Australia and New Zealand. 7 patients have been enrolled. STATEC is registered with. Clinical trial information: NCT02566811.

6000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Results of a randomized phase III study of nimotuzumab in combination with concurrent radiotherapy and cisplatin versus radiotherapy and cisplatin alone, in locally advanced squamous cell carcinoma of the head and neck. *First Author: Vijay Maruti Patil, Tata Memorial Centre, Mumbai, India*

Background: We conducted an investigator-initiated, phase 3 randomized study to evaluate the efficacy and toxicity of addition of Nimotuzumab during concurrent chemoradiation in locally advanced squamous head and neck cancer (LASHNC). **Methods:** Adult subjects (age ≥ 18 years), with stage III-IV, LASHNC, Karnofsky performance status of ≥ 70 and adequate organ function were randomized 1:1 into either radical radiotherapy (66-70 Gy) with weekly cisplatin (30 mg/m2) (CRT arm) or the same schedule of chemoradiation along with weekly Nimotuzumab (200 mg) (NCRT arm). The primary endpoint was progression free survival (PFS) and the other key secondary endpoints were disease free survival (DFS), duration of locoregional control (LRC) and overall survival (OS). Intent to treat analysis was performed. The planned sample size was 536 for superiority margin of 12%, assuming PFS of 60% with 80% power and alpha of 0.05. **Results:** 536 patients were equally allocated between both arms. The median follow up was 33.0 months (95%CI 30.7-35.2 months). The PFS was significantly longer in the patients treated in the NCRT arm (2 year PFS 58.9% versus 49.5%, HR = 0.74; 95% CI 0.56-0.95; P = 0.022). The median duration of PFS was 60.3 months (95% CI 29.4-NA) in the NCRT arm (P = 0.023) and 21 months (95% CI 15.1-NA) in the CRT arm. Addition of Nimotuzumab improved the LRC (HR = 0.75; 95% CI 0.57-0.97, P = 0.030), DFS (HR = 0.75; 95% CI 0.57-0.97, P = 0.030) and had a trend towards improvement in OS (HR = 0.85, 95% CI 0.65-1.10, p = 0.222). Grade 3-5 adverse events (CTCAE version 4.03) were similar between the 2 arms except for the higher incidence mucositis in the NCRT arm (66.7% versus 55.8%, p = 0.010). **Conclusion:** In conclusion, Nimotuzumab in combination with cisplatin and radiotherapy was superior to cisplatin and radiotherapy in improving the PFS, LRC and DFS. This combination provides a new therapeutic option in the armamentarium against LASHNC. Clinical trial information: CTRI/2014/09/004980.

6001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Definitive cetuximab-based (CRT-CX) vs. non-cetuximab based chemoradiation (CRT) in older patients with squamous cell carcinoma of the head and neck (HNSCC): Analysis of the SEER-Medicare linked database. *First Author: Dan Paul Zandberg, University of Maryland, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD*

Background: Overall survival (OS) after definitive CRT-CX vs. definitive CRT has not been adequately evaluated outside of younger more highly selected clinical-trial populations with locally advanced HNSCC. **Methods:** We used the SEER-Medicare linked database to evaluate OS in HNSCC patients diagnosed over 2005-2011, following FDA approval of cetuximab in combination with radiation therapy (RT) in March 2006. **Results:** 2135 beneficiaries were identified. Median age was 73 (66-104) years. Primary subsites were oropharynx (61%), hypopharynx (15%), nasopharynx (5%), and larynx (19%). CRT-CX was associated with worse OS compared to CRT (P < 0.005), and similar OS to RT (P = 0.21); 5-year OS was 46% for CRT, 35% for CRT-CX, 32% for RT. Median survival was 4.5(3.8-4.9), 2.5(2.2-3.0), and 2.2 (2.0-3.0) years after CRT, CRT-CX, RT, respectively. Patients were more likely to receive CRT-CX vs. CRT if they had oropharyngeal vs nasopharyngeal primary, Charlson comorbidity index 2 vs 0, older age at diagnosis. Multivariable Cox regression showed that CRT-CX was associated with a higher risk of death compared to CRT (HR = 1.23, 1.07- 1.42; p = 0.005), after stratifying by stage and primary site, and adjusting for gender, race, age, income, Charlson comorbidity index, marital status, hospital type, and year of diagnosis. Regarding treatment-related toxicity, CRT was associated with significantly higher hearing loss within the first 3 months compared to CRT-CX (9.3% vs. 4.1%, p < 0.001), but there were no differences in dysphagia, gastrostomy tube placement, pneumonia, and weight loss over the first 12 months after diagnosis. **Conclusions:** Definitive treatment with CRT-CX was associated with inferior OS compared to CRT even after adjustment for established prognostic factors, and with similar toxicity, in the SEER-Medicare patient population. Survival after CRT-CX was not significantly different from RT alone. Despite the limitations to comparative effectiveness evaluation in population-based registries, our data suggest that non-cetuximab based chemoradiation should be used for eligible older HNSCC patients.

LBA6002 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Are women with head and neck cancer undertreated? *First Author: Annie Park, Kaiser Permanente, Santa Clara, CA*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

6003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Treatment deintensification to surgery only for stage I human papillomavirus-associated oropharyngeal cancer. *First Author: John David Cramer, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: Human papillomavirus-associated (HPV+) oropharyngeal cancer (OPC) is an emerging entity with improved prognosis and distinct staging system. We assessed if deintensificaiton to surgery only decreased survival for stage I patients at low or intermittent risk compared with surgery with adjuvant radiation (RT) or chemoradiation (CRT). **Methods:** From the National Cancer Data Base (2010-2014), we identified patients with stage I HPV+ OPC (after restaging with eighth edition guidelines) treated with surgery only or with adjuvant RT or CRT. We compared survival for low risk patients (≤1 metastatic lymph nodes with no adverse features) and intermediate risk patients (2-4 metastatic lymph nodes, microscopic extranodal extension (ENE) or lymphovascular invasion). We excluded high risk patients with positive margins or macroscopic ENE. **Results:** We identified 2,463 patients with median follow-up of 44.3 months. In the low risk group 4-year overall survival was 93.0% with surgery only versus 95.6% with surgery + RT and 93.0% with surgery + CRT. In the intermediate risk group, 4-year overall survival was 92.2% with surgery only versus 93.3% with surgery + RT and 93.2% with surgery + CRT. On multivariate analysis, we observed no difference in survival with treatment between surgery only versus surgery + RT or surgery + CRT for both the low risk group (hazard ratio (HR) 0.75; CI 0.32-1.79 and HR 1.03; CI 0.42-2.51 respectively) or the intermediate risk group (HR 0.78; CI 0.42-1.46 and HR 0.85; CI 0.47-1.53 respectively). **Conclusions:** This offers retrospective evidence that surgery only for stage I patients at both low and intermediate risk provides equivalent survival to surgery and adjuvant therapy. This offers clinical equipoise for randomization to surgery only for stage I patients in future deintensification trials.

Overall survival based on treatment and risk level.

Group	1-y	2-y	3-y	4-y	Log Rank
Low Risk					
Surgery Only (n = 308)	96.7%	95.0%	94.2%	93.0%	0.59
Surgery + RT (n = 167)	99.4%	97.0%	95.6%	95.6%	
Surgery + CRT (n = 171)	99.4%	96.9%	94.9%	93.0%	
Intermediate Risk					
Surgery Only (n = 228)	97.8%	96.8%	94.1%	92.2%	0.77
Surgery + RT (n = 589)	99.3%	97.6%	96.2%	93.3%	
Surgery + CRT (n = 1,000)	99.0%	97.6%	95.8%	93.2%	

6004 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase II study: Induction chemotherapy and transoral surgery as definitive treatment (Tx) for locally advanced oropharyngeal squamous cell carcinoma (OPSCC): A novel approach. *First Author: Robert S. Siegel, George Washington University School of Medicine, Washington, DC*

Background: The standard of care for OPSCC includes chemoradiation (CRT) or surgery with adjuvant radiation (RT). However, RT is associated with significant life long morbidity. We assessed the efficacy of a two-drug induction regimen, followed by transoral robotic assisted surgery (TORS) & neck dissection for locally advanced OPSCC. **Methods:** This is an IRB approved single-arm phase II study for untreated stage III or IVA (AJCC 7th edition) OPSCC patients (pts) with an ECOG < 2 and GFR >50 cc. Induction chemotherapy consisted of cisplatin 75 mg/m2 and docetaxel 75 mg/m2 every 21 days for 3 cycles. Tumor shrinkage was examined after each cycle. If the primary tumor was $\geq$ 80% smaller, pts underwent TORS and neck dissection(s). At post-op visits, flexible laryngoscopy, blood tests, and imaging with PET/CT and/or MRI were done. Short and long term toxicity, progression-free survival, overall survival, and quality of life (QOL) were evaluated. **Results:** Twenty pts were treated, nineteen were male, 17 were Caucasian, and 19 were HPV+. Median age at diagnosis was 57. Tumors involved the tonsil (13 pts) and base of tongue (7 pts). Three pts were stage III, and 17 were stage IVA. Tumor size was reduced by 53.4%, 80% and 90.5% after the 1st, 2nd and 3rd induction cycles respectively. Pathologic CR of the primary site occurred in 15 pts and CR among LN neck dissections occurred in 13 pts. Four pts were given dose-reduced chemo and one pt was changed to carboplatin per protocol because of renal dysfunction. Pre vs post tx QOL scores did not change. At a mean follow-up of 21 months (range 7.6 to 32.1), 18 pts are alive and NED. Three pts recurred a mean of 2.2 months after surgery, and were treated with salvage CRT. Two pts died of metastatic disease, the third is alive and well. All 3 pts had positive LN (9 LN, 3 LN and 1 LN) at surgery. **Conclusions:** Cisplatin + docetaxel followed by TORS & neck resections appears to be an effective model for the definitive treatment for OPSCC, while avoiding the adverse effects of RT. Clinical trial information: NCT02760667.

6005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Survival outcomes by HPV status in non-oropharyngeal head and neck cancers: A propensity score matched analysis of population level data. *First Author: Sibo Tian, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: The impact of HPV status in non-oropharynx (OPX) cancers is unclear. Limited sample sizes, and unadjusted comparisons have confounded interpretation. Our goal was to evaluate the prognostic value of HPV status in non-OPX cancers using an administrative database. **Methods:** The National Cancer Data Base was queried to capture patients diagnosed between 2010-2013 with invasive cancers of OPX, hypopharynx (HPX), larynx (LX), and oral cavity (OC). HPV positivity was defined by high-risk subtypes, i.e. 16 & 18. Patients with HPV status, survival outcomes and non-metastatic disease were analyzed. Survival was estimated using the Kaplan-Meier method, and log-rank tests were used to compare distributions. Propensity matched methods were utilized by reweighting patients using the inverse probability of treatment weighting (IPTW) approach; included variables were: age, sex, Charlson-Deyo score, treatment with surgery, chemotherapy, radiotherapy, group stage, and subsite where appropriate. Analyses were stratified by AJCC 7th edition stage I-II vs III-IVB. **Results:** A total of 27,954 patients were included: 1,140 cases of HPX, 5,074 cases of LX, 4,540 cases of OC, and 17,200 cases of OPX. The proportion of HPV positive cases were: 20.9% in HPX, 14.2% in LX, 12.2% in OC, and 67.5% in OPX. HPV positivity was associated with superior overall survival (OS) in multiple non-OPX groups. In HPX, actuarial OS by HPV status were at 2-yr 75.9% vs 59.6%; at 5-yr 60.2% vs 33.6% (HPV+ vs HPV-); survival was significant with IPTW (HR 0.56, $p < 0.001$). HPV-positivity was associated with superior OS for stage III-IVB LX cancer; OS at 2-yr was 75.3% vs 66.2% (IPTW HR 0.81, $p = 0.029$). HPV status was not prognostic overall in OC. HPV status in stage III-IVB OC patients trended towards significance (IPTW HR 0.82, $p = 0.059$); OS at 2-yr was 64.9% vs 59.1%. Survival outcomes by HPV status in OPX were: stage I-II IPTW HR 0.45 ($p < 0.001$); stage III-IVB HR 0.42, ($p < 0.001$). **Conclusions:** HPV positivity was associated with improved survival in HPX, locally-advanced LX, and potentially locally-advanced OC patients. These finding, if prospectively validated, may have implications for future risk stratification.

6006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Results of a randomized, placebo (PBO) controlled, double-blind P2b trial of GC4419 (avisopasem manganese) to reduce duration, incidence and severity and delay onset of severe radiation-related oral mucositis (SOM) in patients (pts) with locally advanced squamous cell cancer of the oral cavity (OC) or oropharynx (OP). *First Author: Carryn M. Anderson, University of Iowa Hospitals and Clinics, Iowa City, IA*

Background: Intensity-modulated radiotherapy (IMRT) plus cisplatin is established treatment for locally advanced OC/OP cancer, but appx. 70% of patients develop SOM, defined as WHO Grade 3 or 4, which limits patients' ability to eat solids (Gr 3) or liquids (Gr 4, requiring artificial nutrition). An RT-induced burst of superoxide initiates oral mucositis (OM) development. GC4419, a superoxide dismutase mimetic, interrupts this process by potently converting superoxide to H_2O_2. It showed promising reductions of SOM in a published open-label Phase 1b/2a trial (IJROBP 1 Feb 2018). **Methods:** 223 pts with OC or OP cancer receiving 70 Gy IMRT ($\geq$50 Gy to $>$ 2 oral sites) plus cisplatin (qwk or q3wk), were randomized 1:1:1 to PBO, 30 or 90 mg of GC4419, by 60-minute IV infusion, M-F before each RT fraction. OM by the WHO scale was assessed by trained evaluators biw during RT & qwk for up to 8 wks post RT. Primary endpoint was duration of SOM. Secondary endpoints included incidence & time to onset of SOM. Analyses (each active dose v PBO, ITT) proceeded by a sequential, conditional approach; 2-sided $\alpha = 0.05$. **Results:** 90 mg GC4419 reduced SOM across endpoints, including a statistically significant reduction in the primary endpoint of duration. Efficacy results with 30 mg were intermediate and did not reach significance. Baseline patient & tumor characteristics, & treatment delivery, were well-balanced. Safety was comparable across arms with no significant GC4419-specific toxicity or increased toxicity of IMRT/cisplatin. **Conclusions:** GC4419 provides a clinically meaningful reduction of SOM in terms of duration, incidence and severity (Grade 4), with a safety profile comparable to placebo. Clinical trial information: NCT02508389.

	PBO	30mg	90mg	90mg vs. PBO	
N	74	73	76	Relative δ	p =
Duration SOM, median days	19	8	1.5	92%	0.024
Incidence SOM thru 60 Gy	58%	40%	37%	36%	0.010*
Incidence SOM thru last RT	65%	60%	43%	34%	0.009*
Incidence Grade 4 OM	30%	21%	16%	47%	0.045*
Onset SOM, median days	39	47	61	56%	0.080*

*nominal p value, pre-specified secondary endpoint

6007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Phase II trial of high-dose melatonin oral gel for the prevention and treatment of oral mucositis in H&N cancer patients undergoing chemoradiation (MUCOMEL). *First Author: Alicia Lozano, Institut Català d'Oncologia, Barcelona, Spain*

Background: Severe Oral Mucositis (SOM) is one of the most significant adverse events (AE) in H&N cancer patients undergoing concurrent chemo/bio-radiotherapy. The objective of the trial is to evaluate the safety and efficacy of melatonin (MLT) oral gel in the prevention and treatment of oral mucositis (OM) in H&N cancer patients. **Methods:** Multicenter, prospective, randomized, double-blind, placebo-controlled study. Eligible patients were randomly assigned (1:1 ratio) to receive 3% MLT or matching placebo (PLC) oral gel. Patients received once daily (5 days/week) IMRT radiation therapy (total dose $\geq$ 66 Gy). Concurrent systemic treatments were cisplatin Q3W or cetuximab Q1W. All patients received concomitant standard symptomatic treatment for OM. Efficacy analyses were performed on a mITT population (patients receiving at least one medication dose) or ITT. Efficacy endpoints were either RTOG or NCI CTCv4, G3-4 oral mucositis (SOM) and G2-4 ulcerative oral mucositis (UOM). Comparison of incidence rates of SOM/UOM: Fisher exact test; comparison of duration of SOM/UOM: U Mann-Whitney test. **Results:** 84 patients (ITT: 42 MLT/42PLC; mITT: 40 MLT/39 PLC) were included. Most frequent tumor sites were oropharynx (n = 38; 45%) and oral cavity (n = 24; 29%). Concurrent systemic treatments were cisplatin (n = 54; 64%) or cetuximab (n = 30; 36%). Efficacy results in the mITT population (incidence) and ITT (duration) Clinical trial information: NCT02630004. No relevant differences for AEs between groups or for overall response rate after 2 months of IMRT completion. **Conclusions:** Treatment with MLT oral gel resulted in a consistent trend to a lower incidence and shorter duration of SOM as well as a significantly shorter duration of UOM. These benefits were more marked in the subgroup of patients receiving cisplatin. These results warrant further clinical development.

					Median duration in SOM/UOM patients (days)					
		SOM Incidence (%)			SOM			UOM		
	Scale	MLT	PLC	p value	MLT	PLC	p value	MLT	PLC	p value
Overall	NCI	50	67	0.17	17	22	0.21	39	58	**0.004**
	RTOG	53	64	0.36	18	24	0.11	42	49	**0.06**
	RTOG or NCI	57	79	**0.05**			-			
Cisplatin	NCI	41	64	**0.09**	20	24	0.82	35	52	**0.03**
	RTOG	37	61	0.16	12	19	0.41	38	52	**0.03**
	RTOG or NCI	44	78	**0.02**			-			
Cetuximab	NCI	62	63	1.00	7	21	**0.07**	51	75	0.12

6008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Multicenter phase II trial of palbociclib, a selective cyclin dependent kinase (CDK) 4/6 inhibitor, and cetuximab in platinum-resistant HPV unrelated (-) recurrent/metastatic head and neck squamous cell carcinoma (RM HNSCC). *First Author: Douglas Adkins, Washington University School of Medicine in St. Louis and Siteman Cancer Center, St. Louis, MO*

Background: In platinum-resistant RM-HNSCC, the efficacy of cetuximab is modest with a tumor response rate of 13%, median time to progression of 2.3 months and median overall survival (OS) of 6 months (Vermorken *JCO* 2007). In HPV (-) HNSCC, p16 inactivation and/or CCND1 (cyclin D1) amplification are ubiquitous events that result in hyperactivation of the CDK/cyclin D regulatory complex and Rb inactivation. Deregulated cyclin D1 expression is a mechanism of resistance to EGFR inhibitors. In a phase I trial, palbociclib, a potent CDK4/6 inhibitor, given with cetuximab, was safe and tumor responses were observed in RM HNSCC (Adkins *Oral Oncology* 2016). **Methods:** In a phase II trial, patients with platinum-resistant, cetuximab-naive HPV (-) RM HNSCC were treated with palbociclib 125 mg po/d Days 1-21 of 28 day cycles and weekly cetuximab. Platinum-resistance was defined as: progression on platinum in the RM setting; cetuximab-naïve was defined as: no prior cetuximab for RM disease. HPV (-) disease was defined as SCC of the oral cavity, larynx, hypopharynx or p16 negative SCC of the oropharynx. Tumor response assessments (RECIST 1.1) were performed every 2 cycles. We hypothesized that palbociclib and cetuximab would increase the tumor response rate from 13% (historical data with cetuximab) to $>$ 26%. Futility assessments of response and toxicity occurred after every 6 patients (sample size: 30) using a Bayesian monitoring method. **Results:** 30 patients were enrolled. Median age 67 years (range: 26-84). Sites of recurrence: local/regional (6), distant (8), or both (16). Tumor response occurred in 35% (8 of 23 evaluable to date). Decrease in target lesions occurred in 57% (13 of 23 evaluable). Median progression free survival (PFS) was 6.4 months and median OS was 12.1 months. Immunotherapy was given to three patients before and eight after study participation. **Conclusions:** Palbociclib and cetuximab resulted in a robust tumor response rate and prolongation of PFS and OS in platinum-resistant HPV (-) RM-HNSCC. The median OS of 12.1 months is the longest reported for patients with platinum-resistant RM HNSCC. Clinical trial information: NCT02101034.

6009 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

A phase II randomized trial of nivolumab with stereotactic body radiotherapy (SBRT) versus nivolumab alone in metastatic (M1) head and neck squamous cell carcinoma (HNSCC). *First Author: Sean Matthew McBride, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A minority of patients with metastatic HNSCC respond to the anti-programmed death (PD-1) monoclonal antibody, Nivolumab (Nivo). We sought to determine whether targeted radiation to a single lesion combined with Nivo would enhance tumor regression in non-irradiated lesions (abscopal response) and improve outcomes. **Methods:** Patients with M1 HNSCC (including nasopharynx) with at least two RECIST 1.1 measurable lesions were randomized with stratification for viral status (EBV/HPV pos vs. neg) 1:1 to either Nivo alone q 2 weeks or Nivo with SBRT to a single lesion (9 Gy x 3) between the 1st and 2nd doses of Nivo. The primary end-point was objective response rate (ORR) in non-irradiated lesions using RECIST 1.1. Secondary analyses included overall survival (OS), progression free-survival (PFS), and duration-of-response (DOR). We hypothesized that SBRT added to Nivo would increase ORR from 15% to 45%. Enrolling 53 patients thus provides a one-sided alpha of 0.10 and a power of 0.80. **Results:** 53 patients were randomized, 26 to Nivo alone and 27 to Nivo+SBRT; the lung was the most common irradiated site (59%). There were no significant differences between arms in terms of age ($p = 0.12$), viral status (pos vs neg; $p = 0.786$), primary site (oropharynx vs. nasopharynx vs other; $p = 1.0$), or median lines of prior chemotherapy (1; $p = 0.73$). ORR in the Nivo alone arm was 26.9% (95% CI: 13.7, 46.1%) vs 22.2% (95% CI: 10.6%, 40.8%) in the Nivo+SBRT arm ($p = 0.94$). Median DOR with Nivo alone was not reached (NR) vs 9.3 months (95% CI: 5.52, NR) with Nivo+SBRT ($p = 0.21$). Median follow-up amongst surviving patients was 12.8 mos; OS at 1 year was 64% (95% CI: 47%, 88%) in the Nivo alone arm vs 53% (95% CI: 36%, 79%) in the Nivo+SBRT arm ($p = 0.79$); median PFS was 1.9 mos (95% CI: 1.78, NR) with Nivo vs 2.4 mos (95% CI: 1.0, 11.4) with Nivo+SBRT ($p = 0.8$). Treatment-related $\geq$ Grade 3 toxicities in the Nivo alone vs Nivo+SBRT arms occurred in 15% vs. 11% of patients ($p = 0.96$). **Conclusions:** While safe, the addition of SBRT to Nivo in M1 HNSCC failed to improve ORR, PFS, or OS. This is the first randomized evaluation of the abscopal response in any tumor histology. Biomarker analyses are near completion. Clinical trial information: 02684253.

6010 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Safety evaluation of nivolumab (Nivo) concomitant with cetuximab-radiotherapy for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG 3504. *First Author: Robert L. Ferris, University of Pittsburgh Medical Center and University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Nivolumab, which inhibits the programmed death-1 (PD-1) receptor, improved survival for patients (pts) with platinum-refractory recurrent/metastatic HNSCC compared with standard therapy. This trial evaluates the safety of adding nivo to 4 standard radiotherapy (RT) regimens for pts with newly diagnosed IR/HR HNSCC (Table). Safety data for cohort 3 (cetuximab) are reported. Efficacy data for cohorts 1, 2, and 3 will be reported at the presentation. **Methods:** Eligibility includes IR (p16+, oropharynx (OP) T1-2N2b-N3/T3-4N0-3, $>$10 pack-years (pys) or T4N0-N3, T1-3N3 $\leq$10 pys) and HR HNSCC (oral cavity, larynx, hypopharynx, or p16(-) OP, stage T1-2N2a-N3 or T3-4N0-3). 10 pts are enrolled to obtain 8 evaluable pts. Primary endpoint is dose-limiting toxicity (DLT), defined as nivo-related: $\geq$grade 3 adverse event (AE) unresolved to $\leq$grade 1 in $\leq$28 days; RT delay $>$2 wks; incomplete RT; or inability to receive $\geq$70% of cetuximab. DLT window was from first nivo dose (day -14) to 28 days post RT. $>$2 DLTs in 8 evaluable pts is unacceptable. **Results:** Of 10 enrolled pts for cohort 3: median age 61.5, 80% male, 70% Caucasian, 70% PS 0, 80% $>$10 pys, 60% p16(+) OP cancer, 60% T3-4 and 100% N2-3 disease. 1 pt was inevaluable for DLT due to withdrawal of consent and 1 pt has not yet completed the DLT observation period. 1 DLT (mucositis) was reported in 8 evaluable pts; 1 other grade 3 AE attributed to nivo was reported (lipase increase) but was not a DLT. 11 SAEs in 3 pts, but none nivo-related. 7/8 pts completed RT, 7/8 pts completed cetuximab; 5 pts completed 10 concurrent doses of nivo, 1 pt received 6 doses, 1 pt 7 doses, and 1 pt is ongoing after 8 doses. **Conclusions:** Nivo is safe and feasible to administer concomitant with a cetuximab-RT regimen for patients with newly diagnosed IR/HR HNSCC. Clinical trial information: NCT02764593.

Cohort	Cis Eligible	Nivo C: concurrent A: adjuvant	Chemotherapy	RT IMRT 70 Gy/7 wk	N enrolled
1	Y	C: 240 mgs q14d X10 A: 480 mgs q28d X7	Weekly Cis (40 mg/m2)	Y	10
2	Y	C : 240-360 mg q21d X6 A : 480 mg q28d X7	High dose Cis (100 mg/m2 q 21d)	Y	10
3	Y	C: 240 mgs q14d X10 A: 480 mgs q28d X7	Cetuximab	Y	10
4	N	C: 240 mgs q14d X10 A: 480 mgs q28d X7	–	Y	5

6011 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Neoadjuvant anti-OX40 (MEDI6469) prior to surgery in head and neck squamous cell carcinoma. *First Author: Richard Bryan Bell, Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR*

Background: This phase Ib clinical trial was performed to investigate an agonistic murine antibody to OX40 (MEDI6469) at various dose intervals prior to definitive surgical resection in patients with head and neck squamous cell carcinoma (HNSCC). **Methods:** 17 patients with resectable stage III-IVA HNSCC (11 = HPV-; 7 = HPV+) received MEDI6469 0.4mg/kg x 3 doses administered on day 1, day 3-4 and day 5-6 of the study, followed by definitive surgical excision and neck dissection either 2 days, 1 week or 2 weeks after infusion of anti-OX40. Primary tumor, lymph nodes and peripheral blood (PB) were obtained at baseline and at the time of surgery to characterize the circulating and tumor infiltrating lymphocyte (TIL) cell populations based on flow cytometry (FC) and multiplex immunohistochemistry (mIHC) as well as whole transcriptome analysis via RNA-sequencing (seq). **Results:** MEDI6469 administration was well tolerated, surgery was not delayed, and there were no grade 3 or 4 adverse events related to MEDI6469 treatment. With a median follow up of 20 months, 13/17 patients are alive without disease. 4 patients had evidence of an immunological response to treatment on FC and mIHC that peaked between 12 and 19 days after MEDI6469 infusion and was characterized by: 1) increased Ki67+CD38+ICOS+ CD4+ and CD8+ memory T-cell populations in both the TME and PB, 2) increased expression of CD39, ICOS and PD-1 on CD4+ TIL (N = 10), and 3) increased frequency of tumor-reactive, tissue resident CD39+CD103+CD8+ T cells (N = 5). RNA-seq analysis of the primary tumor in a subset of patients (N = 7) revealed significant differences between immunological responders and non-responders in genes associated with MHC I-mediated antigen processing and presentation. Subsequent immune-subtype deconvolution analysis of the RNA data revealed all responders segregated with above median levels of CD39+CD103+CD8+ T cells, consistent with flow and mIHC. **Conclusions:** Preoperative MEDI6469 administration is safe and resulted in increased activation and proliferation of T cells within the tumor, peaking two weeks following infusion. Immunologic changes are associated with MHC I-mediated antigen processing machinery. Clinical trial information: NCT02274155.

6013 Poster Discussion Session; Displayed in Poster Session (Board #1), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs standard of care (SOC) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) in KEYNOTE-040. *First Author: Ezra E.W. Cohen, Moores Cancer Center at UC San Diego Health, University of California, San Diego, La Jolla, CA*

Background: In KEYNOTE-040 (NCT02252042) (N = 495), pembro 200 mg Q3W for 24 mo yielded a clinically meaningful improvement in overall survival over SOC choice of methotrexate (Mtx), docetaxel (Dtx), or cetuximab (Ctx) in patients (pts) with R/M HNSCC, with fewer grade 3-5 drug-related adverse events. We present results of prespecified exploratory HRQoL analyses. **Methods:** The EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D were administered electronically at baseline; wks 3, 6, 9; then every 6 wk up to 1 y or end of treatment; and at 30-day safety follow-up visit. HRQoL was analyzed in pts who received ≥1 dose of study drug and had ≥1 HRQoL assessment. Mean change from baseline to wk 15 was compared using a constrained longitudinal data analysis model. Time to deterioration (TTD) (defined as ≥10-point decline from baseline) was estimated by Kaplan-Meier method and Cox regression model. **Results:** The HRQoL population included 469 pts (241 pembro; 228 SOC). HRQoL compliance at wk 15 was 75.3% for pembro and 74.6% for SOC. From baseline to wk 15, global health status (GHS)/QoL scores were stable for pembro (least-squares [LS] mean, 0.39; 95% CI, –3.00, 3.78) but worsened for SOC (LS mean –5.86; 95% CI, –9.6 8, –2.04); difference in LS mean between arms was 6.25 points (95% CI, 1.32, 11.18; nominal 2-sided *P*= 0.013). Subgroup analyses by SOC choice identified a greater difference in LS mean for GHS/QoL scores with pembro vs Dtx (10.23; 95% CI, 3.15, 17.30) compared with pembro vs Mtx (6.21; 95% CI, –4.57, 16.99) or Ctx (–1.44; 95% CI, –11.43, 8.56). Median TTD in GHS/QoL with pembro vs SOC was 4.8 and 2.8 mo (HR, 0.79; 95% CI, 0.59, 1.05; nominal 1-sided *P*= 0.048). Pts in the pembro arm generally had stable functioning and symptom scores at wk 15; no notable between-group differences were seen. **Conclusions:** Over 15 wks, pembro-treated pts had stable GHS/QoL; those receiving SOC generally showed a decline. This effect was more marked for Dtx-treated pts. Additional HRQoL analyses by SOC choice will further assess trends. Along with previously presented efficacy and safety results, these data support the clinically meaningful benefit of pembro in R/M HNSCC. Clinical trial information: NCT02252042.

6014 Poster Discussion Session; Displayed in Poster Session (Board #2), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Association of immune-related adverse events (irAEs) with improved response, progression-free survival, and overall survival for patients with metastatic head and neck cancer receiving anti-PD-1 therapy. *First Author: Corey Christian Foster, Department of Radiation & Cellular Oncology, The University of Chicago Medicine, Chicago, IL*

Background: Anti-programmed death receptor-1 (PD-1) therapies are approved for recurrent/metastatic head and neck (H&N) cancer progressing on or after platinum-based chemotherapy, and immune competence may modulate anti-tumor response. We hypothesized that developing immune-related adverse events (irAEs) while receiving anti-PD-1 therapy for metastatic H&N cancer would be associated with improved outcomes. **Methods:** 114 patients with metastatic H&N cancer unselected for PD-ligand 1 (PD-L1) status received anti-PD-1 therapy. Adverse events (AEs) were prospectively graded using CTCAE v4.0. irAEs were any possibly immune-mediated AE regardless of attribution. Univariate and multivariate logistic regression analyzed the relationship between irAEs and overall response rate (ORR) measured by RECIST v1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. **Results:** Median follow-up was 8.6 months, and follow-up did not significantly differ between irAE+/- groups (p = 0.72). Baseline characteristics including known PD-L1+ (53.1% irAE+ vs. 49.2% irAE-, p = 0.76) were comparable. 59 irAEs occurred in 49 patients. irAEs were classified as dermatologic (n = 20), pulmonary (n = 1), GI (n = 1), endocrine (n = 14), musculoskeletal (n = 15), ophthalmologic (n = 2), or hepatic (n = 6). 5 patients (10.2%) experienced grade ≥3 irAE. ORR was higher for the irAE+ (30.6%) compared to the irAE- (12.3%) group (p = 0.02). Median PFS was 6.9 months for irAE+ and 2.1 months for irAE- patients (p = 0.0004), while median OS was 12.5 months and 6.8 months (p = 0.007), respectively. On multivariate analyses, irAE+ was independently associated with improved ORR (p = 0.03), PFS (p = 0.009), and OS (p = 0.003). **Conclusions:** Developing irAEs while receiving anti-PD-1 therapy is associated with superior ORR, PFS, and, in particular, OS in this cohort of H&N cancer patients unselected for PD-L1 status. The ability to develop irAEs may be an indicator of immune competence and further investigation of biomarkers of immune competence is warranted.

6015 Poster Discussion Session; Displayed in Poster Session (Board #3), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Response to salvage chemotherapy after progression on immune checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck. *First Author: Khalil Saleh, Departemnt of Head and neck, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Immune checkpoint inhibitors (ICI) have shown efficacy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) with an overall response rate (ORR) ranging from 13 to 17%. Recent data suggest that exposure to ICI potentially improves ORR to salvage chemotherapy (SCT) in advanced non-small cell lung carcinoma. We evaluated responses to chemotherapy in R/M SCCHN patients after progression on ICI. **Methods:** A retrospective study was conducted at 4 French referral centers. Eligibility criteria were patients treated with ICI for R/M SCCHN, who progressed after treatment with ICI (primary or secondary resistant to ICI) and received SCT between September 2014 and January 2018 and for whom efficacy data were available. Clinical and radiological data were collected from review of medical records. **Results:** Of 232 patients treated with ICI (anti-PD-1, anti-PD-L1, anti-CTLA-4 and anti-KIR), 82 met eligibility criteria: 84% were male, median age was 60 years old. ICI was given as monotherapy in 45% of patients or as combination in 55%. SCT included taxane-based regimen (56%), platinum-based regimen (37%), and methotrexate (7%). Cetuximab was administered in combination with taxanes or platinum in 50% of patients. The median number of treatment lines prior to SCT was 2 (range 1-6). The ORR to SCT was 30% (95% confidence interval: 21%-40%). Three patients (4%) presented complete response and 22 patients (27%) had partial response. The disease control rate was 57%. The age at initiation of SCT, initial tumor location, number of prior chemotherapy regimens, type of chemotherapy prior to ICI, best response to ICI, site of relapse and ECOG at SCT were not significantly associated with response to SCT on univariate analysis. **Conclusions:** In R/M SCCHN pretreated with ICI, the ORR to SCT was 30% higher than figures of historical cohorts in this setting. This suggests that exposure to ICI may increase tumor sensitivity to chemotherapy. Further investigations are warranted.

6016 Poster Discussion Session; Displayed in Poster Session (Board #4), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck. *First Author: Matthew H. Taylor, Knight Cancer Institute, Oregon Health and Science University, Portland, OR*

Background: Lenvatinib (LEN) is a multikinase inhibitor of vascular endothelial growth factor receptor 1−3, fibroblast growth factor receptor 1−4, platelet-derived growth factor receptor α, RET, and KIT. Pembrolizumab (PEM) is an anti-PD-1 antibody approved for the second-line treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) based on durable responses and an objective response rate (ORR) of 16% (Bauml J et al, *J Clin Oncol* 2017). We report initial results of the SCCHN cohort from a phase 1b/2 trial of the LEN + PEM combination (NCT02501096). **Methods:** In this multicenter, open-label study, patients (pts) with measurable, confirmed metastatic SCCHN and ECOG performance status ≤1 received LEN (20 mg/day orally) + PEM (200 mg Q3W, IV). Pts were not preselected based on PD-L1 status. Tumor assessments were performed by study investigators using immune-related RECIST (irRECIST). The phase 2 primary endpoint was ORR at 24 weeks (ORR_{WK24}). Secondary endpoints included ORR, progression-free survival (PFS), and duration of response (DOR), which is calculated for pts with complete or partial responses. **Results:** At data cutoff of August 1, 2017, 22 pts with SCCHN (regardless of PD-L1 status) were enrolled. 86% of pts had ≥1 prior anticancer therapy. Median follow-up for PFS was 7.6 months (95% confidence interval [CI], 4.2–12.6) per irRECIST. Efficacy outcomes are summarized in the table. Grade 3 or 4 AEs occurred in 91% of pts (grade 4 AEs in 14%). However, 4 (18%) discontinued study treatment due to AEs. The most common AEs were fatigue (55%), decreased appetite (41%), hypertension (41%), diarrhea (36%), and nausea (36%). Updated data will be presented. **Conclusions:** LEN + PEM demonstrated promising clinical activity and manageable toxicities, supporting further evaluation of the LEN + PEM combination in pts with SCCHN. Clinical trial information: NCT02501096.

Outcome	irRECIST (N = 22)
ORR_{WK24}, n (%)*	8 (36.4)
95% CI	17.2–59.3
ORR, n (%)†	8 (36.4)
95% CI	17.2–59.3
Median DOR, months (95% CI)‡	8.2 (2.2–not estimable)
Median PFS, months (95% CI)	8.2 (4.3–not estimable)
PFS rate at 12 months, % (95% CI)	37.2 (12.8–62.2)

*8 partial responses (PR). †7 PRs, 1 complete response. ‡4 of the 8 (50%) responders achieved a DOR of > 6 months.

6017 Poster Discussion Session; Displayed in Poster Session (Board #5), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase II multi-site investigation of neoadjuvant pembrolizumab and adjuvant concurrent radiation and pembrolizumab with or without cisplatin in resected head and neck squamous cell carcinoma. *First Author: Trisha Michel Wise-Draper, University of Cincinnati Cancer Institute, Cincinnati, OH*

Background: 2Despite aggressive adjuvant treatment, locally advanced HNSCC patients undergoing primary surgical resection with high risk [HR] features (extracapsular extension of lymph nodes (LN) and/or positive margins) have 3 year disease free survival (DFS) of 47-57%. Pre-clinically, radiation upregulates the immune checkpoint PD-L1 and importantly PD-L1 blockade concurrently with radiation resulted in improved overall survival (OS) in mice bearing HNSCC tumors. Therefore, we initiated a window of opportunity study "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093) supported by Merck. **Methods:** Clinically high risk (T3/4 stage and/or ≥2 + LNs) patients received the PD-1 antibody, pembrolizumab (200 mg I.V. x 1), 1-3 weeks before resection. Adjuvant concurrent pembrolizumab (q3 wks x 6 doses) and radiation (60-66Gy) were administered, along with weekly cisplatin (40mg/m2) for those with HR features. Pre- and post-surgical specimens were archived for H&E, immunohistochemistry, RNAScope and Nanostring. Safety lead-in included first 8 patients of each arm and dose limiting toxicity (DLT) was determined by delay in surgery, radiation and/or cisplatin. **Results:** Twenty-eight of 80 planned patients have been enrolled with 23 evaluable for efficacy. Characteristics included median age of 52 (range, 27-80), 32% female, T3-21%, T4- 46% and 64% ≥ N2b. The lead-in safety period is near completion (15/16) without DLT with 9/19 (47%) patients demonstrating a pathological response (> 10% tumor effect [TE]) and 6/19 (32%) achieving major response (> 70% TE), one of which had a pathological complete response after 1 dose. Pathological response was associated with robust immune cell infiltration, increased PD-L1 and PD-L2. Two patients (neither attaining pathological response) have recurred. **Conclusions:** Pathological response was seen after one dose of pembrolizumab in HNSCC. Increased tumor immune cell infiltration predicted pathological response. Adjuvant combination treatment with pembrolizumab has an acceptable safety profile. Clinical trial information: NCT02641093.

6018 Poster Discussion Session; Displayed in Poster Session (Board #6), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase II randomized trial of pembrolizumab versus cetuximab, concomitant with radiotherapy (RT) in locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN): First results of the GORTEC 2015-01 "PembroRad" trial. *First Author: Xu Shan Sun, CHRU Jean Minjoz, Besancon Cedex, France*

Background: Based on the hypothesis of a potential synergistic effect of the anti-PD1 pembrolizumab when combined with RT, this new combination was tested in a phase II randomized trial against the SoC cetuximab-RT in LA-SCCHN. **Methods:** Patients (pts) were randomized between cetuximab (Arm A : 400 mg/m^2 loading dose and 250 mg/m^2 weekly) and Pembrolizumab (Arm B : 200 mg Q3W during RT). In both arms, patients received IRMT (69.96 Gy in 33 fractions). Main Inclusion criteria were : pts unfit for high dose cisplatin, non operable stage III-IVa-b SCC of oral cavity, oropharynx, hypopharynx and larynx. Treatment allocation was performed by randomization 1:1, stratified on N stage (N0-1 vs N2-3) , tumor location and p16 status. To detect a difference between arms of 60% to 80% in locoregional control at 15 months (primary endpoint), inclusion of 66 pts per arm was required to achieve a power of at least 0.85 at 2-sided significance level of 0.20, with less than 15% unevaluable pts. **Results:** from 05/16 to 10/17, 133 pts were randomized in 27 centers, 66 in Arm A and 67 in Arm B. Median age was 65 years, 92% were smokers, 60% of oropharynx, 28% p16+ and 26%, 56% and 19% of stage III, IVa and IVb respectively. Both arms were well balanced. At the time of the abstract writing, full and cleaned safety and compliance data were available for 77 pts (58%). Data for all the randomized pts will be presented at the meeting. In Arm A and B, 25 and 18 Serious Adverse Events (SAE) occurred and 94% and 78% pts had at least one CTCAE v4 grade 3 AE in arm A and B respectively. The compliance to RT was not different (full total dose received by 86% and 88% pts in Arm A and B respectively). Mucositis >= grade 3 was observed in 57% (Arm A) versus 24% (Arm B) of pts (p = 0.004) (but no difference in dysphagia, 34% versus 39%). In radiation field dermatitis >= grade 3 occurred more frequently in Arm A (49% versus 17%) (p=0.003). **Conclusions:** Preliminary data indicate that tolerance of pembrolizumab-RT was good when compared to cetuximab-RT in LA-SCCHN. Updated and complete safety results will be presented at the meeting. Clinical trial information: NCT02707588.

6019 Poster Discussion Session; Displayed in Poster Session (Board #7), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Discovery of a reliable and robust methylome classifier of HPV driven head and neck cancer with favorable response to chemoradiation: A multicenter study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). *First Author: Bouchra Tawk, German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK), core center Heidelberg, Heidelberg, Germany*

Background: Human Papilloma Virus (HPV)-driven head and neck cancer (HNSCC) is associated with good prognosis. The prognostic value of HPV-DNA and p16 IHC was recently reported by this consortium. Discordance between HPV and p16 status is consistently observed impacting patient stratification and treatment outcome. We sought to overcome this limitation by developing a next-generation methylome-based classifier of HPV-driven HNSCC. **Methods:** HPV-DNA and p16 status of a DKTK-ROG multicenter retrospective cohort of patients (n = 194) with oropharynx cancer (OPC), oral cavity- and hypopharynx cancer (non-OPC), homogenously treated with surgery and adjuvant cisplatin-based radiochemotherapy (RCHT), was employed as a training set. Five validation cohorts were utilized including DKTK-ROG patients with definitive RCHT (n = 110), three additional RCHT cohorts from Heidelberg, Dresden, Munich (n = 222) and The Cancer Genome Atlas – HNSCC cohort (TCGA, n = 206). Overall methylome data from 732 samples including two different sources (FFPE/FrFr) and platforms (Illumina 450K and EPIC 850K) were studied. **Results:** A 24-probe set methylome-based classifier of HPV-driven HNSCC was discovered (HPV-M) to significantly correlate with improved clinical outcomes: HR for local recurrence (range 0.11-0.19), disease progression (range 0.16-0.29) and overall survival (OS, range 0.19-0.42) were significant in all cohorts ($p < 0.05$). Notably, HPV-M+ classification was superior to HPV-DNA+ status or p16+ IHC in predicting OS in all cohorts independent of tumor localization (OPC/non-OPC). Likewise, HPV-M showed a strong correlation with HPV-DNA and p16 status ($p < 0.0001$). Across cohorts ~ 10% discordance between HPV-M and HPV-DNA or p16 status was found, respectively. Among these patients (n = 71), OS was significantly reduced in patients with HPV-M negative vs. positive tumors ($p < 0.009$). **Conclusions:** We present a novel robust and independent methylome-based classifier of HPV-driven HNSCC that could be instrumental for accurate patient stratification in the era of de-escalation trials.

6020 Poster Discussion Session; Displayed in Poster Session (Board #8), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

High-accuracy HPV testing versus p16 IHC using multiple clinically relevant outcomes: The University of Chicago Experience. *First Author: Sara Kochanny, Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL*

Background: The current most widely used standard for HPV status testing in head & neck cancer is p16 IHC. However, p16 IHC is a surrogate method which does not test directly for HPV genetic material and p16 expression is known to occur in HPV- tumors also. Furthermore, HPV strain identification can influence prognosis necessitating HPV typing. We have developed a dual testing method using both p16 IHC in combination with multiplex HPV PCR to accomplish the high sensitivity HPV testing with overall high specificity, sensitivity, and overall accuracy. **Methods:** As part of our clinical experience, we evaluated the HPV status of 317 patients with head & neck cancer suspicious for HPV involvement using a dual testing method with both p16 IHC and multiplex PCR. For discrepant cases where p16 and PCR do not agree, we confirmed status by performing genetic profiling (OncoPlus). The sensitivity and specificity of the method was tested with a combined validation cohort of 87 HPV negative (n = 48) and HPV positive (n = 39) tumor samples. **Results:** In our clinical experience with oropharyngeal HPV testing, including as part of de-escalation trials, we identified that 5% of oropharynx cases have false positive p16, where the PCR does not support HPV. 8% of PCR confirmed HPV positive cases were non-HPV16, which were associated with poorer prognosis. In the combined HPV- and HPV+ validation cohort, sensitivity was 97.4%, specificity 93.75%, PPV was 95%, NPV = 97.8%, with an overall accuracy of 95.4%. **Conclusions:** Dual testing by p16 and PCR is feasible, and increases accuracy. Using p16 alone results in a 5% false positive and 8% misclassification rate for HPV(-) and non-HPV16 cancers, respectively. In the era of de-escalation where treatment decisions are based on HPV status, it is critical to identify patients who are actually HPV(-) or non-HPV16. Such patients likely should not be treated on de-escalation trials unless appropriate safeguards are in place.

6021 Poster Discussion Session; Displayed in Poster Session (Board #9), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A randomized doubled blind phase II study exploring the safety and efficacy of nintedanib (BIBF1120) as second line therapy for patients (pts) with differentiated thyroid carcinoma (DTC) progressing after first line therapy: EORTC 1209. *First Author: Martin Schlumberger, Department of Nuclear Medicine and Endocrine Oncology, Gustave Roussy and University Paris-Sud, Villejuif, France*

Background: Radioiodine refractory advanced DTC may benefit from treatment with TKI. Most DTC pts will ultimately progress after treatment with a TKI and those in good general condition are candidates for further treatment lines. Nintedanib (N) is an oral triple angiogenesis inhibitor of VEGF, FGF and PDGF receptors. We conducted a randomized phase II trial of N vs placebo (P) in pts with locally advanced or metastatic DTC who received 1 or 2 lines of prior TKI. **Methods:** Eligible pts had documented RECIST v1.1 progression on a prior treatment with TKI. The primary endpoint was progression free survival (PFS) using RECIST v1.1 according to local radiologist. Tumor assessment occurred every 8 weeks. With a 1-sided alpha 10%, the study was powered at 90% level to detect a Hazard Ratio (HR) of 0.6 in PFS. **Results:** Between July 2014 and December 2016, 70 pts were randomized 2:1 to N (45 pts starting dose 400 mg/d) or matching P (25 pts). Pt characteristics were similar in both arms. Median (med) age was 65.8 years, 56 % female, all had distant metastases, 76% received 1 prior line of TKI and 24% received 2 lines. At the time of database lock, 2 N pts and 1 P pt were still receiving study treatment. Among pts who completed treatment, med duration of treatment was 17.7 weeks (W) in N and 10.4 W in P. Med relative dose intensity was 100% in N. AEs led to decrease N treatment dose in 21 pts and to permanent discontinuation in 5 pts. Grade ≥3 AEs occurred 50% in N and 36% in P, among others hypertension (9 vs 4%), diarrhea (9 vs 4%), abdominal pain (2.3% vs 0), nausea (4.5% vs 0), anorexia (11.4% vs 0), weight loss (2.3% vs 0), fatigue (6.8 vs 4%), anemia (2.3 vs 4 %) and lymphopenia (6.8% vs 0). Based on 53 events observed in 56 per protocol population pts (37 in N and 19 in P), med PFS was significantly prolonged from 2.86 months in P to 3.71 in N (HR [80% CI]: 0.65 [0.42, 0.99], stratified logrank test p = 0.095). **Conclusions:** N as second line therapy for pts with DTC progressing after 1st or 2nd line therapy was well tolerated. Based on per protocol population, N slightly prolonged med PFS compared to P. Clinical trial information: NCT01788982.

6022 Poster Discussion Session; Displayed in Poster Session (Board #10), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

A phase II study of lenvatinib in patients with progressive, recurrent/metastatic adenoid cystic carcinoma. *First Author: Vatche Tchekmedyian, Memorial Sloan Kettering Cancer Center, NY, NY*

Background: Recurrent/metastatic adenoid cystic carcinoma (R/M ACC) is a malignant neoplasm of salivary gland origin with no standard treatment. The majority of ACCs are characterized by MYB over-expression which correlates to upregulation of several genes, including lenvatinib-relevant targets such as vascular endothelial growth factor A, the receptor tyrosine kinase *KIT* and fibroblast growth factor 2. We hypothesize that the multi-tyrosine kinase inhibitor (TKI) lenvatinib could be an effective therapy for R/M ACC. **Methods:** In a minimax two stage phase II study, patients with R/M ACC were treated with lenvatinib 24mg orally once daily. The protocol required new or progressive lesions radiographically and/or new or worsening disease related symptoms within 6 months of enrollment. The primary endpoint was overall response rate (ORR) (ORR= complete response (CR)+partial response (PR)) as documented by RECIST v1.1. The objective was to detect a difference in ORR of 5% versus 20% (with a one-sided type I error of 10% and power of 90%). ≥4 responses out of 32 patients was the pre-specified target for a positive study. **Results:** From 6/2/2016-5/22/2017, 33 patients were enrolled and 32 were evaluable for the primary endpoint (1 screen fail). The ORR was 15.6%. For best overall response (BOR), 5 patients (15.6%) had confirmed PR, 24 (75%) had stable disease (including 16 (50%) with tumor regression), and 1 (3.1%) had progression of disease (POD); 2 (6.3%) were removed prior to re-imaging. Five patients remain on therapy (range 11.0-19.9m). Reasons for discontinuation included POD (7), withdrawal of consent (9), physician discretion (6), and protocol-mandated removal for toxicity (5: myocardial infarction, posterior reversible encephalopathy syndrome, proteinuria, oral cavity fistula, and intracranial hemorrhage). 20 patients underwent at least one dose reduction.Median progression free survival (PFS) was 16.4 months (95% CI 7.2-not reached). **Conclusions:** The trial reached its primary endpoint, demonstrating impressive efficacy with the highest ORR and longest PFS of any phase II multi-TKI ACC study published in the literature to date. Clinical trial information: NCT02780310.

6023 Poster Discussion Session; Displayed in Poster Session (Board #11), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Facilitating rapid precision oncology in anaplastic thyroid cancer: Clinical implications of next generation sequencing (NGS) mutation testing and impact on survival. *First Author: Jennifer Rui Wang, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anaplastic thyroid cancer (ATC) is a rare malignancy characterized by rapid progression and median overall survival (OS) of less than 6 months. With the goal of improving ATC outcomes, a multi-disciplinary program ("FAST") was developed at our institution, which provides rapid access to care, mutation testing, and personalized treatment. The objective of this study was to examine whether results of mutation testing are associated with OS in ATC patients. **Methods:** ATC patients seen between 2012-2017 at our institution who had adequate tumor samples for NGS testing were included. DNA was extracted from pre-treatment core biopsies or surgical specimens of primary ATC. Targeted mutation testing was performed using NGS platforms for 46-158 genes. Cox proportional hazards models were used to assess the associations between mutation status and OS. **Results:** A total of 101 pts were included (median age: 65.7 years, 55.5% male). 84% presented with T4b disease. 50% were M1 at presentation. Median OS at 1 and 2 years was 52% and 29%. The most common mutations detected were p53 (54%), BRAFV600E (50%), RAS (21%), PIK3CA (23%), and CDKN2A (7%). RAS and BRAFV600E mutations were mutually exclusive. In univariate analysis, BRAFV600E was associated with better OS (HR 0.59, 95% CI 0.35-0.98, p = 0.043) while RAS mutation was associated with worse OS (HR 3.41, 95% CI 1.94-5.99, p < 0.001). P53 mutation was not significantly associated with OS. After adjustment for additional clinical variables, RAS mutation was most significantly associated with OS (adjusted HR 3.03, 95% CI 1.45-6.33, p = 0.03). Twenty-four of 51 (47%) BRAFV600E+ pts were treated with a BRAF inhibitor. In BRAFV600E+ patients, BRAF inhibitor treatment was significantly associated with improved OS at 1 year (HR 0.25, 95% CI 0.08-0.78, p = 0.018). **Conclusions:** This is the largest study of mutation status and survival outcome in ATC to date. BRAFV600E and RAS are mutually exclusive drivers that impact prognosis in ATC. Mutation analysis at diagnosis offer prognostic evaluation and may lead to improvement in outcome by facilitating treatment with targeted therapies and enrollment in clinical trials.

6024 Poster Discussion Session; Displayed in Poster Session (Board #12), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Phase I/II study of spartalizumab (PDR001), an anti-PD1 mAb, in patients with anaplastic thyroid cancer. *First Author: Lori J. Wirth, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Spartalizumab, a humanized IgG4 mAb, binds programmed death-1 (PD-1) with subnanomolar affinity and blocks interaction with PD-L1/PD-L2. Anaplastic thyroid cancer (ATC) is an aggressive tumor, with nearly 100% disease-specific mortality (NCCN Guidelines 2018) and few treatment options. **Methods:** This Phase I/II, open-label, dose escalation/expansion study (NCT02404441) characterized the safety and efficacy of spartalizumab in patients (pts) with advanced solid tumors. The recommended Phase II dose was 400 mg once every 4 weeks (Q4W). **Results:** During the dose escalation phase of the study, a patient with ATC treated at 3 mg/kg Q2W experienced a mixed response with overall stable disease (SD) for 7 months before developing progressive disease. Based on this encouraging patient, an expansion cohort was opened in ATC. At the safety cut-off of Nov 13, 2017, 26 pts with ATC had been treated in the spartalizumab 400 mg Q4W expansion group. The median age was 62 (46–79), 54% were men, and ECOG performance status was 0 (42%) or 1 (58%). 77% of pts had received prior treatment for ATC, with 19% of pts receiving ≥2 prior therapies. AEs suspected to be related to treatment (> 5% of pts) were diarrhea, pruritus, and asthenia (8% each). G3/G4 AEs suspected to be related to treatment were anemia, hypophosphatemia, lymphopenia, and oncologic complication (inflammation around the tumor; 1 pt each). At the efficacy cut-off of Jan 23, 2018, 37 pts had been treated and 30 pts were evaluable for efficacy. The overall response rate (ORR) by RECIST 1.1 (confirmed + unconfirmed PRs) was 5/30 (17%), with four confirmed responses and one patient awaiting a confirmatory scan. At the efficacy cut-off, all responses were ongoing, and PFS and OS data were immature. The ORR by irRC was 6/30 (20%). Three additional pts had RECIST and/or irRC SD ongoing after 5, 5, and 12 months of treatment. The overall disease control rate was 8/30 (27%) by RECIST and 10/30 (33%) by irRC. **Conclusions:** Spartalizumab showed encouraging response rates, clinical benefit, and durability in pts with ATC, with no unexpected safety concerns. Clinical trial information: NCT02404441.

6025 Poster Session (Board #13), Sat, 1:15 PM-4:45 PM

Phase I/II trial of pembrolizumab(P) and vorinostat(V) in recurrent metastatic head and neck squamous cell carcinomas (HN) and salivary gland cancer (SGC). *First Author: Cristina P. Rodriguez, Division of Medical Oncology, University of Washington, Seattle, WA*

Background: Epigenetic modification is increasingly recognized as a mechanism for tumor immune evasion. This clinical trial explored the activity of P with the HDAC inhibitor V in HN and SGC. **Methods:** Patients(pts) with progressing incurable HN and SGC with ECOG ≤1, no prior immunotherapy, RECIST 1.1 measurable disease, and normal organ function were eligible. Controlled brain metastases were permitted. PDL1 expression was not an eligibility criterion. P 200mg was given IV q21 days (d) , with V 400mg QD PO, 5d on and 2d off, both started on d1 of each cycle. The primary endpoint was safety according to CTCAE v. 4.03. Secondary endpoints were RECIST 1.1 objective response rates and biomarker collection. **Results:** From 11/2015 to 8/2017, 25 HN and 25 SGC pts were enrolled. Among all 50 pts, median age was 61 (range 33-86) yrs, 39 (78%) were male, 21(62%) were never smokers, 27 (54%) had ECOG 0. In HN, primary sites were oropharynx 17 (68%), nasopharynx 4 (16%), oral cavity 1(4%), skin 2 (8%) and unknown 1 (4%). Thirteen(52%) were p16+ oropharynx HN. SGC histologies were adenoid cystic (ACC) 12(48%), acinic cell (AciC) 3(12%), mucoepidermoid 3(12%), ca ex. pl. adenoma 2(8%). There was 1(4%) pt each with adenocarcinoma, salivary duct, epithelial-myoepithelial, clear cell, parotid lymphoepithelioma-like(LEL-C) carcinoma. The median (range) treatment cycles received in HN was 6 (1-33), and SGC 9 (1-34). Adverse events regardless of cause (AEs) in all pts were: 27 (54%) Grade ≥1, 18(36%) Grade≥ 3. Nine(18%) pts required V dose reductions. The most common AEs in all pts were renal insufficiency in 7 (14%), fatigue 6 (12%) and nausea 3 (6%). There were 3 (12%) deaths on study, 1 aspiration pneumonia, 1 myocardial infarction, and 1 presumed pneumonitis from P. Responses in HN were: complete response (CR) 0, partial response(PR) 8 (36%), stable disease(SD) 5 (20%). Efficacy in SGC:CR 0, PR 4 (16%) in 1 LEL-C, 2 AciC and 1 ACC, SD 14(56%). With a median follow up of 8.7 mos for all pts, in HN median PFS was 4.5 mos, median OS, 12.6 mos; in SGC median PFS was 7 mos, and median OS 13 mos. **Conclusions:** P+V demonstrated activity in HN, with fewer responses in SGC. Serum and tissue biomarker analyses are ongoing. Clinical trial information: NCT02538510.

6026 Poster Session (Board #14), Sat, 1:15 PM-4:45 PM

Phase II trial of apatinib in patients with recurrent and/or metastatic adenoid cystic carcinoma of the head and neck: Updated analysis. *First Author: Guopei Zhu, Department of Oral and Maxillofacial Head & Neck Oncology, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine, Shanghai, China*

Background: There is no specific therapy, including targeted agents, has consistently improved clinical outcomes in recurrent/metastatic adenoid cystic carcinoma of the head and neck (ACCHN). Recently, anti-angiogenic targeted therapy represents a potential effective strategy. We conducted a single-arm, phase II trial to evaluate apatinib, a small-molecule inhibitor of VEGFR-2, in ACCHN, and promising response was observed (2018 Multidisciplinary Head and Neck Cancers Symposium Abstract: 20160). Here we report the updated efficacy and safety data. **Methods:** Pathologically confirmed recurrent and/or metastatic ACCHN patients (pts) who had evidence of disease progression within 3 months or had failed at least 1 line of systemic chemotherapy were eligible. All pts received continuous apatinib 500 mg qd until disease progression, death, or intolerable toxicity. **Results:** Between Apr 2016 and Dec 2017, 59 pts were recruited, including 22 (37.3%) males and 37 (62.7%) females. The median age was 47.5 years. 61.0% cases had metastases, and the main metastatic site was lung. All pts were evaluable for efficacy and safety analyses. At the cutoff date of 12/31/2017, 9 progression-free survival (PFS) events and 2 deaths after progression occurred. The median PFS and overall survival (OS) had not been reached; however, the median time of apatinib treatment was already 6.4 (IQR, 3.8–9.9) months. The 6-month PFS rate was 87.9% (95%CI, 76.6%–99.1%), and the 12-month PFS rate was 50.7% (95%CI 21.8%–79.7%). The 12-month OS rate was 96.3% (95% CI, 91.3%–101.3%). Moreover, the objective response rate and disease control rate was 47.1% and 98.1%, respectively. 34 (57.6%) pts experienced dose reduction. The incidence of drug-related adverse events (AEs) was 88.1% (52/59). 22.0% (13/59) pts developed AEs of Grade ≥3. Main AEs were hypertension (54.2%), hand-foot syndrome (33.9%), and proteinuria (23.7%). **Conclusions:** This updated analysis further confirmed that apatinib appears to be effective and safe for recurrent/metastatic ACCHN. It did achieve the best reported response rate and long duration of disease control with a good safety profile. Further investigation is warranted. Clinical trial information: NCT02775370.

6028 Poster Session (Board #16), Sat, 1:15 PM-4:45 PM

Nivolumab (nivo) vs investigator's choice (IC) in patients (pts) with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Analysis of CheckMate 141 by age. *First Author: Nabil F. Saba, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: Nivo is the only immunotherapy to significantly improve overall survival (OS) in pts with platinum (plt)–refractory R/M SCCHN. In the randomized, open-label, phase 3 CheckMate 141 trial (NCT02105636), nivo significantly improved OS vs IC (HR [95% CI] = 0.68 [0.54, 0.86]) in pts with R/M SCCHN who had progressed on or within 6 mo of plt-based therapy. The safety profile of nivo in the overall pt population was favorable compared with IC. With conventional treatments, there has been concern regarding efficacy and tolerability in elderly patients owing to age-related factors and comorbidities. Here we describe efficacy and safety of nivo compared with IC, by age. **Methods:** Eligible pts were randomized 2:1 to nivo 3 mg/kg every 2 weeks (n = 240) or IC (methotrexate, docetaxel, or cetuximab, n = 121). The primary endpoint was OS. Outcomes were analyzed by age < 65 and ≥65 yrs. Data cut: September 2017 (minimum follow-up: 24.2 mo). **Results:** At baseline, 68 pts (28.3%) in the nivo arm and 45 pts (37.2%) in the IC arm were ≥65 yrs old. Baseline characteristics and relative nivo dose intensity were generally similar across age groups. OS and tumor response benefits with nivo vs IC were maintained regardless of age (Table). The 30-mo OS rates of 11.2% (< 65 yrs) and 13.0% (≥65 yrs) with nivo were more than tripled vs corresponding IC rates of 1.4% and 3.3%, respectively. As in the overall pt population, the nivo arm had a lower rate of treatment-related adverse events (TRAEs) vs IC (Table). **Conclusions:** Nivo improved OS and objective response rate (ORR) vs IC in pts < 65 yrs and ≥65 yrs in CheckMate 141, with a manageable safety profile in both age groups. OS benefit with nivo was maintained through 2 yrs of follow-up for both groups. These data support the use of nivo, regardless of age, in pts with R/M SCCHN who progress within 6 mo of plt therapy. Clinical trial information: NCT02105636.

	< 65 yrs		≥65 yrs	
	Nivo (n = 172)	IC (n = 76)	Nivo (n = 68)	IC (n = 45)
Median OS (95% CI), mo	8.2 (6.1, 9.1)	4.9 (3.9, 5.8)	6.9 (4.0, 9.7)	6.0 (4.0, 7.5)
HR (95% CI)	0.63 (0.47, 0.84)		0.75 (0.51, 1.12)	
ORR (95% CI), %	12.8 (8.2, 18.7)	6.6 (2.2, 14.7)	14.7 (7.3, 25.4)	4.4 (0.5, 15.1)
TRAEs, any grade, %	64	77	57	83
TRAEs, grade 3/4, %	16	31	13	48

6029 Poster Session (Board #17), Sat, 1:15 PM-4:45 PM

Comparison between lobaplatin and cisplatin plus 5-fluorouracil combined with intensity-modulated radiotherapy for locoregionally advanced nasopharyngeal carcinoma: A multicenter randomized phase III clinical trial. *First Author: Kuiyuan Liu, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Cisplatin-based chemoradiotherapy(CRT) has been widely applied as a first-line regimen in patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC). However, cisplatin can induce severe side effects .Our previous phase II trial revealed that lobaplatin combined with 5-fluorouracil (5-FU) followed by concurrent chemoradiotherapy (CCRT) showed encouraging anti-tumor effects with tolerable toxicities for LA-NPC. Here, we assess the efficacy and toxicities of a regimen of lobaplatin versus cisplatin plus 5-FU as induction chemotherapy (ICT) followed by concomitant lobaplatin versus cisplatin with intensity-modulated radiotherapy (IMRT). **Methods:** Stage III-IVB NPC patients were randomly assigned to receive lobaplatin or cisplatin plus 5-FU as ICT followed by CCRT. In the lobaplatin arm, patients received lobaplatin at a dose of 30 mg/m^2 on days 1 and 22 combined with a continuous 120-h intravenous injection of 5-FU at a dose of 4 g/m^2 followed by lobaplatin at a dose of 30 mg/m^2 on days 43 and 64 concomitant with IMRT. Lobaplatin was replaced by cisplatin (100mg/m^2) in the cisplatin arm. The primary end-point was progression-free survival (PFS). **Results:** Of the 494 eligible patients, 250 were assigned to lobaplatin arm and 244 to cisplatin arm. No difference was observed in overall tumor response between two arms (98.6% vs. 97.7%, P= 0.459). After a median follow-up of 42.6 months, no statistically significant differences in 3-year PFS rate was observed between two arms (PFS: 78.9% vs. 82.0%, P= 0.985). During ICT, more patients suffered grade 3-4 leucopenia, neutropenia, nausea and vomiting in cisplatin arm (all P< 0.001). During CCRT, grade 3-4 anemia, nausea and vomiting were more common in cisplatin arm (all P< 0.001). **Conclusions:** The regimen of ICT with lobaplatin plus 5-FU followed by concomitant lobaplatin and IMRT achieved similar survival outcomes with less acute toxicity compared to cisplatin-based CRT in LA-NPC. Long-term follow up is required to determine whether lobaplatin-based systemic chemotherapy should be the first line of therapy for LA-NPC. Clinical trial information: ChiCTR-TRC-13003285.

6030 Poster Session (Board #18), Sat, 1:15 PM-4:45 PM

Anti-VEGF treatment to modulate tumor microenvironment (TME) prior to chemotherapy in EBV-positive nasopharyngeal carcinoma (NPC). *First Author: Wan Qin Chong, National University Cancer Institute, National University Health System, Singapore, Singapore, Singapore*

Background: EBV-related NPC is chemosensitive but stage 4 disease has high relapse rate and short progression free survival (PFS). Almost all NPCs overexpress VEGF.We hypothesized that anti-VEGF (bevacizumab) prior to chemotherapy could promote vascular normalisation, improve tumor perfusion, and enhance immune response in NPC. **Methods:** We conducted a study using bevacizumab in 2 doses, 7.5mg/kg (Arm A) or 2.5mg/kg (Arm B), starting 7 days prior to 3 weekly cycle of cisplatin 75mg/m^2 (Day 1) and gemcitabine 1g/m^2 (D1, D8), for 3 cycles followed by concurrent chemoradiotherapy in stage 4A/B (locally advanced) patients, and for 6 cycles in stage 4C (metastatic) patients, with the primary objectives to determine safety and response rate (RR), and secondary objectives to evaluate PFS and effects on the TME. Immunohistochemistry studies were performed by a blinded pathologist on serial fresh tumor biopsies at baseline and 7 days post cycle 1 bevacizumab. **Results:** 20 patients were recruited to Arm A, and 10 to Arm B. 1 screen failed and 2 withdrew consent. Objective RECIST response was seen in arm A (17/18 [94.4%] partial response (PR), 1/18 [5.6%] stable disease (SD)), vs arm B (8/9 [88.9%] PR, 1/9 SD [11.1%]). Metabolic PET-CT response was seen in all 25 evaluable patients with complete response in 4/17 [23.5%] patients in arm A. EBV DNA was detectable in 17 patients at baseline, and 12 patients had undetectable plasma EBV DNA by day 1 of cycle 2. 9/13 (69.2%) in arm A vs 1/4 (25%) in arm B had undetectable plasma EBV DNA post treatment. TME response to bevacizumab included increase in stromal inflammatory infiltrate, specifically CD4 ($p = 0.0002$) and CD8 T cells ($p = 0.0069$), and reduction in hyaluronic acid binding protein score ($p = 0.0116$), indicating increased vascular permeability within the TME. 3 patients had grade 3 hypertension and no patients had tumoral bleed related to bevacizumab use. **Conclusions:** In this first evaluation of bevacizumab prior to chemotherapy for NPC, tolerability and efficacy was established, and bevacizumab enhances stromal immune infiltration, and modulates TME, potentially improving vascular permeability. Clinical trial information: 2010/00693.

6031 Poster Session (Board #19), Sat, 1:15 PM-4:45 PM

A phase I/II trial adding poly(ADP-ribose) polymerase (PARP) inhibitor veliparib to induction carboplatin-paclitaxel (Carbo-Tax) in patients with head and neck squamous cell carcinoma (HNSCC) Alliance A091101. *First Author: Michael J. Jelinek, University of Chicago, Department of Medicine, Comprehensive Cancer Center, Chicago, IL*

Background: This phase I/II study evaluates safety and efficacy of veliparib, a PARP inhibitor, with induction carbo-tax in patients (pts) with locoregionally advanced HNSCC. Since PARP is involved in DNA repair, inhibition of PARP may augment damaging effects of chemotherapy on tumor DNA. We report on the completed phase I portion of the trial. **Methods:** Eligible pts had newly diagnosed stage IVa-b non-oropharyngeal cancer (OPC) or stage IVa-b, human papillomavirus-negative OPC. The primary endpoint is the maximum tolerated dose (MTD) or recommended phase II dose using a 3+3 pt cohort design. Pts received induction carboplatin (AUC 6 day 1), paclitaxel (100 mg/m^2 day 1, 8, 15), and veliparib (days 1-7) every 21 days for 2 cycles. Veliparib doses were 200, 250, 300 and 350 mg BID. Standard chemoradiotherapy followed induction. **Results:** 20 pts enrolled. Two withdrew prior to treatment, leaving 18 pts for analysis. Median age was 62.5 years: 50% were female. Primary sites (# pts) included hypopharynx (5), larynx (5), oral cavity (4), oropharynx (3) and nasal cavity (1). The most common grade (gr) 3+ adverse events (AEs) were decreased neutrophil count (33%), decreased platelet count (33%) and anemia (11%). Gr 3+ hematologic AEs were more common at higher veliparib doses. Three pts had gr 4 AEs, all hematologic (1 pt: neutropenia, 1 pt: thrombocytopenia (dose-limiting), 1 pt: both). The recommended phase II dose and MTD for veliparib in combination with carbo-tax is 350 mg. Of 13 pts currently evaluated for response, 9 (69%) had partial or complete response. At an early median follow-up of 16.7 months (mo) across dose levels for all pts, the 12-mo overall survival was 76% (95% CI: 55-100%), and 12-mo progression-free survival was 75% (95% CI: 54-100%). Medians have not been reached. Data for 350 mg is not fully mature. **Conclusions:** Addition of veliparib 350 mg BID on days 1-7 to carbo-tax was well tolerated in pts with advanced HNSCC. This dose is higher than previously tested in other trials. Hematologic toxicities were the most common AEs. Support: U10CA180821, U10CA180882; Clinical trial information: NCT01711541.

6032 Poster Session (Board #20), Sat, 1:15 PM-4:45 PM

Randomised phase II study with cetuximab in combination with 5-FU and cisplatin or carboplatin versus cetuximab in combination with paclitaxel and carboplatin for treatment of patients with relapsed or metastatic squamous cell carcinoma of the head and neck (CETMET trial). *First Author: Signe Friesland, Dep. of Oncology, Karolinska University Hospital, Stockholm, Sweden*

Background: Platinum-based chemotherapy with cetuximab is the standard of care for relapsed or metastatic squamous cell carcinoma of the head and neck (SCCHN). The aim of this trial was to investigate whether cetuximab and paclitaxel/carboplatin can achieve similar progression free survival (PFS) with less toxicity compared to standard cetuximab and 5-FU/platinum based chemotherapy. **Methods:** In this multicentre, randomised, controlled, phase 2 trial, 85 patients with relapsed or metastatic SCCHN were randomised in a 1:1 ratio to cetuximab and 5-FU/cisplatin or carboplatin (arm A, n = 42), versus cetuximab and paclitaxel/carboplatin (arm B, n = 43). Patients without disease progression continued with cetuximab maintenance every second week until progression or toxicity. Eligibility criteria included age $\geq$18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, and adequate organ functions. The primary endpoint was to investigate whether PFS in arm B is non-inferior to PFS in arm A using a liberal non-inferiority margin of 1.5 for the PFS hazard ratio (HR). **Results:** The median age for the whole study population was 60.9 years with a male predominance (69.4%). Clinically significant parameters, such as tumour localization, tumour stage, PS, HPV status and age were well balanced between the two treatment arms. Adverse events $\geq$ grade 3 were more frequent in arm A than in arm B (60% vs 40%; $p = 0.034$). Median PFS in arm A was 4.37 months (95% CI: 2.9- 5.9 m) and 6.5 months (95% CI: 4.8-8.2 m) in arm B, ($p = 0.064$). Median overall survival (OS) was 8.4 months (95% CI: 5.3-11.5 m) in arm A and 10.2 months (95% CI: 5.4-15 m) in arm B (HR = 0.71; 95% CI: 0.43-1.16). PFS HR for arm B was 0.65 (95% CI: 0.41- 1.03) and the predefined non-inferiority criterion was met. **Conclusions:** Cetuximab and paclitaxel/carboplatin was found to have similar efficacy and less toxicity compared to cetuximab and 5-FU/cisplatin or carboplatin. The experimental arm is easier to administer rendering it a favourable alternative to standard therapy in daily clinical practice. Clinical trial information: NCT01830556.

6034 Poster Session (Board #22), Sat, 1:15 PM-4:45 PM

Hyperfractionated reirradiation with cetuximab for recurrent head and neck cancer: The GORTEC 2008-01 multicentric phase II study. *First Author: Mathilde Saint-Ghislain, Centre Guillaume Le Conquérant, Le Havre, France*

Background: Most head and neck cancer (HNC) patients die of locoregional progression. Surgery is feasible in less than half the patients only and chemotherapy only offers palliation. Locoregional reirradiation of recurrent HNC or second HNC primary may achieve long-term disease control in some patients, at the expense of high rates of late sequelae. We evaluated the feasibility and tolerance of slightly accelerated hyperfractionated reirradiation and cetuximab in recurrent inoperable/unresectable HNC in a prospective GORTEC phase II study. **Methods:** Patients from 13 GORTEC centers underwent twice-daily reirradiation (1.2 Gy / fraction, 5 days a week, over 5.5 weeks) to 66 Gy. Weekly cetuximab was delivered as 400mg/m2 load dose one week before reirradiation and 250mg/m2 thereafter for 6 weeks. **Results:** From October 2010 to October 2014, 48 patients with recurrent inoperable/unresectable HNC were enrolled. Of those, 71% were in the oropharynx. Median age was 61 years (range 40-75). The median delay between the first and second irradiation was 5 years (0.5-35) years. Median tumor size was 3.5 cm (range 1.3-7.0). Acute grade 3-4 toxicities were dermatitis (15%), mucositis (49%) and dysphagia (24%). Anaphylaxis with cetuximab was observed in one patient (2%). Radiotherapy was completed in 90 %. The full cetuximab course was completed in 79%. Complete response was observed in 40% of the patients. Objective response was 53%. Median follow-up for living patients was 24 months. In 28 evaluable patients, there were 7, 1, 4 and 2 patients with late grade 3 dermatitis/fibrosis, osteoradionecrosis, xerostomia or dysphagia. There was two grade 4 toxicities, mucositis and laryngeal. There was one late grade 5 toxicity carotid blowout. Median survival was 9 months and two-year overall survival rate was 22%. Tumor size at recurrence was identified as a prognostic factor for survival with a median survival time of 11.9 months ($<$ 35 mm) vs 7.4 months ($\geq$35 mm). **Conclusions:** High dose twice-daily HNC reirradiation with cetuximab is feasible in this population. Median survival was similar to those observed in previous studies, with 22% of long survivors, especially in patients with tumor diameter $<$ 35 mm. Clinical trial information: A91168-41.

6035 Poster Session (Board #23), Sat, 1:15 PM-4:45 PM

Saline alone vs saline plus mannitol hydration for the prevention of acute cisplatin nephrotoxicity: A randomized trial. *First Author: Bradley Beeler, USAF, Fort Sam Houston, TX*

Background: Cisplatin is a widely used chemotherapeutic in treating malignancies. One of the common side effects of cisplatin is kidney injury, or nephrotoxicity. This can be a reason for discontinuation of treatment. The majority of the cisplatin is excreted by urination. Mannitol is a compound that has been thought to help negate cisplatin -induced nephrotoxicity. Mannitol is a diuretic, causing increased amount of urination, thereby enhancing excretion of cisplatin. Multiple studies have indirectly looked into the effect of mannitol in preventing kidney damage in patients receiving cisplatin. However, there are limited prospective data that evaluate the effect of mannitol in preventing cisplatin-induced nephrotoxicity. In this study, we determine the effects of pre-hydration with mannitol on reducing the risk of cisplatin-induced nephrotoxicity, as opposed to normal saline pre-hydration in patients receiving cisplatin. **Methods:** 48 patients eligible to receive IV cisplatin therapy at a dose of $\geq 50 mg/m^2$ were identified and randomized to receive 1 L saline alone (A) or saline plus mannitol (B) before and after chemotherapy. Serum creatinine and BUN were drawn on days 1, 5 and 14. **Results:** Renal function as measured by BUN/Cr ratio, GFR, creatinine, and BUN between group A and B are similar at baseline (BL), day 1, day 5, and day 14. Cisplatin caused acute decline in renal function as determined by ser Cr, BUN to ser Cr ratio and GFR, however, the addition of mannitol to NS pre-hydration did not change the outcome. The decline in renal function is limited to grade 1 and most patients recover **Conclusions:** Mannitol does not prevent acute nephrotoxicity in patients receiving cisplatin. This underscores the importance of adequate hydration in patients treated with cisplatin.

Change in mean values	A (n=23)	B (n=25)	p-value
BL to Day 1			
Cr	-0.047	-0.035	0.647
BUN	-0.737	-1.051	0.333
GFR	7.823	7.391	0.462
BL to Day 5			
Cr	0.296	-0.0116	0.0801
BUN	11.993	6.229	0.0340
GFR	-9.512	-7.073	0.629
BL to Day 14			
Cr	0.0606	0.9016	0.833
BUN	1.132	1.641	0.603
GFR	-3.772	-2.353	0.594
Grade 1 increase in Cr	25%	17%	0.078

6036 Poster Session (Board #24), Sat, 1:15 PM-4:45 PM

Safety and preliminary efficacy of talimogene laherparepvec (T-VEC) in combination (combo) with pembrobrolizumab (Pembro) in patients (pts) with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M HNSCC): A multicenter, phase 1b study (MASTERKEY-232). *First Author: Kevin J. Harrington, The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, Surrey, United Kingdom*

Background: We evaluated the safety and efficacy of the combo of T-VEC, the first FDA-approved oncolytic immunotherapy that enhances systemic antitumor immune responses, and Pembro, an immune checkpoint inhibitor against programmed death receptor-1 (PD-1), in pts with R/M HNSCC. **Methods:** Pts were eligible for enrollment if they had histologically confirmed R/M HNSCC unsuitable for curative resection or radiotherapy, and platinum-refractory and injectable disease. T-VEC was injected intralesionally at a dose of up to 8.0 mL of 10^6 PFU/mL on day 1. After 3 weeks, subsequent doses of up to 8.0 mL of 10^8 PFU/mL were administered every 3 weeks (Q3W). Pembro was administered intravenously at a dose of 200 mg Q3W. The primary objective was to evaluate safety, as assessed by the incidence of dose limiting toxicity (DLT). Key secondary objectives were objective response rate (ORR), best overall response per immune-related RECIST, and long-term safety. **Results:** 36 pts were enrolled and treated: 28 (77.8%) had confirmed PD-L1-positive tumor; 5 (13.9%) were HPV-positive and 13 (36.1%) were HPV-negative, with 18 (50%) unknown. One (6.3%) DLT, fatal arterial hemorrhage, was observed among 16 DLT-evaluable pts. Overall, 24/36 (66.7%) pts had grade 3 or higher treatment-emergent adverse events (TEAEs): 5 (13.9%) and 3 (8.3%) pts had TEAEs related to T-VEC and Pembro; 2 (5.6%) and 1 (2.8%) pt discontinued treatment due to T-VEC- and Pembro-related TEAEs, respectively. The most common TEAEs were pyrexia (36.1%), dyspnea (33.3%), and fatigue (25.0%). 24/36 (66.7%) pts had serious AEs. 7 deaths were reported during the study, 1 of which was related to T-VEC (the DLT pt) and none to Pembro. The ORR was 16.7% (6/36 pts; 5 PD-L1-positive; 95% CI, 6.4–32.8), and the disease control rate (objective response/stable disease) was 38.9% (14/36 pts; 11 PD-L1-positive; 95% CI, 23.1–56.5). **Conclusions:** The combo demonstrated a manageable safety profile. Preliminary ORR showed clinical activity in R/M HNSCC. Further follow-up is ongoing for PFS/OS. Clinical trial information: NCT02626000.

6037 Poster Session (Board #25), Sat, 1:15 PM-4:45 PM

An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of the interim safety analysis. *First Author: Assuntina Gesualda Sacco, University of California San Diego Moores Cancer Center, La Jolla, CA*

Background: Pembrolizumab (a humanized monoclonal antibody blocking programmed death receptor-1), and cetuximab (a chimeric monoclonal antibody inhibiting epidermal growth factor receptor) are both FDA-approved as single agents for second-line R/M HNSCC treatment. This is the first trial to combine pembrolizumab with cetuximab to evaluate anti-tumor synergy. As this specific drug combination has not been previously tested, an interim safety analysis was completed per protocol. **Methods:** Patients (pts) with R/M HNSCC were treated with pembrolizumab at a fixed dose of 200mg IV on day 1 with cetuximab 400mg/m2 loading dose followed by 250mg/m2 weekly (21-day cycle). The first 10 pts who enrolled and completed at least 1 cycle of therapy were included in the safety analysis. A mandatory study hold and Data Safety Monitoring Committee (DSMC) review were required if at least 4 of the 10 pts developed any grade (G) 3-4 non-hematologic toxicity. **Results:** Of the 10 patients included in the analysis, median age 58y (range 47-79y), M: F 5:5. 8 pts had mucosal (6 oral cavity, 1 oropharynx, 1 nasopharynx) and 2 had cutaneous HNSCC primaries. 65 adverse events (AEs) were reported in 9 pts; G1: 39, G2: 15, ≥G3: 11. Of the 11 ≥G3 AEs, only 1 was treatment-related (see Table). There were no treatment-related deaths or dose-limiting toxicities (DLTs). 3 pts discontinued treatment, none of which were due to toxicity (2 had disease progression, 1 withdrew from study). DSMC reviewed the safety data and permitted resumption of trial accrual. Of 7 evaluable pts, 4 partial responses were noted at first radiographic assessment. Clinical trial information: NCT03082534. **Conclusions:** Pembrolizumab combined with cetuximab has a very tolerable safety profile, with no DLTs. Efficacy analysis of this combination will be performed.

Grade	AE Frequency	Description	Related?	Serious?
3	1	Acneiform rash	Definite	N
3	1	Hypotension	Unlikely	Y
3	1	Febrile neutropenia	Unlikely	Y
3	1	Fatigue	Unlikely	N
3	1	Dysphagia	N	Y
3	1	Aspiration	N	Y
3	1	Skin ulceration	N	Y
3	1	Lung infection	N	Y
4	1	Sepsis	N	Y
5	1	Death	N	Y
5	1	Death	N	Y

6038 Poster Session (Board #26), Sat, 1:15 PM-4:45 PM

Association of a baseline neutrophil-to-lymphocyte ratio (NLR) with progression-free and overall survival in head and neck cancer patients receiving anti-PD-1 therapy. *First Author: Corey Christian Foster, Department of Radiation & Cellular Oncology, The University of Chicago Medicine, Chicago, IL*

Background: An elevated neutrophil-to-lymphocyte ratio (NLR) is associated with tumor-induced inflammation and poor prognosis in a variety of treatment settings. Moreover, tumor-derived myeloid growth factors (Seiwert *et al*. ASCO 2017) could elevate the NLR and suppress cytotoxic T-cell activity and anti-PD-1 efficacy. We hypothesized that high baseline NLR will associate with poor outcomes in patients with metastatic head and neck (H&N) cancer receiving anti-PD-1 therapy. **Methods:** 114 patients with metastatic H&N cancer unselected for PD-ligand 1 (PD-L1) status received anti-PD-1 therapy. Baseline NLRs were divided into quartiles with high NLRs being the highest quartile (> 8.77). Univariate logistic regression analyzed the relationship between NLR and overall response rate (ORR) by RECIST v1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. **Results:** Median follow-up was 8.6 months. Baseline characteristics including known PD-L1 positivity (n = 15/29 high NLR vs. n = 38/78 low NLR, p = 0.15) were comparable between groups. ORR was 22.3% with a trend towards lower ORR for the high NLR group (odds ratio: 0.42, 95% confidence interval [CI]: 0.11-1.57, p = 0.20). Median PFS was 1.7 months (95% CI: 1.0-3.6) for high NLR patients and 3.6 months (95% CI: 2.6-5.6) for low NLR patients (p = 0.02). Notably, median OS was 4.1 months (95% CI: 2.1-5.5) in the high NLR group and 12.5 months (95% CI: 9.0-17.2) in the low NLR group (p = 0.007). NLR more strongly associated with outcome than PD-L1+, which was not associated with PFS (p = 0.67) or OS (p = 0.53). On multivariate analyses, a high baseline NLR remained independently associated with reduced PFS (p = 0.04) and OS (p = 0.01). **Conclusions:** A high baseline NLR showed a strong inverse relationship with OS and PFS in patients receiving anti-PD-1 therapy for metastatic H&N cancer regardless of PD-L1 expression. Future investigation of NLR as a clinically-useful biomarker, NLR kinetics over time, and a mechanistic understanding of tumor-driven factors influencing NLR and anti-PD-1 efficacy are warranted.

6039 Poster Session (Board #27), Sat, 1:15 PM-4:45 PM

RM-1929 photo-immunotherapy in patients with recurrent head and neck cancer: Results of a multicenter phase 2a open-label clinical trial. *First Author: Ann M. Gillenwater, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients with recurrent HNSCC (rHNSCC) have limited therapeutic options and poor prognosis. We report promising results of a Phase 2a trial of photoimmunotherapy (PIT) for the treatment of rHNSCC using a novel targeted light activated drug RM-1929; a conjugate of the EGFR-directed monoclonal antibody cetuximab with the phthalocyanine dye, IRDye 700DX. **Methods:** A multi-institutional, open label Phase 2a study of rHNSCC patients who could not be satisfactorily treated with surgery, radiation, or platinum chemotherapy was conducted to evaluate the safety and efficacy of RM-1929. For each treatment, non-thermal red light was applied to the tumors 24 hours after intravenous infusion of RM1929. Light was applied by surface illumination for superficial disease or interstitial illumination via intratumoral placement of fiber optic diffusers for deep tumors. Therapeutic response was calculated using CT RECIST 1.1 determined by an independent blinded radiologist. **Results:** Thirty rHNSCC patients were enrolled in this Phase 2a trial. Safety data are currently evaluable from 30 subjects, outcome data from 28 subjects. There were no dose-limiting toxicities or skin photosensitivity reactions observed. SAEs reported to be possibly related to study treatment, included treatment site pain, tumor hemorrhage, and swelling. Objective response rate was 28% (8/28), complete response was 14% (4/28). Median progression free survival for 28 evaluable patients was 173 days (5.7 months). Median overall survival for the entire 30 patient cohort was 278 days (9.1 months). **Conclusions:** Photoimmunotherapy with RM1929 in patients with rHNSCC is safe and well tolerated. CT RECIST 1.1 PFS, ORR and CR response rates are improved over those of standard therapies in this heavily pretreated population. Future clinical trials are planned to evaluate the therapeutic potential of RM1929 alone or in combination with other treatment modalities. Clinical trial information: NCT02422979.

6040 Poster Session (Board #28), Sat, 1:15 PM-4:45 PM

COTI-2, a potent orally available small molecule targeting mutant p53, with promising efficacy as monotherapy and combination treatment in preclinical tumor models. *First Author: Richard T Ho, Cotinga Pharmaceuticals, Boston, MA*

Background: The p53 tumor suppressor is mutated in more than half of all cancers. COTI-2, an oral 3rd-generation thiosemicarbazone, restores the structure and function of mutant p53 proteins and inhibits growth of p53 mutant cancer cell lines. While few anticancer agents are effective as monotherapies in the clinic in part due to resistance, the COTI-2 mechanism of action to reactivate normal p53 function complements DNA-damaging radiation- or chemo-therapy. Our data demonstrate that COTI-2 has a promising role in combination treatments inducing synergistic anticancer responses. **Methods:** Cell viability was measured with crystal violet stains or indicator dye to assess IC_{50}. Xenograft studies used cancer cell lines with specified p53 mutations. Drug synergy was determined by combination-index and isobolograms generated using CalcuSyn software. **Results:** COTI-2 and chemotherapy agents were tested, singly and in combination, in carcinoma cell lines: colorectal, non-small cell lung (NSCLC), and head and neck squamous cell (HNSCC). Cell lines had wild-type p53, a variety of p53 mutations, or unknown status. COTI-2 IC_{50} for the HNSCC lines, both established and early passaged, were 9.6-370.0 nM with most p53 mutants having lower IC_{50} than wild-type. In other work, single agent and combination treatment with COTI-2 and approved anticancer agents in colorectal carcinoma, NSCLC, or HNSCC cells *in vitro* showed strong synergism against mutant p53 cell lines. In mice bearing A2780 or PCI13 tumors with mutant p53, COTI-2 and doxorubicin or cisplatin, singly and in combination, demonstrated significant enhancement of tumor growth inhibition, and combinations were well tolerated. Lastly, COTI-2 and radiotherapy were administered singly and in combination in a PCI13 tumor model and showed strong synergy against tumor growth. **Conclusions:** COTI-2 is a highly potent, orally bioavailable compound active against many tumors with p53 mutations. This work highlights the potential of combination treatment using COTI-2 with other anticancer agents to provide synergistic tumor growth inhibition with good tolerability.

6041 Poster Session (Board #29), Sat, 1:15 PM-4:45 PM

CAPTN: A nomogram for predicting survival and guiding therapy for patients with de novo metastatic head and neck squamous cell carcinoma. *First Author: Jared R. Robbins, Medical College of Wisconsin, Milwaukee, WI*

Background: Determining prognosis for de novo metastatic head and neck squamous cell carcinoma (mHNSCC) is difficult with limited data to direct clinical management. Recommendations for aggressive treatment must be measured since the duration and toxicity of treatment may exceed the projected lifespan. For this reason, tools to predict survival are needed to guide decisions like the appropriateness of radiation, standard verses experimental therapy, or supportive care alone. Purpose/Objective: To develop and evaluate a model for predicting survival for patients with de novo mHNSCC. **Methods:** We identified 8,441 patients diagnosed with de novo mHNSCC (oral cavity, oropharynx, larynx, hypopharynx, nasopharynx, and paranasal sinuses) in the National Cancer Database from 2004-2013. Test and validation cohorts were randomly generated. Univariate and multivariate Cox regression models were used to identify factors associated with overall survival. A simple scoring system based on clinically-relevant factors was used to generate the CAPTN nomogram (see table). **Results:** For all patients, the median OS was 9.5 months with 1-year OS of 43%. In both the test and validation cohorts, the CAPTN accurately predicted outcomes between each group by pairwise comparison (all $p < 0.001$, see table). A CAPTN score of 0 correlated to the best prognosis while higher score represented step-wise worse prognosis. **Conclusions:** Patients with de novo mHNSCC have heterogeneous outcomes, but the CAPTN score can accurately discriminate survival. Although further validation in other cohorts is needed, the CAPTN model is usefully clinically for tailoring treatment intensity to prognosis and may be pertinent to clinical trial design as a stratification factor.

Factor	0 points	1 point	2 points		Score	Median OS	6-m OS	1-yr OS	3-yr OS
Charlson Deyo	0	1 (mild)	2 (severe)	Test	0	16.8 m	78%	60%	29%
Age (yrs)	< 70	70-79	≥80		1-2	10.7 m	68%	46%	19%
Primary Site	Oropharynx nasopharynx	Larynx	All other sites		3-4	7.0 m	56%	33%	10%
					≥5	4.9 m	41%	21%	6%
T-stage (4)	No	Yes		Validation	Score	Median OS	6-m OS	1-yr OS	3-yr OS
N-Stage (3)	No	Yes			0	16.3 m	78%	61%	30%
					1-2	10.6 m	68%	46%	18%
					3-4	7.3 m	56%	34%	12%
					≥5	4.8 m	42%	20%	5%

6042 Poster Session (Board #30), Sat, 1:15 PM-4:45 PM

Absolute lymphocyte count (ALC) during and after chemoradiation (CRT) for squamous cell carcinoma of the head and neck (SCCHN): Effect of the regimen and potential therapeutic implications. *First Author: Marit Uglane, NorthShore University HealthSystem, Evanston, IL*

Background: Radiation (RT) or (CRT) is a component of treatment (tx) for locoregionally advanced (LA) SCCHN. ALC and lymphocyte subsets are known to decrease as a result of RT for SCCHN. The changes in and variables affecting ALC during or after RT/CRT are not well described. **Methods:** We retrospectively reviewed the ALC of 298 consecutive patients (pts) treated with IMRT based therapy for LASCCHN from 7/2003-7/2015. ALC was categorized using a prespecified algorithm at day 0 of RT, weeks (wk) 1,2,3,4,5,6,7,8,9, months (mo) 3, 6, 12 and years (yr) 2,3,4,5. Chemotherapy (CT) was categorized as induction (IC) yes/no and CRT as one of 4 groups: none/weekly cisplatin/ FHX (5FU, hydroxyurea, taxol)/"other", and RT was recorded as unilateral or bilateral neck tx. Regression analysis was used to assess survival as a function of ALC. VZV (shingles) infection was noted and recorded. **Results:** ALC nadir for the entire group occurred at week 9 at a mean level of 0.4 (CTCAE 4.03 grade 3, normal range 1.0 - 4.0 10^3/uL) for CRT patients and 0.76 for RT only patients ($p = 0.016$). At yr 1, ALC ranged from 0.83-1.04 ($p = 0.2$) amongst 4 groups. By year 5, ALC had only recovered to 69% of baseline with no significant differences between groups. The use of IC did not affect nadir ALC. Pts receiving bilateral neck RT vs. unilateral had significantly lower mean ALC nadirs from wk 3-9 (wk 9: 0.38 vs. 0.88 $p < 0.001$) but not after 3 mo. ALC nadir had no effect on relapse or survival parameters. 19 pts had documented cases of shingles (VZV) occurring at a median time of 10 mo. There was no effect on nadir ALC by p16 status for oropharynx pts. **Conclusions:** Pts undergoing RT or CRT for SCCHN have a quick and severe ALC nadir which never recovers to normal. CRT compared with RT decreased the severity of the nadir but not recovery. IC does not impact ALC, but bilateral neck RT leads to a deeper nadir than unilateral. ALC nadir does not affect survival. VZV could be a related adverse event as it follows CRT in at least 6% of patients at a median of 10 mo. The severe and sustained ALC nadir may also have important effects on the timing of the use of checkpoint inhibitor therapy during RT or CRT.

6043 Poster Session (Board #31), Sat, 1:15 PM-4:45 PM

The use of exosome and immune profiling to analyze a phase 2 study on the addition of patritumab or placebo to cetuximab and a platinum agent for recurrent / metastatic head and neck cancer (R/M HNSCC) patients. *First Author: Tony Ng, King's College London, London, United Kingdom*

Background: The use of patritumab (Daiichi Sankyo), an internalizing anti-HER3 monoclonal antibody, in combination with cetuximab and cisplatin was investigated in a cohort of patients with R/M HNSCC in a Phase II trial (NCT02633800). We investigated the EGFR-HER3 dimer (an established marker of cetuximab resistance within a previous study) in the circulating exosomes from patients enrolled in this trial. The objective was to identify non-invasive treatment stratification and longitudinal monitoring markers. Since antibody-directed cytotoxicity is involved as a mechanism of action for these therapies, exosomal microRNAs (miR21 and miR142), which promote the expansion of functional myeloid-derived suppressor cells (MDSC), as well as other suppressive adaptive and innate immune cell components are postulated as potential immune monitoring parameters. **Methods:** We extracted exosomes from patient serum at 2 timepoints: pretreatment (c1) and pre-cycle 2 (c2, day 1). Exosomes were stained with fluorescently labelled antibodies for fluorescence lifetime imaging microscopy (FLIM) to assess EGFR-HER3 dimerization by FRET. Serum exosomal miRs were analyzed using ddPCR. PBMCs were analyzed by flow cytometry with antibodies against CD3, CD4, CD8, CD25, CD127, CD45RO, CCR6, CCR7, and HLA-DR (T cells panel), or CD3, CD11b, CD14, CD16, CD19, CD24, CD27, CD33, CD38, and IgD (B cells/MDSC panel). We used Bayesian multivariate survival analysis, blinded, with overfitting prevention, to prospectively determine parameter contributions to risk. **Results:** Multivariate risk scores/signatures were derived that predicted either: progression free survival (PFS), with parameters including c1 MDSC, and c2 CD27-IgD-double-negative exhausted memory B cells; or RECIST response, with parameters including suppressive transitional B cells (c1 - c2 difference predicting response), and exosomal EGFR-HER3 dimer (c1 - c2 difference negatively predicting response). **Conclusion:** This study prospectively establishes an effect of exosomal and immunological factors on the efficacy of anti-HER/chemo combination therapies, paving the way for future stratification strategies that combine with immunological therapies. Clinical trial information: NCT02633800.

6044 Poster Session (Board #32), Sat, 1:15 PM-4:45 PM

Cisplatin dose intensity (CDDP-D) in human papillomavirus-positive (HPV+) localized oropharyngeal carcinoma (OPC) treated with chemoradiotherapy (CRT). *First Author: Marc Oliva Bernal, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: CDDP-D $\leq$ 200 mg/m^2 has been shown to have a detrimental impact on overall survival (OS) in HPV negative disease with a similar trend in T4/N3 HPV+ patients (pts). We evaluated the impact of CDDP-D on OS in a larger cohort of HPV+ OPC, staged using 8th Ed. AJCC/UICC TNM staging criteria (TNM8-S). **Methods:** We performed a retrospective single institution analysis of HPV+ OPC pts treated with CRT (IMRT) between 2005-2015. HPV status was tested by p16 staining, supplemented by HPV DNA (ISH or PCR) if equivocal. All cases were re-classified using TNM8-S. Kaplan-Meier 5-year OS (5yOS) was calculated and compared by log-rank test between CDDP-D ($<$ 200, = 200 or $>$ 200 mg/m^2) stratified by stage. Significant univariate variables including TNM8-S, smoking history and CDDP-D were tested in multivariable analysis (MVA) to identify OS predictors. **Results:** A total of 506 pts were evaluated: median age 57.4 (range 31.3-80.9); smoking $\leq$ vs $>$ 10 pack-year (PY), 52% vs 48%; TNM8-S I/II/III N = 200/183/123. Median CDDP-D: 200mg/m^2. Median follow-up: 4.9 (range 0.6-12.7) years. 5yOS differed by TNM8-S I, II and III: 93 vs 82 vs 78% ($p < 0.001$). In the MVA, PY had a detrimental impact on OS (HR = 1.16, 95%CI: 1.05-1.29 $p = 0.003$); CDDP-D did not impact OS overall (HR: 0.71, 95%CI: 0.41-1.21 $p = 0.4$), but in the TNM8-S III subgroup there was a trend toward decreased OS with CDDP-D $<$ 200 mg/m^2 (table). **Conclusions:** No linear CDDP-D effect on OS was seen for HPV+ OPC overall, although $<$ 200 mg/m^2 may be detrimental in TNM8-S III. TNM8-S separated OS well in this large cohort of uniformly treated pts. Suboptimal 5yOS (78%) in TNM8-S stage III HPV+ disease suggests the need for novel strategies in this setting.

5yOS and MVA by TNM8-S.

			TNM8-S (No of pts)		
Variable	**CDDP-D mg/m^2**	**No of pts**	**I (200)**	**II (183)**	**III (123)**
5yOS % (95%CI)	**< 200**	125	89% (79-100)	82% (71-95)	**63% (44-89)**
	= 200	224	93% (88-99)	80% (71-90)	90% (82-99)
	> 200	157	95% (90-100)	85% (75-96)	74% (61-89)
	p value		*0.14*	*0.63*	*0.11*
MVA:HR (95%CI)	**= 200 vs < 200**		0.58 (0.19-1.8, *p = 0.35*)	1.18 (0.52-1.33 *p = 0.69*)	**0.38 (0.14-1.05, *p = 0.06*)**
	> 200 vs < 200		0.31 (0.08-1.28,*p = 0.11*)	0.85 (0.31-2.3 *p = 0.74*)	0.88 (0.37-2.11, *p = 0.77*)

6045 Poster Session (Board #33), Sat, 1:15 PM-4:45 PM

Randomized phase 2 trial of patritumab (P) or placebo (PBO) + cetuximab (C) + cisplatin (CIS) or carboplatin (CAR) for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *First Author: Kevin J. Harrington, Royal Marsden Hospital/Institute of Research, London, United Kingdom*

Background: P, a fully human monoclonal antibody can block HER3 activation. HER3 activation is a resistance mechanism to C, induced by the ligand heregulin (HRG). This randomized phase 2 study in Europe evaluated first-line C + CIS or CAR + P or PBO for R/M SCCHN. **Methods:** Patients (pts) age $\geq$ 18 y with confirmed R/M SCCHN, stratified by HRG high vs low expression (via RT-PCR from tumor RNA) and human papilloma virus (HPV)+ vs HPV-, received IV P (18 mg/kg loading dose [LD]; 9 mg/kg maintenance dose [MD] every 3 weeks [q3w]) or PBO, and C (400 mg/m^2 LD; 250 mg/m^2 MD weekly) + $\leq$6 cycles of CIS (100 mg/m^2 q3w) or CAR (AUC of 5). Co-primary endpoints were progression-free survival (PFS) in the intent-to-treat (ITT) and HRG high arms. **Results:** In all, 87 pts (44 P, 43 PBO; median age 59 y; 83% male) were treated; a median 6 (1-20) P cycles were completed. Pts received CAR (70%) or CIS (34%) (median 5 [2-6] CAR and 5 [1-6] CIS cycles) in the P arm and CAR (7%) or CIS (20%) (median 5 [1–6] cycles each) in the PBO arm. Discontinuations due to adverse events (AEs) were higher with P (16%) vs PBO (5%). Treatment-emergent AEs grade $\geq$3 were more frequent with P (84%) vs PBO (58%) (most frequent: acneiform dermatitis [14% vs 7%] and rash [14% vs 0%]). Serious AEs occurred in 43% (41% grade $\geq$3) (P) and 37% (33% grade $\geq$3) (PBO) of pts. In P and PBO arms, PFS and objective response rates (ORR; complete + partial response) in ITT, HRG-high (Table), HRG low (difference in PFS: HR 1.2, 95% CI 0.6–2.6, and ORR: 11.1%, 95% CI -15.8–36.0) and HPV- (difference in PFS: HR 1.5, 95% CI 0.9–2.7, and ORR: 4.7%, 95% CI -16.6–25.3) arms were similar (HPV+ arm was too small [n = 16] to draw meaningful results). **Conclusions:** P + C + CIS or CAR was not more effective than C + CIS or CAR. Clinical trial information: NCT02633800.

	PFS, mo, median (95% CI) P	**PFS, mo, median (95% CI) PBO**	**PFS difference, HR (95% CI) P vs PBO**	**ORR, % (95% CI) P**	**ORR, % (95% CI) PBO**	**ORR difference, % (95% CI) P vs PBO**
ITT (N = 87)	n = 44 5.6 (4.1–6.5)	n = 43 5.5 (4.2–6.5)	1.11 (0.7–1.9) *P*= 0.70	n = 16/44 36.4 (22.8–52.3)	n = 12/43 27.9 (15.8–43.9)	8.5 (-10.9–26.8)
HRG high (n = 51)	n = 26 5.6 (4.1–7.1)	n = 25 5.6 (3.1–8.3)	1.12 (0.6–2.3) *P*= 0.75	n = 11/26 42.3 (24.0–62.8)	n = 9/25 36.0 (18.7–57.4)	6.3 (-19.1–30.4)

6046 Poster Session (Board #34), Sat, 1:15 PM-4:45 PM

Incidence of ototoxicity in head and neck cancer (HNSCC) patients (pts) receiving concomitant chemo-radiation (CRT) with weekly or triweekly cisplatin (Cis). *First Author: Jishu Das, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: Cisplatin (Cis) is one of the most ototoxic chemotherapy drugs, resulting in a permanent and irreversible hearing loss in up to 50% of patients. Little is known about the incidence of hearing loss when using different cisplatin schedules in patients receiving concomitant CRT. We, therefore, assessed prospectively the incidence of ototoxicity in patients receiving weekly or triweekly Cis concomitantly with radiation. **Methods:** Head and Neck Squamous Cell Cancer patients receiving definitive or adjuvant cisplatin-based CRT were included. Cisplatin was administered weekly (40 mg/m2 weekly, 7 cycles) or triweekly (100 mg/m2 every three weeks, 3 cycles). Radiation was administered to a total dose of 70 Gy as definitive treatment or 66 Gy as adjuvant treatment (2 Gy/fraction). Intensity-modulated radiation therapy was used in all cases. Pure-tone air-conduction audiometry was performed in all pts before starting and after completion of CRT. The primary endpoint of the analysis was Common Terminology Criteria for Adverse Event (CTCAE v4.0) hearing change $\geq$3 at the end of CRT. **Results:** A total of 96 pts (M:77/F:19) were included (oropharynx 56 pts, other 40). Age: 55y (26-78). 68 pts received weekly cis and 28 triweekly regimen. 58 pts received definitive treatment and 38 adjuvant treatment. Nine pts receiving weekly cis (13%) experience G3 ototoxicity vs 14 pts (50%) receiving triweekly cis ($P < 0.001$, OR = 6.4, 95% CI 2.1-20.7). Risk of ototoxicity was not associated with age, cis cumulative dose, sex, tumor primary site, or CRT modality (definitive vs. adjuvant). After adjusting for these factors in a multivariable model cis schedule remained significant (OR = 8.7, 95% CI 2.31-32.75, p = 0.001). With a minimum follow-up of three months, the complete response rate after treatment was 84% for weekly CRT and 86% for triweekly CRT. **Conclusions:** Triweekly Cis-based CRT increases the risk of irreversible severe ototoxicity. This risk should be discussed with patients that are candidates for cis-based CRT.

6047 **Poster Session (Board #35), Sat, 1:15 PM-4:45 PM**

Interference between mutational load, immune signatures and outcome in patients with head and neck cancer treated with definitive chemoradiation: A multicenter study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). *First Author: Inge Tinhofer, Department of Radiooncology and Radiotherapy, Charité University Hospital and German Cancer Research Center Heidelberg (DKFZ)/German Cancer Consortium (DKTK), Berlin, Germany*

Background: Mutational load and immune expression signatures have previously been established as efficacy biomarkers in immune checkpoint inhibitor (ICI) trials. It is important to know the value of these biomarkers for predicting outcome after concurrent chemoradiation (cCRTX), for defining patient subgroups likely to benefit from ICI/cCRTX combinations. **Methods:** FFPE tumor samples from 101 patients with locally advanced SCCHN from a retrospective DKTK-ROG biomarker trial were available for this study. All patients had been treated with standard definitive cCRTX. Mutation profiling was performed using a large gene panel targeting the complete coding sequence of 327 genes. Mutational load was calculated based on the number of somatic non-synonymous mutations per megabase (Mb). Immune mRNA profiles were determined using the nanoString PanCancer Immune panel. Mutational load was correlated with immune profile and outcome. **Results:** The mean number of somatic mutations per Mb was 4.9 (range 0-36), in line with previous reports from TCGA/ICGC studies. No association was found between mutational load and HPV status. Univariate Cox regression analysis revealed a significant correlation of high mutational load with reduced OS (HR for death: 1.9; 95%-CI: 1.1-3.3, P= 0.028). Conversely, detection of immune profiles linked to T-cell functions was associated with improved OS (HR: 0.3; 95%-CI: 0.1-0.9, P= 0.033). There was a significant interaction between mutational load and immune profiles in their effects on outcome ($P_{interaction}$= 0.03). High mutational load was associated with low T-cell infiltration, IFN-gamma signature scores and expression of genes involved in T-cell functions including PD-L1 and LAG3, indicative of immune dysfunctions in neoantigen-rich tumors. **Conclusions:** We established mutational load and T-cell immune signatures as interdependent predictors of the efficacy of cCRTX, thereby providing first evidence that both parameters might serve for selection of patients with benefit from combined cCRTX/ICI regimens.

6048 **Poster Session (Board #36), Sat, 1:15 PM-4:45 PM**

Cisplatin-induced ototoxicity in head and neck squamous cell carcinoma (HNSCC) patients treated with chemoradiation: The role of WFS1 and ABCC2 heritable variants. *First Author: Mary Mahler, Western Univeristy, London, ON, Canada*

Background: Ototoxicity is a common adverse drug reaction associated with cisplatin therapy and with radiation to the HN region. We evaluated the differential effect on hearing impairment in HNSCC patients by candidate polymorphisms of genes associated with either hearing loss or cisplatin function. **Methods:** In this observational study of locally-advanced HNSCC patients treated with cisplatin chemoradiation, hearing impairment attributed to treatment was defined as ≥grade 2 audiometric change from baseline to post-treatment, evaluated within 18 months of completing therapy (CTCAE v4.02). Patients were genotyped for 30 polymorphisms using Sequenom. Logistic regression evaluated associations between genetic variants and ototoxicity. Cox regression assessed relationships between genetic variants and locoregional control (LRC), distant control (DC), disease free survival (DFS) and overall survival (OS). **Results:** Of 246 patients who had audiometric testing pre- and post-chemoradiation, 79% were male; 76%, oropharyngeal cancers; 11%, oral cavity cancers; 8%, laryngeal cancer; 91%, stage IV; 58% had hearing loss. Two polymorphisms had significant associations with hearing loss post treatment: WFS1 rs62283056 and ABCC2 rs3740066. In an additive inheritance model, individuals with WFS1 variants had a significantly decreased risk of ototoxicity (P= 0.012; adjusted odds ratio (aOR) = 0.56; 95% CI, 0.4-0.9, per increase in one minor allele), while the minor allele of ABCC2 was associated with greater risk of ototoxicity (P = 0.016; aOR = 1.68; 95% CI, 1.1-2.6). In contrast, the same genetic variants were not associated with LRC, DC, DFS or OS in a larger cohort of 642 HNSCC patients. **Conclusions:** WFS1 genetic variant is associated with differential hearing loss in LA-HNSCC patients. An ABCC2 variant, involved with removal of cisplatin from cells, is associated with increased cisplatin-induced ototoxicity. The same genetic variants were not associated with any efficacy outcomes. This information could be useful in the development of predictive models for cisplatin-induced ototoxicity.

6049 **Poster Session (Board #37), Sat, 1:15 PM-4:45 PM**

Development and validation of a combined metabolic and immune prognostic classifier for head and neck cancer. *First Author: Hisham Mohamed Mehanna, University of Birmingham, Birmingham, United Kingdom*

Background: Genomic characterisation of head and neck cancer (HNC) has identified 3-5 subgroups with distinct biological properties, including metabolic profile and immune status. Both facets could impact on response to standard and novel targeted therapies for HNC, but are not currently considered for treatment selection due to lack of validated biomarkers. **Methods:** A 54-gene metabolic-immune signature (MIGS) was constructed. Gene expression was analysed *in silico* using the TCGA HNC dataset (whole transcriptome RNA-Seq, n = 275) and validated using two independent cohorts (*Chicago* microarray [Agilent], n = 130; *Birmingham* targeted RNA-Seq [Illumina] on FFPE tissue, n = 123). We then evaluated MIGS in a cohort of anti-PD-1 treated R/M HNC patients. Immunohistochemistry (IHC) was used to investigate the utility of a surrogate protein signature. Spatial distribution of metabolic and immune markers was examined using Opal/Vectra multiplex immunofluorescent staining. **Results:** Analysis of TCGA dataset using unsupervised hierarchical clustering identified three patient subgroups with distinct metabolic-immune phenotypes and survival profiles: (1) immune^{high}/metabolic^{low}, (2) metabolic^{high}/immune^{low} and (3) intermediate, with 5-yr overall survival (OS) rates of 71%, 51% and 49% respectively (p = 0.0015). The prognostic nature of MIGS was replicated in both validation cohorts (*Table*). Protein IHC signature was not prognostic. Metabolic and immune markers showed inverse expression patterns on multiplex staining. Preliminarily, presence of metabolic^{high}/immune^{low} signature was associated with ~ 20% worse OS at 1yr in PD-1 treated R/M HNC patients. **Conclusions:** We developed and validated a prognostic molecular classifier based on metabolic profile and immune status. This classifier may have clinical application to guide use of metabolic modification and targeted immunotherapies for HNC treatment.

Cohort	Subgroup	5year OS (%)	p value	p value adjusted for HPV status
TCGA	1	71	0.0015	0.0005
	2	51		
	3	49		
Chicago	1	76	0.012	0.0025
	2	65		
	3	60		
Birmingham	1	80	0.097	0.0006
	2	64		

6050 **Poster Session (Board #38), Sat, 1:15 PM-4:45 PM**

A study to evaluate immunological response to PD-1 inhibition in squamous cell carcinoma of the head and neck (SCCHN) using novel PET imaging with [18F]F-AraG. *First Author: A. Dimitrios Colevas, Stanford Cancer Institute, Stanford, CA*

Background: Immune checkpoint blockade has demonstrated remarkable responses in a subset of patients with head and neck squamous cell carcinoma (HNSCC). However, the response rate is only ~20% or less for HNSCC. Currently, there are no good biomarkers to predict and assess responses after patients have initiated therapy. We evaluated the ability of a PET metabolic tracer ([^{18}F]F-AraG), that preferentially accumulates in activated CD8$^+$ T cells, to assess response to anti-PD-1 ab. We hypothesize that uptake of this agent within the tumor will correlate with the accumulation and activation of T cells within the tumor. **Methods:** Locally advanced HNSCC patients undergoing surgical resection received an infusion of anti-PD-1 ab in a window-of-opportunity study. A novel radiofluorinated AraG imaging agent, [^{18}F]F-AraG (Cellsight), was used to image patients by PET/CT before and 2-3 weeks after their infusion. The tissue volume of interest (VOI) for the pre- and post-infusion [^{18}F]F-AraG PET/CT scans was defined using pre-treatment conventional FDG-PET/CT scans. To assess for correlation of the [^{18}F]F-AraG with immune response, pre- and post-infusion samples of the patients' tumors were obtained and dissociated into cell suspensions. Tumor-infiltrating T cells were evaluated by flow cytometry to determine T cell infiltration and activation. Tumor tissue also underwent whole exome sequencing to assess for potential immune mediated selection and elimination of neoantigens. **Results:** In a patient with oral cavity HNSCC, there was an approximately 50% increase in total [^{18}F]F-AraG SUV in the VOI representing the tumor volume, following anti-PD-1 ab. Concurrently we observed an approximately 4-fold increase in the proportion of CD8+ T cells and an approximately 5-fold increase in the proportion of CD4+ T cells within the tumor tissue. The CD8+ T cells exhibited an activated state based on surface marker expression. **Conclusions:** [^{18}F]F-AraG accumulation in the tumor tissue correlates with an increase in T cell infiltration and activation. Further study of this novel PET tracer is underway in HNSCC to assess its utility for predicting clinical response. Clinical trial information: NCT03129061.

6051 Poster Session (Board #39), Sat, 1:15 PM-4:45 PM

Cardiovascular disease risks among head and neck cancer survivors in a large, population-based cohort study. *First Author: Mei Wei, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Over 63,000 Americans develop head and neck cancer (HNC) yearly. The 5-year survival rate for HNC patients is 40-90%. HNC shares risk factors to cardiovascular disease (CVD), such as age > 60 years, male sex, low fruit and vegetable intake, tobacco and alcohol use. Our study was to investigate cardiovascular complications and risk factors for CVD among HNC survivors. **Methods:** A total of 1,901 HNC patients diagnosed between 1997 and 2012, and 7,796 age and sex matched individuals from the general population were identified. CVD diagnoses were identified in electronic medical records: statewide ambulatory surgery and inpatient visit databases linked to the Utah Population Database. Multivariate Cox proportional hazard models were used to calculate hazard ratios (HR) for cardiovascular outcomes at 0-2 years, 2-5 years and 5+ years after HNC diagnosis. **Results:** Within the first 2 years after cancer diagnosis, HNC survivors had higher risks of developing CVD than matched comparison individuals, such as heart valve disease (HR 3.33, 95% 2.60-4.28), cardiomyopathy(HR3.21, 95% 2.04-5.03), systolic heart failure (HR 3.90, 95% 3.10-4.89), conduction disorders (HR 5.73, 95% 4.02-8.16), acute myocardial infarction (HR 3.11, 95% 2.08-4.65), coronary atherosclerosis (HR 3.42, 95% 2.90-4.03) and cardiac dysrhythmias (HR 4.26, 95% 3.68-4.93). The risks persisted even 5 years after cancer diagnosis. More baseline comorbidities(HR 1.27, 95%1.01-1.58), late stage of disease (HR 2.20, 95% 1.64-2.96), age > = 65 years old (HR 1.56, 95% 1.27-1.92), radiation therapy (HR 1.33, 95% 1.07-1.65) and chemotherapy (HR 1.72, 95% 1.39-2.13) were associated with increased CVD risk. Baseline comorbidities such as diabetes (HR 3.68, 95% 2.82-4.80), hyperlipidemia (HR 4.59, 95% 3.62-5.82), hypertension (HR 2.90, 95% 1.60-2.52) and chronic kidney disease (HR 5.14, 95% 4.19-6.30) were associated with increased CVD risk. **Conclusions:** Compared to the general population, HNC survivors have higher risk of developing CVD. Older age, late stage of cancer, comorbidities, radiation therapy and chemotherapy were risk factors. Close CVD monitoring and preventive treatments should be considered in this population.

6052 Poster Session (Board #40), Sat, 1:15 PM-4:45 PM

ICR gene signature to identify differential immune landscapes in anatomic subsites of head and neck squamous cell carcinomas and implications in personalized medicine. *First Author: Sara I. Pai, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Head and neck squamous cell carcinoma (HNSCC) patients have a 16-25% response rate to single agent immune checkpoint inhibitors (ICI). Prognostic biomarkers to ICIs are needed to identify patients who may most benefit from immunotherapy and to deliver personalized treatment to patients. The Immunologic Constant of Rejection (ICR) 18-gene signature reflects activation of both innate and adaptive immune effector mechanisms required for successful host immune-mediated tissue-specific destruction. **Methods:** The ICR transcriptional signature was applied to 109 primary HNSCCs and matched tumor-involved lymph nodes (oral cavity (OC, N = 40), oropharynx (OP, N = 32), and larynx/hypopharynx (L/HP, N = 37)). **Results:** The ICR signature varied substantially across anatomic subsites, with OC and OP tumors having significantly higher ICR scores than L/HP tumors (p = 1.5e-06). The ICR signature between primary and matched metastatic lymph nodes were concordant in most cases, suggesting that sampling of either the primary or metastatic site yields concordant results in determining an immune-inflamed or immune-deserted landscape. **Conclusions:** Our data suggest that L/HP primaries are less likely to respond to ICIs based on a reduced ICR gene expression profile within the tumor microenvironment. Based on this hypothesis, we are performing a retrospective analysis of HNSCC patients treated with ICIs and will evaluate their objective clinical responses with respect to anatomical subsite. This is the first report that identifies anatomic subsites within the head and neck region to have differential immune landscapes. Correspondingly, differential responses to ICIs may be linked to the evolutionary biology of the various HNSCC primary subsites.

6053 Poster Session (Board #41), Sat, 1:15 PM-4:45 PM

Comprehensive proteomic and genomic profiling to identify therapeutic targets in adenoid cystic carcinoma. *First Author: Sheeno P. Thyparambil, NantOmics, LLC, Rockville, MD*

Background: Adenoid cystic carcinoma (ACC) is a rare cancer of secretory glands accounting for 10% of salivary gland cancers and 1% of head and neck cancers. ACC rarely responds to chemotherapy or targeted therapy and there is no standard therapy for advanced ACC. Comprehensive molecular profiling of ACC tumors could identify targets of FDA-approved or investigational therapies. **Methods:** ACC specimens (n = 24) were analyzed with the GPS Cancer test, which includes whole genome sequencing, RNA-seq, and mass spectrometry-based targeted proteomic analysis. Tumor areas of FFPE tissue sections were marked by a pathologist, microdissected and solubilized for mass spectrometric quantitation of 30 clinically relevant proteins. A subset of tumors was further analyzed by global proteomics and compared with results from squamous cell carcinoma of the head and neck (SCCHN). RNA-seq results from ACC tumors was compared with that of various solid tumor types using the k-nearest neighbors algorithm. **Results:** Targeted proteomic analysis of chemopredictive proteins suggested that 17% of patients were likely to respond to irinotecan, while 33% were likely to be resistant to taxane. The vast majority of patients (96%) did not express any target proteins of FDA-approved targeted therapies. Global proteomic analysis with unsupervised hierarchical clustering of 4,002 proteins from 8 ACC specimens and 6 SCCHN specimens revealed a clear separation between the two groups. In genomic analysis, tumor mutational burden was lower in ACC than in SCCHN (1.53 vs 3.53 per MB). In ACC, MYB-NFIB fusion and missense mutations involved in transcriptional regulation (ZNF43, ZNF519 and ZNF429) were frequent. Expression of CDK6 protein and CDK6 mRNA (transcripts per million) were 4-fold and 3-fold higher in ACC than in SCCHN, respectively. None of the ACC tumors exhibited *RB1* deficiency. Among solid tumors, breast cancer was closest to ACC based on mRNA expression. **Conclusions:** Proteogenomic analysis identified CDK6 overexpression at both protein and mRNA levels in ACC. The combination of CDK6 overexpression and *RB1* proficiency suggests that ACC patients may benefit from CDK6 targeted therapy.

6054 Poster Session (Board #42), Sat, 1:15 PM-4:45 PM

Molecular prediction of lymph node metastases using immunohistochemical analysis of primary oral tongue squamous cell carcinomas. *First Author: Furrat Amen, Addenbrooke's Hospital, Cambridge, United Kingdom*

Background: Patients that present with oral tongue squamous cell carcinoma (OTSCC) may have a clinically and radiologically N0 neck at presentation. Should we observe these patients without treatment to the neck, waiting for lymph node metastases to occur, or should they be treated with a prophylactic neck dissection or irradiation, with their associated mortality and morbidity? **Methods:** This is translational research, using a tissue microarray constructed from formalin-fixed paraffin-embedded glossectomy specimens from 186 patients with OTSCC treated in 7 cancer centers in the United Kingdom. Full clinical follow up for at least 5 years and pathology data were obtained for all patients retrospectively. Up to 3 cores were taken from the centre of the tumour, 3 from the periphery, 3 from areas of perineural or vascular invasion and 1 core from normal tissue surrounding the tumor. 30 antibodies were selected from a previous cDNA microarray study (novel antibodies) and previous research studies, for confirmation of these reports. We standardized and performed immunohistochemistry using 19 antibodies: p16, FAS, desmoglein, P4HA1, involucrin, MMP8, S100, orniithine, SRP19, MRP2, LLGL2, laminin 5, FTH1, CD44, IL22, p53, Kif2a, anticollagen V, and VEGF. **Results:** Nodal metastases were related to central cores being P4HA1 negative and p53 positive, and peripheral cores being MMP8 positive and VEGF positive. SRP19 expression in the centre (56% vs 78% 5-year survival p = 0.004) and periphery of tumor (60% vs 78% 5-year survival p = 0.015) predicted significantly worse survival. VEGF expression in the periphery of tumor predicted significantly worse survival (60% vs 80% 5-year survival p = 0.001). All other tumor and patient specific predictors of metastases and survival will also be presented. **Conclusions:** The "Amen signature" (P4HA1 central negative, MMP8 peripheral positive and VEGF peripheral positive), in the primary tumor, is highly predictive of nodal metastases (p = 0.000). This will help predict which patients need a neck dissection. Poor survival can also be predicted so that these patients can have aggressive therapies or be entered into therapeutic trials of new regimens.

6055 Poster Session (Board #43), Sat, 1:15 PM-4:45 PM

Prognostic role of pretreatment plasma EBV DNA on stage III nasopharyngeal carcinoma staged by AJCC/UICC 8th edition TNM staging classification. *First Author: Victor Lee, Department of Clinical Oncology, Queen Mary Hospital, The University of Hong Kong, Hong Kong, Hong Kong*

Background: The AJCC/UICC 8th edition TNM staging classification for nasopharyngeal carcinoma (NPC) was launched in 2018. We previously proposed new stage groups which incorporated pretreatment plasma EBV DNA and T-, N-classifications into recursive partitioning analysis. Stage III disease remains heterogeneous with different combinations of T and N-classifications. We investigated if pretreatment plasma EBV DNA can stratify stage III into high-risk vs. low-risk groups (NCT02476669). **Methods:** 518 patients with non-metastatic NPC confirmed by PET-CT and MRI scans were prospectively recruited from 2010 to 2016. They all had plasma EBV DNA measured at baseline, and then 8 weeks and 6 months following IMRT with/without concurrent +/- adjunct chemotherapy. They were treated based on 7th edition TNM but were re-staged by 8th edition TNM for subsequent analysis. Covariates including age, sex, ACE-27, pretreatment LDH and plasma EBV DNA were analyzed by Cox regression for prognostic factors of progression-free survival (PFS), cancer-specific survival (CSS) and overall survival (OS). **Results:** 234 (45.2%) patients had stage III disease (see Table). 11 (4.7%) patients received IMRT alone, 39 (16.7%) received concurrent chemoradiation alone and the remaining 184 (78.6%) received concurrent chemoradiation and adjunct chemotherapy. The median pretreatment plasma EBV DNA was 494 copies/ml (range 0-175000 copies/ml). After a median follow-up of 5.2 years, 5-year PFS, CSS and OS in this cohort were 77.1%, 90.4% and 84.4% respectively. Pretreatment plasma EBV DNA 500 copies/ml stratified patients into high-risk vs. low-risk groups (PFS: 88.9% vs. 68.2%, p = 0.009; CSS: 96.8% vs. 85.4%, p = 0.033; OS: 91.2% vs. 79.4%, p = 0.124). Cox regression with multivariable analyses demonstrated that pretreatment plasma EBV DNA 500 copies/ml was the only significant prognostic factor of PFS (p = 0.005) and CSS (p = 0.027) while no prognostic factor was found for OS. **Conclusions:** Patients with high pretreatment plasma EBV DNA had a higher risk of relapse and additional therapy may be necessitated.

	N0	N1	N2	Total
T1	0	0	43	43
T2	0	0	18	18
T3	21	46	106	173
Total	21	46	167	234

6056 Poster Session (Board #44), Sat, 1:15 PM-4:45 PM

Tracking tumor-specific mutations in plasma, saliva and para-carcinoma tissues from patients with head and neck squamous cell carcinomas. *First Author: Ping Wu, Xiangya Hospital of Central South University, Changsha, China*

Background: In this study, tumor derived Cell-free DNA (cfDNA) is detected in plasma and saliva samples in head and neck squamous carcinomas (HNSCC), as well as genomic variants in para-carcinoma tissues (PCT). The utility of cfDNA and alterations in PCT to predict tumor relapse is evaluated. **Methods:** A cohort of 27 patients with HNSCC were enrolled, plasma and saliva samples collected pro and post surgery. Tumor samples and PCT were also taken at surgery for each patient. Targeted next generation sequencing with a panel of 1021 genes was performed on all samples. **Results:** Average number of somatic mutations in each tumor was 5.86 alterations (range, 1 to 13). Tumor-specific mutations were observed in 70% patients (n = 19) in plasma and 52% patients (n = 14) in saliva. At least one somatic mutation was identified in 73% (19 of 26) of PCT. TP53 was the most common mutated gene in all categories of sample. Tumor-specific DNA was detected in 94% of stage III-IV patients, comparing 67% of stage I-II. It is more likely to identified somatic mutations in plasma in hypopharyngeal carcinoma (90% in hypopharynx versus 50% in oral cavity and 64% in larynx). Approximately, they were more likely detected in saliva in oral cancer (83% in oral cavity versus 46% in larynx and 40% in hypopharynx). Disease free survival (DFS) was 50% in patients with detectable postoperative cfDNA in plasma and 86% in patients undetectable (HR = 8.09, $P < 0.05$). Similarly, patients (n = 7) with detectable postoperative cfDNA in saliva were significantly lower DFS than those patients undetectable (n = 20) (HR = 22.18, $P < 0.01$). Interestingly, patients whose PCT harbored more than one TP53 mutations or its frequency more than 5% have more tendency to relapse ($P < 0.01$). **Conclusions:** Tumor-specific mutations can be detected in cfDNA from plasma or saliva samples, including PCT, and tracking these mutations in cfDNA and in PCT can predict disease relapse after surgery in patients with HNSCC. Patients with cfDNA positive in post-surgery samples are at higher risk of relapse and are more likely to derive benefit from adjuvant treatment.

6057 Poster Session (Board #45), Sat, 1:15 PM-4:45 PM

Association of low serum albumin concentration with reduced overall survival for patients with metastatic head and neck cancer receiving anti-programmed death receptor-1 therapy. *First Author: Sara Kochanny, Section of Hematology/Oncology, Department of Medicine, The University of Chicago Medicine, Chicago, IL*

Background: Immunotherapy efficacy is modulated by immune competence which lacks well established clinical measures. Nutritional status influences immune competence and has been associated with poor outcomes with antimicrobial and oncologic therapies. The relationship between nutritional status and outcomes with anti-PD-1 checkpoint blockade has not been reported, and we examined this association in patients with metastatic head and neck (H&N) cancer. **Methods:** 114 patients with metastatic H&N cancer unselected for PD-ligand 1 (PD-L1) status received anti-PD-1 therapy. Low baseline serum albumin concentration was < 4.0 g/dL. Univariate logistic regression analyzed the relationship between albumin and overall response rate (ORR) measured by RECIST v1.1, and the association with body mass index (BMI) was performed with Chi-square analysis. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and Cox proportional hazard regression. **Results:** Median follow-up was 8.6 months. Baseline characteristics including known PD-L1+ (n = 27/48 high albumin vs. n = 27/60 low albumin, p = 0.38) were comparable between groups. ORR was 22.3%. Albumin status not associated with ORR (p = 0.41) but was associated with BMI (p = 0.04). There was a trend towards lower median PFS for the low albumin group (2.4 months, 95% confidence interval [CI]: 1.9-3.7) compared to the high albumin group (4.6 months, 95% CI: 2.6-7.5) (p = 0.1). OS was significantly reduced for the low albumin group (median: 5.4 months, 95% CI: 3.6-9.5) compared to the high albumin group (median: 12.5 months, 95% CI: 9.1-17.3) (p-0.03). On multivariate analysis, albumin was the strongest independent predictor of poor OS (p = 0.01). **Conclusions:** Poor nutritional status as measured by low baseline serum albumin concentration is associated with worse outcomes in patients with metastatic H&N cancer receiving anti-PD-1 therapy and is a potential measure of immune competency. Investigation of clinical measures of immune competency including albumin as a marker of nutritional status in larger patient cohorts is warranted.

6058 Poster Session (Board #46), Sat, 1:15 PM-4:45 PM

Impacts of plasma EBV DNA load during different time-points of induction chemotherapy plus radiotherapy for nasopharyngeal carcinoma. *First Author: Jin-Ching Lin, Taichung Veterans General Hospital, Taichung City, Taiwan*

Background: To investigate the prognostic impacts of plasma EBV DNA measured at different time-points in patients with advanced nasopharyngeal carcinoma who received induction chemotherapy (IndCT) plus radiotherapy (RT). **Methods:** We retrospectively review 206 previously untreated, biopsy-proven, and no distant metastasis NPC patients who received IndCT consisting of biweekly P-FL (cisplatin 60 mg/m^2, day 1 and 5-fluorouracil 2500 mg/m^2 + leucovorin 250 mg/m^2, day 8) × 10 weeks, followed by RT 70-74 Gy. Quantification of EBV DNA was done before treatment, the 5th week (during-IndCT) and the 10th week (post-IndCT) in the IndCT period, one week after RT (post-RT). We set cut-off values as > vs. < 1500 copies/ml for pretreatment, and detectable (> 0) vs. undetectable (= 0) for other time-points (during-IndCT, post-IndCT and post-RT) and analyze the relationship between the EBV DNA status at different time-points and clinical outcome. **Results:** Pretreatment EBV DNA (median, 1550 copies/ml; interquantile range, 375-5688) was detectable in 95.1% (196/206) patients. The EBV DNA load decreased markedly as treatment going- 114 (55.3%), 84 (40.8%), and 30 (14.6%) patients showing detectable results during-IndCT, post-IndCT, and post-RT with a lower copy numbers (median 37, 18, and 236 copies/ml). The pretreatment, post-IndCT, and post-RT EBV DNA levels can discriminate relapse rates between the two subgroups (47.1% vs. 21.6%, P = 0.0001; 50.0% vs. 23.8%, P < 0.0001; 83.3% vs. 26.1%, P < 0.0001) whereas during-IndCT viral load cannot (37.7% vs. 30.4%, P = 0.2741). Overall survivals were significantly affected by the pretreatment (HR = 2.26, 95%CI = 1.45-3.52, P = 0.0002), post-IndCT (HR = 2.02, 95%CI = 1.32-3.09, P = 0.0010), and post-RT (HR = 4.86, 95%CI = 3.05-7.73, P < 0.0001) but not during-IndCT (HR = 1.27, 95%CI = 0.82-1.95, P = 0.2859) EBV DNA load. Relapse-free survivals showed the same results. **Conclusions:** Pre-treatment, post-IndCT, and post-RT EBV DNA are important variables to predict outcome for NPC patients. Those who had high pre-treatment levels, detectable after IndCT and one week after RT should be searched for more intensive post-RT adjuvant therapy in future trials.

6059 Poster Session (Board #47), Sat, 1:15 PM-4:45 PM

Gene expression signature after one dose of neoadjuvant pembrolizumab associated with tumor response in head and neck squamous cell carcinoma (HNSCC). *First Author: Eejung Kim, University of Cincinnati Medical Center, Cincinnati, OH*

Background: Immune checkpoint inhibitors have been shown to induce durable tumor response in a subset of recurrent and/or metastatic HNSCC. Higher expression of PD-L1, INF-γ, and composite signatures such as "T cell-inflamed" profiles have been reported as biomarkers of response. However, prospective study of gene expression profiles after a single dose of Pembrolizumab compared to pre-treatment biopsy have not been reported. As a part of study "Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC" (NCT02641093), we have investigated gene expression changes associated with Pembrolizumab pathological response in HNSCC. **Methods:** Total RNA was extracted from 11 paired samples of pre- and post- one dose of Pembrolizumab. Total RNA was subjected to a hybridization-based digital counting assay (Nanostring®), which measures mRNAs of 770 immune-related genes and controls. RNA counts were normalized and log-transformed. Gene expression comparison analysis was performed between pre- and post- Pembrolizumab treatment and between five responders and six non-responders. Response was defined as more than 10% of pathologic treatment effect. **Results:** Higher expression of PD-L1, PD-L2, and INF-γ in pre-treatment samples were associated with tumor response after one dose of Pembrolizumab (Welch's t-test, $p = 0.015$, 0.021, 0.006). Existence of T cells, B cells, NK cells, macrophages, neutrophils in pre-treatment samples were not predictive with response. However, macrophages, T and B lymphocytes were increased in post-treatment samples of responders, implying that these were recruited effectors. There was no such difference in NK cells and neutrophils. INF-γ induced genes including CXCL9, OASL, IFI35, and IDO1 showed higher expression in responders (Welch's t-test $p = 0.004$, 0.005, 0.007, 0.01). **Conclusions:** Inflamed tumor microenvironment, evidenced by increased INF-γ irrespective of lymphocyte infiltration is associated with pathological response after a single dose of Pembrolizumab in HNSCC.

6060 Poster Session (Board #48), Sat, 1:15 PM-4:45 PM

Second primary thyroid cancer following index head and neck cancer. *First Author: Katherine M. Polednik, Saint Louis University School of Medicine, Saint Louis, MO*

Background: Thyroid cancer incidence has increased in the last three decades, and studies have shown that radiation treatment for index cancers may play a role in its development. We examined the rate of second primary thyroid cancer (SPTC) following index head and neck cancer (HNC) and determined whether radiation treatment among HNC survivors increased risk of developing SPTC. **Methods:** Patients with index HNC diagnosed from 1975-2014 in the Surveillance, Epidemiology, and End Results 9 database were included. We calculated incidence rate for SPTC per 100,000 person-years. A multivariable competing risk proportional hazards model tested risk of developing a SPTC following an index HNC. Covariates included age, county-level poverty percentage, year of diagnosis, anatomic site, stage, grade, surgery, radiation, chemotherapy, race, marital status, and sex. Two sensitivity analyses using proportional hazards models were also performed: (1) comparing patients who received both radiation and chemotherapy to those who did not receive both; and (2) restricting the main model to patients who received radiation. **Results:** There were 229 SPTC cases out of 127,563 HNC patients (0.2% SPTC). The rate of SPTCs was 26.1 per 100,000 person-years. In the main model, for every increasing year of age at diagnosis, patients were 3% less likely to develop an SPTC (adjusted hazard ratio [aHR] = 0.97, 95% confidence interval [CI]: 0.96, 0.98. Compared with non-Hispanic white patients, non-Hispanic Asian/Pacific Islander/Native American/Alaskan Native patients were 66% more likely to develop an SPTC (aHR = 1.66, 95% CI: 1.10, 2.50). Males were 27% less likely to develop an SPTC than females (aHR = 0.73, 95% CI: 0.55, 0.96). Radiation (aHR = 0.92, 95% CI: 0.68, 1.25), surgery (aHR = 0.79, 95% CI: 0.56, 1.11), and chemotherapy (aHR = 1.13, 95% CI: 0.76, 1.69) were not significantly associated with developing SPTC. The sensitivity models also did not find an association between treatment and risk of SPTC. **Conclusions:** Rate of developing SPTC following index HNC was very low, and previous exposure to radiation did not significantly increase risk in our study population. More studies are needed to understand the increasing incidence of thyroid cancer across the United States.

6061 Poster Session (Board #49), Sat, 1:15 PM-4:45 PM

Immune profiling of head and neck squamous cell carcinoma (HNSCC) by a multiplex immunofluorescence (mIF) panel using multispectral microscopy. *First Author: Janis De La Iglesia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Treatments based on immune checkpoint inhibition have shown great promise in HNSCC. Comprehensive evaluation of lymphoid-inflamed tumor-immune microenvironment may contribute to the identification of a subgroup of patients that may have a favorable outcome using immunotherapy. **Methods:** HNSCCs were analyzed by a mIF panel (CD3, CD8, FOXP3, PD-1, PD-L1, pancytokeratin AE1/AE3, and DAPI) using multispectral microscopy and image analysis. Three regions of tumor core, tumor margin and adjacent stroma were chosen for measurement. The mIF results were correlated with clinical parameters. **Results:** Sixty-eight HNSCC were stained and numbers of positive cells from all 7 markers could be obtained. In the subset of 9 tumors with known p16 status (4 positive, 5 negative), numbers of PD-L1+ cells were marginally significantly higher in p16- tumor cores ($p < 0.1$) compared to p16+ tumor cores while numbers of CD3+ and CD8+ cells were higher in stroma of p16- tumors compared to p16+ tumors ($p < 0.01$ and $p = 0.02$, respectively). Regardless of p16 status, numbers of CD3+ and CD8+ cells in the tumor cores were marginally significantly higher in never smokers (N = 12) (both $p < 0.1$) and numbers of CD8+ cells within 25 micron from the tumor cells were again higher in never smokers ($p = 0.048$) compared to former (N = 14) and current smokers (N = 42). Patients with tumors harboring high numbers of CD8+ cells within 25 micron of the tumor cells showed a trend towards longer survival times ($p = 0.16$). **Conclusions:** This is the first study to examine the distribution of immune cells in tumor core, the invasive margin, and adjacent stroma and the proximity between immune and tumor cells. Our data suggest that p16- tumors may be more immunosuppressed by increased expression of PD-L1 while CD8+ cells are unable to infiltrate the tumor mostly residing in the stroma. In addition, never smokers may have more active immune response by having closer proximity of CD8+ cells to tumor cells compared to never and former smokers. Complete data from a total of 176 patients will be presented at the meeting.

6062 Poster Session (Board #50), Sat, 1:15 PM-4:45 PM

Number of nodal metastases associated with overall survival in HPV-negative head and neck cancer. *First Author: Doug Farquhar, University of North Carolina, Chapel Hill, NC*

Background: The 8th edition AJCC staging guidelines for HNSCC incorporated the number of positive nodal metastases into the pathologic staging criteria for HPV-positive oropharyngeal HNSCC. However, the number of positive nodes is not used for pathologic staging of HPV-negative HNSCC and may have prognostic significance. In this study, we evaluated whether the number of nodal metastases and other surgical pathology characteristics, including extracapsular extension (ECE), positive surgical margins (PSM), and perineural invasion (PNI), were associated with overall survival (OS) in HPV-negative HNSCC. **Methods:** Patients were identified from the Carolina Head and Neck Cancer Study (CHANCE). All HPV-negative patients without distance metastasis (M0) who received surgical treatment for their primary tumor were included. The number of positive nodes on surgical pathology was divided into 0, 1-4, and > 4 nodes. T and N stage were based on 8th edition AJCC guidelines. Hazard ratios (HR) were calculated by Cox proportional hazard models. **Results:** We identified 212 HPV-negative HNSCC patients who received primary surgery with neck dissections; (81 had no positive nodes, 90 had 1-3 positive nodes, and 41 had ≥4 nodes). Number of positive nodes, LVI, and ECE were all associated with 5-year OS in univariate models. In a multivariate model that controlled for T and N staging, the number of positive nodes remained significantly associated with OS (HR 2.8, 95% CI 1.8–4.3 for 1-4 nodes; HR 6.4 95% CI 3.6-11.1 for > 4 nodes). In this model, N-stage as defined by AJCC 8 was no longer significantly associated with survival (HR 1.2, 95% CI 0.5–2.6 for N1 vs. N0, HR 1.1 95% CI 0.5–2.4 for N2 vs. N0, HR 2.1 95% CI 0.8–5.7 for N3 vs N0). ECE, PSM and LVI were not independently predictive of OS in adjusted models. **Conclusions:** In this population of HPV-negative HNSCC patients, the number of positive nodes had a stronger association with 5-year OS than N staging based on nodal size and laterality found in AJCC 8. No other pathologic variables were associated with survival after adjusting T and N for stage. Further research is necessary to determine whether the number of positive nodes should replace other criteria in future prognostic staging systems.

6063 Poster Session (Board #51), Sat, 1:15 PM-4:45 PM

Using mobile and sensor technology to identify early dehydration risk in head and neck cancer patients undergoing radiation treatment: Impact on symptoms. *First Author: Susan K. Peterson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Assessment and intervention with mobile and sensor technology may improve early detection and mitigation of treatment-related symptoms, impact quality of life (QOL), reduce complications, and lower health care costs. The CYCORE (CYberinfrastructure for COmparative effectiveness Research) system utilizes sensor and mobile technology to remotely assess daily weight, blood pressure (BP)/pulse, and patient-reported outcomes in head and neck cancer (HNC) patients undergoing radiation treatment (RT). Clinicians reviewed data daily to identify early risk of dehydration and support early intervention to improve symptom management. We compared longitudinal symptom data in patients randomized to use CYCORE during RT versus those randomized to usual care. **Methods:** Methods: HNC patients (n = 357) completed the 28-item MD Anderson Symptom Inventory (MDASI) at RT initiation (baseline), completion of RT (6-7 weeks post-baseline), and 6-8 weeks post-RT completion. Symptom severity and interference were rated on 0-10 scales; lower scores indicated better outcomes. Repeated measures ANOVA evaluated time point and group differences in MDASI scores. **Results:** Mean age was 60 years (range 25-86), 21% were female, 85% were White, and 54% completed college. Baseline MDASI mean scores were similar in patients randomized to CYCORE (n = 169) or usual care (n = 188). Mean scores on the severity of general and HNC-specific symptoms were lower in the CYCORE versus usual care group at completion of RT (2.92 vs. 3.4, p = .003; 4.21 vs 4.83, p = .009), and at 6-8 weeks post-RT completion (1.69 vs 1.96; p = .003; 1.78 vs. 2.11, p = .009). Mean scores on symptom interference in daily life were similar in both groups across time. **Conclusions:** HNC patients randomized to the CYCORE group during RT self-reported lower severity of general and HNC-specific symptoms compared to usual care. Sensor and mobile technology can enable monitoring of patients' symptoms and related outcomes during critical periods of outpatient cancer treatment, can provide timely information to facilitate rapid clinical decision making about care, and may ultimately result in better QOL and health outcomes. Clinical trial information: NCT02253238.

6064 Poster Session (Board #52), Sat, 1:15 PM-4:45 PM

Minimally-invasive dual testing for active HPV E6,E7 and PD-L1 expression in HNSCC. *First Author: Haitham Mirghani, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) have better prognosis when HPV associated or with a positive PD-L1 status. The often invasive nature of testing as well as the turnaround time for results are impactful on the doctor-patient relationship as available testing influences level of care. This assay was performed with minimally invasive swabs of lesions from HNSCC patients. Non-subjective and quantitative results for E6,E7 mRNA overexpression as well as PD-L1 expression in these tumors were obtained by a three color flow cytometry assay. **Methods:** Swabs from patients with oropharynx lesions at the Institut Gustave Roussy were fixed with a proprietary solution (IncellMAX, IncellDx) and sent for processing. Received samples were strained through a 35 uM filter, underwent ISH with E6, E7 mRNA probes (HPV OncoTect, IncellDx), stained with a PD-L1 Antibody (28-8), and stained with a cell cycle dye to verify cells. Stained samples were analyzed by flow cytometry. Institut Gustave Roussy provided FFPE lesion biopsy tissue collected from the same area of swab collection. Slides from FFPE lesion biopsy tissue were processed by Gustave Roussy with p16 IHC. Positive p16 results were confirmed by HPV gDNA ISH (Inform HPV III, Ventana). Slides were also processed by Bioreference Laboratories for PD-L1 expression by IHC (PD-L1 IHC 28-8 pharmDx, Agilent). **Results:** Oral pharynx swab samples from 40 unique patients with HNSCC were tested by flow cytometry for E6,E7 and PD-L1 overexpression. Results were compared to p16/ISH and PD-L1 IHC results from the tumor biopsy. Initial analysis of 30 samples show concordance of 73.3% between E6,E7 over expression by flow cytometry and p16 by IHC. [Additional data to be presented at the conference, currently pending PD-L1 IHC results]. **Conclusions:** Providing quantification of HPV E6, E7 mRNA and PD-L1 expression through a minimally invasive method presents a profound ability for clinicians to decide treatment options for patients. Ease of sampling coupled with the ability to both multiplex targets and scale-up the assay provides great possibility in treatment in disease.

6065 Poster Session (Board #53), Sat, 1:15 PM-4:45 PM

A double-blind, randomized pilot study of NS-21 in the prevention of radiation dermatitis for patients with head and neck cancer. *First Author: Chen-Hsi Hsieh, National Yang-Ming University, Taipei, Taiwan*

Background: The purpose of this single-institution pilot study was to evaluate the feasibility and safety of NS-21, a natural cortisone-free ingredient, on skin-related toxicity in patients with head and neck cancer (HNC) undergoing concurrent chemoradiation (CCRT) or radiotherapy (RT). **Methods:** Between July 2015 and November 2017, 29 HNC patients underwent RT or CCRT were double-blind, randomly allocated to application of either NS-21 (14 patients) or placebo (aloe vera gel, 15 patients) to the irradiated fields in neck three times per day from the first day of RT to the 2 weeks after RT is completed or to the development of severe skin toxicity. The skin moisture and dermatitis in the left and right irradiated-area of neck were recorded separately. The area in the level I-II-III-Va was named as upper neck and the area in the level IV was named as lower neck. The RT dose to the low- and intermediate-risk area was 46 Gy and 60 Gy, respectively. The maximum grade of radiation used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The relative humidity of skin was monitored by digital hygrometer. **Results:** The number of neck fields received radiation dose larger than 46 Gy ($Neck_{> 46Gy}$) was 80 and 82 in the study and placebo group, respectively. The occurrence of acute grade 3 or higher dermatitis in $Neck_{> 46Gy}$ was significantly lower in the NS-21 group than in the placebo group (5.0% vs. 20.3%; p = 0.024). The median time of grade 3 or higher dermatitis occurred was 6 and 7 weeks for the control and NS-21 group, respectively ($p < 0.001$). From beginning of RT to 2 weeks after the completion of RT, $Neck_{> 46Gy}$ ($p < 0.001$) and applying NS-21 (p = 0.014) were independent factors for the incidence of grade 3 dermatitis. There was a trend of skin moisture protection by using NS-21 in HNC patients under RT or CCRT (p = 0.052). Moreover, $Neck_{> 46Gy}$ ($p < 0.001$) and dermatitis grading (p = 0.006) were independent factors associated with the skin moisture. **Conclusions:** For HNC patients, applying NS-21 from the first day of RT or CCRT and through the treatment course that can decrease the incidence of acute grade 3 or higher dermatitis in the neck effectively and protect the skin moisture in the neck potentially. Clinical trial information: FEMH 104048F.

6066 Poster Session (Board #54), Sat, 1:15 PM-4:45 PM

Safety and effectiveness of transoral surgery for superficial head and neck cancer: The National Registration Survey of superficial head and neck cancer in Japan. *First Author: Chikatoshi Katada, Kitasato University, Kanagawa, Japan*

Background: The national registration survey of transoral surgery (TOS) for superficial head and neck cancer (SHNC) was performed to retrospectively examine safety and effectiveness. **Methods:** From April 2001 through July 2012, a total of 599 patients with SHNC (954 lesions) who underwent TOS as initial treatment were enrolled in 27 hospitals in Japan. Of these patients, we studied 899 lesions (665 initially treated lesions and 234 metachronous multiple cancers) in 568 patients who were given a central pathological diagnosis of initially treated squamous-cell carcinoma. The study variables were clinicopathological findings, the incidences of adverse events, and treatment outcomes. **Results:** The median age was 66 years, and 534 (94%) of the patients were men. A total of 202 lesions (22.4%) were located in the oropharynx, 660 (73.3%) in the hypopharynx, 23 (2.6%) in the larynx, 12 (1.3%) in the oral cavity, 2 (0.2%) in other sites. The surgical procedures were endoscopic mucosal resection in 374 lesions (41.6%), endoscopic submucosal dissection in 359 (39.9%), endoscopic laryngopharyngeal surgery in 48 (5.3%), transoral videolaryngoscopic surgery in 40 (4.4%), direct mucosectomy in 28 (3.1%), laser microlaryngeal surgery in 20 (2.2%), and others in 28 (3.1%). The median clinical tumor diameter was 12 mm. The histopathological findings of the 869 lesions treated by TOS were carcinoma in situ in 536 lesions (61.7%) and subepithelial invasive cancer in 333 lesions (38.3%). The median treatment time of 777 sessions of TOS was 49 minutes. Adverse events occurred in 89 patients (11.5%). Life-threatening complications occurred in 10 patients (1.3%), but there was no treatment-related death. Tracheotomy was performed in 72 patients (9.3%). Local recurrence was found in 53 lesions (5.9%), nodal recurrence in 26 patients (4.6%), and distant recurrence in 3 patients (0.5%). The median follow-up period was 46.1 months. At 3 years, the overall survival rate, the relapse-free survival rate and the cause-specific survival rate were 88.1%, 84.4% and 99.6%, respectively. **Conclusions:** TOS for SHNC is a safe and effective, minimally invasive treatment option. Clinical trial information: UMIN000008276.

6067 **Poster Session (Board #55), Sat, 1:15 PM-4:45 PM**

Neck dissection rate in node positive human papillomavirus associated oropharyngeal carcinoma following chemoradiotherapy. *First Author: Sandro Porceddu, Princess Alexandra Hospital, University of Queensland, Brisbane, Brisbane, Australia*

Background: With results of chemo-radiotherapy de-escalation trials for Human Papillomavirus (HPV)-associated oropharyngeal carcinoma (OPC) pending, any reduction in toxicity may be offset by the increased need for post-therapy neck dissection (PT-ND) for suspected residual nodal disease. We report the rate of PT-ND and overall regional failure rate following standard radiotherapy (RT) with or without chemotherapy (chemo)RT in node positive HPV-associated OPC. Secondary objectives include estimated 5-year regional failure free survival (FFS), loco-regional FFS, distant metastatic FFS and overall survival (OS). **Methods:** Patients treated between Jan 2005-Jan 2016 on a pre-defined (chemo)RT protocol and 12-week restaging PET/CT (treatment package) with a minimum of 18 months follow up (FU) were analysed. Patients receiving concurrent chemo were prescribed high-dose cisplatin and 70Gy/7 weeks to gross disease. Those ineligible for cisplatin received weekly cetuximab. PT-ND was performed if residual nodal disease was suspected on the restaging scan with complete response at the primary site and no evidence of distant disease. **Results:** 343 patients were eligible. Median follow up was 60 months, with 302 (88%) alive at the close-out date. Median age was 59 (range, 21-89) yrs. The predominant AJCC/UICC 7th Edition (Ed) T- & N-stage were T2 (37.3%) & N2b (44.9%), respectively. The 8th Ed group staging were; Stage I-49%, Stage II-28% & Stage III–23%. Median RT dose was 70Gy (range, 66-70Gy) and 336 (95.6%) received systemic therapy. At the completion of the treatment package 4.6% (16pts) underwent a ND. 10 pts (62.5%) were pathologically positive. The overall regional failure rate was 6.4%. The estimated 5-year regional FFS was 93% (95% CI: 90.2-95.9), loco-regional FFS 90.6% (95% CI: 87.3-94.0) and distant metastatic FFS 86.9% (95% CI: 83.1-90.8). 5-year OS by stage were; I–93.4% (95% CI: 89.5-97.5), II–82.9% (95% CI: 75.3-91.3) & III–75.9% (95% CI: 66-87.3). **Conclusions:** Following the treatment package the ND rate was low and regional failure uncommon. These findings serve as a benchmark to assess the benefit of de-escalation trials, which may be offset by an increased need for PT-ND.

6068 **Poster Session (Board #56), Sat, 1:15 PM-4:45 PM**

A randomised, double-blind, placebo-controlled phase IIa trial of AMG319 given orally as neoadjuvant therapy in patients with human papillomavirus (HPV) positive and negative head and neck squamous cell carcinoma (HNSCC). *First Author: Christian H.H Ottensmeier, Cancer Research UK, Southampton, United Kingdom*

Background: AMG319 is a PI3Kδ inhibitor. Preclinically, target inhibition abrogates Treg mediated immunosuppression, augmenting CD8$^+$ T-cell anti-tumour activity. This study aims to quantify the immunological effects of AMG319 on the tumour microenvironment in HNSCC patients (pts). **Methods:** The trial is a neoadjuvant window study of 54 pts, randomised 2:1 to AMG319/placebo for 20-29 days. Eligible pts have operable HNSCC, ECOG 0/1, adequate organ function and no active autoimmune disease. Primary endpoints are changes in tumour-infiltrating immune cell density, safety and toxicity. Changes in circulating immune markers, pAKT and change in tumour volume (pre-dosing vs immediately pre-surgery) are also assessed. Steady state plasma concentrations of AMG319 are determined at days 8, 15 and 22. Humoral and cellular immune responses to a tetanus vaccine are employed to confirm non-tumour immunocompetence. **Results:** Blinded clinical and laboratory data have been reviewed for 22 pts who received 400mg/day of AMG319/placebo. Ten pts experienced grade 2/3 treatment related adverse events (AEs): rash, diarrhoea/colitis, vomiting, fever, flu-like symptoms (days 7-11). AEs resolved with withdrawal of IMP and supportive treatment but led to early discontinuation in 9 pts; 8 pts received less than 80% of the intended dose. pAkt levels on both day 1 and 15 show inhibition of PI3K (51.6-88.9%) 4h post dosing in a proportion of pts. A $\geq$ 2-fold increase was seen in anti-tetanus antibody response in 5/10 pts analysed. One patient experiencing immune-like toxicity with a T1 oral cavity squamous cell carcinoma achieved a complete pathological response. **Conclusions:** The percentage inhibition demonstrated in the pAkt assay and observed in HNSCC is similar in magnitude to that seen previously with AMG319 in patients with advanced B cell malignancies, thereby supporting target inhibition. Cutaneous and GI toxicities are consistent with Treg depletion suggesting that efficacy and toxicity may be mechanistically interrelated. The trial is ongoing to further explore AMG319 solid tumour dosing regimens. Clinical trial information: NCT02540928.

6069 **Poster Session (Board #57), Sat, 1:15 PM-4:45 PM**

Preliminary toxicity data from the combination of pembrolizumab and definitive-dose radiotherapy for locally advanced head and neck cancer with contraindication to cisplatin therapy. *First Author: Jared Weiss, University of North Carolina Hospitals, Chapel Hill, NC*

Background: Bolus cisplatin in combination with radiation therapy is a standard of care for the treatment of locally advanced SCCHN, but contraindications such as hearing loss, tinnitus, inadequate renal function or neuropathy are common. Pembrolizumab is a PD1 inhibitor with FDA approval for the treatment of platinum-refractory recurrent SCCHN. **Methods:** This is a phase II study (NCT02609503) for patients with locally advanced SCCHN who are not optimal candidates for the standard therapy of cisplatin and radiation. The primary endpoint is PFS. Patients are treated with 3 cycles of pembrolizumab concurrent with radiation followed by 3 adjuvant cycles. Planned accrual is 29 subjects and 18 patients have been accrued. Because of rapid advance in studies combining PD1-axis agents with radiotherapy, we report early toxicity data on the first 12 patients who have completed six cycles of pembrolizumab and at least 30 days of followup from last pembrolizumab dose. **Results:** All patients completed 70 Gy radiation. 11 patients completed 6 cycles of pembrolizumab and 1 patient completed 5 (discontinued due to PD, not toxicity). The most common primary reason for cisplatin ineligibility was abnormal hearing (4) followed by tinnitus (3), nephropathy (2), neuropathy (2) and diabetes with poor control (1). The most common toxicities were mucositis and lymphopenia. Pneumonitis and autoimmune toxicity were absent. All toxicities that occurred more than once and listed as possible, probable or definitely related to pembrolizumab and radiation are listed in the table. PEG tubes were placed in 3 patients. **Conclusions:** Early data suggest low toxicity and high feasibility of pembrolizumab combined with radiotherapy. Clinical trial information: NCT02609503.

	Grade 1	Grade 2	Grade 3	Grade 4
Oral mucositis	0	7	2	0
Decreased lymphocyte count	1	1	6	1
Radiation dermatitis	4	1	0	0
Dysgeusia	5	1	0	0
Fatigue	5	0	1	0
Dry Mouth	2	4	0	0
Weight loss	1	3	1	0
Nausea	2	1	0	0
Dysphagia	2	2	0	0
Maculopapular rash	2	1	0	0
Anemia	3	0	0	0
Oral pain	1	1	0	0
Anorexia	0	1	1	0
AST increased	1	1	0	0
Bili increased	2	0	0	0
Hypothyroidism	0	2	0	0
Pain	2	0	0	0
Decreased WBC	1	1	0	0

6070 **Poster Session (Board #58), Sat, 1:15 PM-4:45 PM**

Impact of patient symptoms and caregiver tasks on psychological distress in caregivers for head and neck cancer (HNC). *First Author: Emily Castellanos, Vanderbilt University Medical Center, Nashville, TN*

Background: Caregiver support for HNC patients affects clinical outcomes including survival. Psychological distress in caregivers may impair the quality of support they provide. The impact of patient symptom burden and caregiver tasks on caregiver psychological distress is unknown. **Methods:** Patient symptom burden was assessed with the Vanderbilt Head and Neck Symptom Survey 2.0 (VHNSS 2.0; 10 domains, 3 single items). Caregiver task burden was assessed with the Caregiver Task Inventory (CTI; 11 domains), and quantified as task number and task difficulty/distress. Psychological distress was measured with the Profile of Mood States short form (POMS-SF). Two-step clustering analysis was used to independently generate clusters of caregiver distress, caregiver task burden, and patient symptom burden. Chi-Square and logistic regressions were used to test for associations of the resultant clusters of task burden and patient symptoms with caregiver distress. **Results:** 89 HNC patient-caregiver dyads were included. Patients were mostly male (77%) and Caucasian (88%). Median time since diagnosis was 3.7 months (IQR 2–7); 90% received combined modality therapy. Caregivers were mostly Caucasian (92%), female (85%) and spouses (80%). We found two caregiver clusters of psychological distress (40% mod-high, 60% low), and two clusters of caregiver task scores (40% mod-high, 60% low). Similarly, two clusters of patient symptom burden were found: 51% mod-high, 49% low. Caregivers with mod-high task scores were more likely than low to report mod-high levels of psychological distress (71% vs. 24%, $p < 0.001$). Patients with mod-high symptom burden were more likely than low to have caregivers with mod-high psychological distress (55% vs. 23%, $p = 0.005$). No effect modification of patient symptom burden on the association between caregiver task and caregiver psychological distress was seen ($p > 0.05$). **Conclusions:** Psychological distress in HNC caregivers is associated more strongly with caregiver task scores than patient symptoms. Further work to define the caregiver and task characteristics that lead to psychological distress should inform future interventions to support caregivers and patients.

6071 Poster Session (Board #59), Sat, 1:15 PM-4:45 PM

A phase I study of the PI3K inhibitor buparlisib (B) with concurrent chemoradiotherapy (CRT) in patients with high risk locally advanced squamous cell cancer of the head and neck (LASCCHN). *First Author: Jochen H. Lorch, Dana-Farber Cancer Institute, Boston, MA*

Background: Prognosis in smokers with LASCCHN remains poor. Activating mutations of PI3K are linked to poor outcome and PI3K activation in response to RT is implicated in resistance to CRT. **Methods:** In this phase I study, the oral pan-PI3K inhibitor B combined with CRT was tested in pts with stage III/IV LASCCHN and ≥10 pack-year history of tobacco use treated with curative intent. Pts received B during a 2-week run-in phase and during CRT consisting of 70Gy/35fx of radiotherapy plus weekly cisplatin. **Results:** Twenty-three pts (19 m, 4 f) were enrolled. Four had stage III, 19 (83%) had stage IV disease. 18 were former smokers, 5 smoked currently. Primary tumor locations: Oral cavity (6, 26%), oropharynx (11, 48%), larynx (3, 13%), other 3 (13%). HPV was pos in 14 cases. Among 7 pts enrolled on dose level 1 (DL1) (B 40mg daily, CDDP 30mg/m^2/IMRT), 1 pt experienced gr 4 rash. Among 6 patients on DL2 (B 40mg daily, CDDP 35 mg/m^2/IMRT), DLTs were observed in 4 cases (gr 3 neutropenia, LFT abn, mucositis, rash). Ten additional pts were enrolled at the RP2D (DL1). Additional gr 3 AEs included anorexia, anemia, dysphagia and confusion. One pt experienced grade 4 hyperamylasemia. With a median follow-up of 12 months (range 3-24), 2 pts (2/9%) had recurrence, one of whom died .Five pts had a response to buparlisib alone during the run-in phase assessed clinically or radiographically. To date, targeted NexGen sequencing was available in 8 pts. 4/5 cases with response to B alone had sequencing results and demonstrated mutations in FANCD2/EP300; FANCA/FGFR3; FANCI/FLT1 and PIC3CA/EP300. The patient who died had PIC3CA/STL11 mutations. **Conclusions:** B was tolerable in combination with CRT and appears to have promising activity. Genetic analysis is ongoing and may be helpful to identify patients suitable for this approach. Clinical trial information: NCT02113878.

6072 Poster Session (Board #60), Sat, 1:15 PM-4:45 PM

The prognostic impact of level I lymph node involvement in oropharyngeal squamous cell carcinoma. *First Author: Roy Xiao, Cleveland Clinic Lerner College of Medicine, Cleveland Heights, OH*

Background: Current staging for oropharyngeal squamous cell carcinoma (OPSCC) may not capture the implications of regional lymph node involvement (LNI). We investigated the impact of level I LNI on survival for patients with OPSCC. **Methods:** We used the National Cancer Database for a cohort study of patients with OPSCC who underwent surgical resection from 2010-2014. The primary outcome was level I LNI, modeled by multivariable logistic regression. Overall survival (OS) was modeled by Cox proportional hazards regression. **Results:** Among 7,231 patients with OPSCC, 1,061 (14.7%) had level I LNI. Most patients had pT1 (3,412, 47.2%) or pT2 (2,860, 39.6%) tumors with pN2 (5,482, 75.8%) lymph node stage by AJCC 7th Edition. Independent predictors of level I LNI included higher pT stage (pT3 v. pT1, OR 1.82, 95% CI 1.44-2.31; pT4 v. pT1, OR 2.92, 95% CI 2.28-3.75) and higher number of positive regional lymph nodes (OR 1.06, 95% CI 1.05-1.08). Among included patients, 5,543 had known survival status. Level I LNI was a significant predictor of inferior OS (HR 1.83, 95% CI 1.56-2.15) after adjusting for covariates. Subset analysis by pT and pN stage revealed level I LNI to be a consistent predictor of OS for pN2 patients regardless of pT stage (Table 1). For patients with confirmed HPV status, level I LNI significantly predicted OS among HPV(-) patients (N = 888, HR 1.99, 95% CI 1.43-2.74) but not among HPV(+) patients (N = 2,339, HR 1.38, 95% CI 0.89-2.05). Level I LNI remained a significant predictor of OS within additional analyses subset by age, Charlson/Deyo Comorbidity Score, number of positive regional lymph nodes, and adjuvant treatments. **Conclusions:** Level I lymph node involvement in OPSCC is a significant and independent predictor of mortality. Patients with HPV(-) OPSCC and level I LNI may warrant intensified therapies.

Adjusted hazard ratio of mortality for level I nodal involvement subset by pT/pN. Stage:

	pN1			pN2		
	N	HR (95% CI)	*p*-value	N	HR (95% CI)	*p*-value
pT1	685	0.94 (0.46-1.95)	0.877	1,906	1.80 (1.22-2.66)	0.003*
pT2	512	1.76 (0.97-3.19)	0.064	1,678	1.91 (1.42-2.57)	<0.001*
pT3	109	3.64 (1.31-9.84)	0.014*	338	1.92 (1.19-3.03)	0.008*
pT4	76	1.72 (0.58-4.74)	0.315	239	2.03 (1.34-3.03)	<0.001*

*Statistically significant, $p<0.05$

6073 Poster Session (Board #61), Sat, 1:15 PM-4:45 PM

Cisplatin (CIS) versus cetuximab (CET) with definitive concurrent radiotherapy (RT) for head and neck squamous cell carcinoma (HNSCC): An analysis of veteran's health data. *First Author: Joshua Bauml, University of Pennsylvania, Philadelphia, PA*

Background: The addition of CIS or CET to RT improves outcomes compared to RT alone in the non-operative management of HNSCC, but limited data exist on the comparative effectiveness and safety of these approaches. We compared outcomes of pts treated with RT plus CIS or CET using population-based Veterans Health Administration (VHA) data. **Methods:** We identified stage III-IVb HNSCC patients (pts) treated non-surgically with RT and CIS or CET from 2002 to 2014 in the VHA. Pts were analyzed by the drug used in their first cycle (CIS or CET; intent-to-treat). Variables including primary cancer site, age, stage, smoking/alcohol use, and Charlson Comorbidity Index were used to generate propensity scores (PS) for the use of CET. We compared overall survival (OS) by treatment group using Cox regression models, matching for PS. We determined the risk of toxicities using PS-matched logistic regression. **Results:** A total of 3,986 pts were included in the analysis with a median follow-up of 3 years (yrs): 81% received CIS (19.8% low dose - 30-50 mg/m^2). CIS pts were younger ($p < 0.001$) and had fewer comorbidities ($p < 0.001$). In an unadjusted analysis, CET was associated with inferior OS ($p < 0.001$). This remained significant after matching for PS (HR 1.66, 95% CI 1.48-1.86, $p < 0.001$), corresponding to a median OS of 1.8 vs 4.2 yrs. CET was associated with inferior survival across all primary subsites. CET was associated with inferior survival vs low dose CIS, after PS matching (See Table). Matching for PS, CET was associated with a lower rate of neutropenia, renal failure and hearing loss than CIS (all $p < 0.001$). **Conclusions:** CET yields inferior OS compared to CIS with RT for non-operative management of Stage III-IVb HNSCC. Based on this registry study, CIS should remain the preferred partner for RT in this setting.

	Median OS (yrs)				
	CET	CIS	HR	95% CI	p value
Unadjusted [n = 3,986]	1.5	3.8	1.78	1.63-1.95	< 0.001
PS matched [n = 2,114]	1.8	4.2	1.66	1.48-1.86	< 0.001
Oral Cavity (n = 135)	0.8	1.0	1.62	1.07-2.44	0.02
Oropharynx (n = 1,485)	1.0	4.6	1.63	1.42-1.88	< 0.001
Larynx/Hypopharynx (n = 477)	1.4	3.2	1.87	1.49-2.34	< 0.001
Low dose CIS, PS matched [n = 902]	1.6	3.9	1.53	1.30-1.80	< 0.001

6074 Poster Session (Board #62), Sat, 1:15 PM-4:45 PM

A phase I dose-finding study of metformin in combination with concurrent cisplatin and radiation in patients with locally advanced head and neck squamous cell carcinoma. *First Author: Shuchi Gulati, University of Cincinnati Medical Center, Cincinnati, OH*

Background: Up to 60% of HNSCC present as locally advanced disease (LAHNSCC). Although prognosis has improved significantly, 3 year PFS and OS remain at 62%, and 73% respectively (RTOG 0522) despite definitive cisplatin (Cis) based chemo-radiation (CRT), underscoring the need for improved regimens. Metformin (MET) is hypothesized to suppress tumor cell growth by mTOR pathway inhibition, which mediates the phosphoinositide 3-kinase/Akt signaling pathway (frequently deregulated in HNSCC). Retrospective studies suggest that MET improves survival in HNSCC patients (pts). Therefore, we conducted a phase I open-label single site dose escalation study combining MET with CRT in LAHNSCC (NCT02325401). **Methods:** Previously untreated LAHNSCC (Stage III/IV) pts were enrolled to receive escalating doses of MET with a 7-14 day lead-in prior to CRT based on modified toxicity probability interval design. Starting dose of MET was 2000mg daily in addition to Cis (100mg/m2 days 1, 22 and 43) and standard radiation (70Gy) (Table 1). Adverse events were categorized per CTCAE v4.03. **Results:** 20 pts were enrolled, (2 replaced due to withdrawal of consent during lead-in period). Most common grade ≥ 2 toxicities were nausea (25%), vomiting (25%), diarrhea (20%), and AKI (15%). Dose limiting toxicity (DLT) included Grade 3 diarrhea (cohort 3) and AKI (cohort 2). MTD was established at 2550mg daily in combination with CRT. Median age was 55 (46-65); majority pts were male (95%), Caucasian (95%), tobacco users (70%), and HPV positive (70%). After a median follow up of 18 months (range 1-26), 1-year PFS, and OS remain at 94%. 1 death was reported (sudden cardiac, unrelated, occurred > 8 weeks after stopping MET). Pharmacokinetic data showed that Cis did not affect MET steady state. **Conclusions:** For the first time, MET is shown to be safe and tolerable in combination with CRT with an impressive impact on survival in LAHNSCC pts. This warrants further investigation in a phase II trial, with the established MTD of 2550 mg as the recommended dose. Clinical trial information: NCT02325401.

Dose-escalation schedule.

Dose Level	Dose Met Daily (divided doses)
Level -1	1500mg
Level 1	2000mg
Level 2	2550mg
Level 3	3000mg
Expansion	MTD

6075 **Poster Session (Board #63), Sat, 1:15 PM-4:45 PM**

Suboptimal regimens in sequential treatment (ST) with ICT (induction chemotherapy) followed by CCRT (concomitant chemotherapy) in "real life" patients with locally advanced pharyngo-laryngeal squamous-cell carcinoma (LAPLSCC) and prognosis. *First Author: Carmen Orte, Hospital de Barbastro, Huesca, Spain*

Background: ST is a treatment modality widely used in LAFLSCC. Although ICT with TPF (docetaxel-Cisplatin-5FU) and CCRT with 3- weekly Cisplatin have been proved as the most active regimens, unfit patients (p) often cannot receive them. There are few data about efficacy of modified ST regimens in unselected population. **Methods:** From 1998 to 2013, data from LAFLSCC patients treated in our institution with ST were retrospectively reviewed. Patient and treatment-related prognostic factors (PFs) were collected. Both uni and multivariate proportional hazards were used to determine associations with overall survival (OS) and DFS (disease-free survival). Local Ethical Committee approval was obtained. **Results:** 337 consecutive patients were treated with ST with ICT and CCRT. Median age: 57 years. Male:92%. Stage: 135 p III (40.1%), 202p IV (59.9%). Median follow-up: 38.9 m (0- 222 m). Median OS: 48,3m (95%CI 36-60). Median DFS: 105,3 m (95%CI 90-120). Analyzed tumor-related PFs: location, stage, differentiation. Patient-related PFs: age, blood cells ratios (NLR, dNLR, LMR), ACE-27 comorbidity index, Hemoglobin, albumin. Treatment-related PFs: ICT type , CCTR type, ICT response. In Multivariate analysis (MA) several PFs independently correlated with OS and DFS (Table 1). Use of TPF as ICT was independently linked to better OS and DFS. Use of 3-weekly Cisplatin as CCRT was associated with better OS. **Conclusions:** In unselected LALFSCC patients treated with ST, selection of proved efficacious therapies affects outcome, independently of other tumor and patient-related PFs. Suboptimal regimens work worse. In unfit patients other alternatives should be considered.

Outcome measure	Independent Prognostic factors (MA)	p-value	HR(95%CI)
OS	Stage (IV vs III)	0.007	1,70(1,15-2,49)
	Post-ICT Hemoglobin (< 10vs > 10 gr/dL)	0.001	2,83(1,55-5,14)
	ICT response (Non CR vs CR)	0.009	1,71(1,14-2,56)
	ICT(Non TPF vs other)	0.027	1,58 (1,05-2,38)
	CCRT (Non CDDP vs CDDP)	0.006	1,63 (1,15-2,32)
	LMR (< 3.1 vs > 3.1)	0.013	1,71(1,11-2,61)
DFS	ICT (non TPF vs TPF)	0.035	1,80(1,04-3,13)

6076 **Poster Session (Board #64), Sat, 1:15 PM-4:45 PM**

Avelumab-cetuximab-radiotherapy (RT) versus standards of care (SoC) in locally advanced squamous cell carcinoma of the head and neck (SCCHN): Safety phase of the randomized trial GORTEC 2017-01 (REACH). *First Author: Yungan Tao, Institut Gustave Roussy, Villejuif, France*

Background: Based on the hypothesis of a synergistic effect of the anti-PDL1 avelumab when combined with cetuximab (cetux) and RT, this new combination is tested in a large scale randomized trial against two well established SoC in LA SCCHN. **Methods:** This randomized multicenter phase III trial comprises cohorts of pts deemed fit (Cohort 1) to receive high dose cisplatin (CDDP 100 mg/m^2, Q3W) or unfit (Cohort 2) to receive CDDP. The SoC is IMRT (69.96 Gy, 33 fractions) combined with CDDP in cohort 1 and with cetux in Cohort 2 (400 mg/m^2 Day-7 and 250 mg/m^2 weekly). In both cohorts, experimental (exp) arms are IMRT concomitant with cetux (same as in SoC) and avelumab (10 mg/kg Day-7 and every 2 weeks) followed by avelumab 10 mg/kg bi-monthly for 12 months. The primary objective is to test whether exp arm is superior to SoC for progression-free survival in each cohort, with 400 and 268 pts to be randomized to Cohort 1 and 2 respectively. Monitoring of grade $\geq$ 4 acute adverse events in both exp arms was planned with null and alternative hypotheses of 15% and 35%. Overall 1-sided alpha error of 0.10, Lan-DeMets alpha spending function, 95% power. This safety phase was approved by the study Data and Safety Monitoring Committee" (IDSMC) and planned to be run on the first 82 pts in 3 steps, after 8 weeks follow-up of 14, 27 and 41 pts randomized in exp arms. Here we report the 1st step (stopping rule > = 7/14 gd > = 4 AE). **Results:** Between 09 and 12 2017, 29 pts Stage III/IV SCCHN were randomized including 14 in the exp arms. The 1st step safety analysis was presented to the IDSMC early in 2018. All pts received the entire RT as planned. Six out of the 14 pts in exp arms did not receive the entire systemic regimen: 3 did not receive the last dose of cetux, 2 received 5 doses of cetux and 3 of avelumab, one received 3 cetux and 2 avelumab. Three pts (21.4%) developed a grade 4 AE (1 dermitis, 1 lymphopenia, 1 mucositis, CTCAE v4). **Conclusions:** The safety stopping rule was not crossed and an approval to continue the trial was given by the IDSMC. Updated and completed results of the run in safety phase will be presented at the meeting. Clinical trial information: NCT02999087.

6077 **Poster Session (Board #65), Sat, 1:15 PM-4:45 PM**

Long-term outcomes for re-irradiation of recurrent head-and-neck cancers: Report of acute and long-term toxicity. *First Author: Nima Aghdam, Georgetown University Medical Center, Washington, DC*

Background: Long-term toxicity is a concern in patients undergoing head and neck re-irradiation. Durable local control is achieved in majority of patients in combination with chemotherapy and surgery. Here, we report the incidence and predictors of severe toxicity. **Methods:** From 2002 to 2016, 133 lesions in 123 patients received SBRT to the oropharynx (n = 21), hypopharynx (n = 8), nasopharynx (n = 9), paranasal sinus (n = 7), neck (n = 39), and other sites (n = 49). 92 lesions in 88 patients were treated definitively, and 41 lesions were treated with palliative intent. 36% underwent complete macroscopic resection before SBRT. Seventy-eight patients received chemosensitization. The median initial radiation dose was 70 Gy, and the median re-irradiation SBRT dose was 30 Gy (21-42.5 Gy) in 2-5 fractions. Median planning volume was 75 cm^3 (6-645 cm^3). Locoregional control (LRC) and overall survival (OS) were calculated using the Kaplan Meier method. χ^2 test was utilized for differences in rates of acute and late toxicity. Severe toxicity was defined based on the RTOG Common Toxicity Criteria ($\geq$grade 3). Logistic regression model was constructed to identify independent predictors of toxicity. **Results:** Median follow-up for surviving patients was 24.2 months. For definitively treated patients, 2-year OS and LRC rates were 42% and 36%, respectively. Durable local control was achieved in 56% of all patients. Of the patients treated definitively, 7.7% (n = 7) and 11% (n = 11) experienced severe acute and late toxicity, respectively. Patients who were treated in the neck and oropharynx experienced higher rates of severe late toxicity compared to other sites (19% vs 2%, p = 0.026). Additionally, there was a trend for higher acute severe toxicity in patients who received chemotherapy (11.4% vs. 0 %, p = 0.053). No patient experienced severe acute or late toxicity when re-treated with $\leq$ 30 Gy. Logistic regression model identified higher initial and re-irradiation dose as predictors of late severe toxicity. **Conclusions:** SBRT is an effective treatment for patients with locally recurrent or second malignancy in previously irradiated sites with acceptable toxicity.

6078 **Poster Session (Board #66), Sat, 1:15 PM-4:45 PM**

Regional lymph node metastases oncogenic mutations compared to primary tumors in HPV+ oropharynx patients. *First Author: John F. Deeken, Inova Schar Cancer Institute, Falls Church, VA*

Background: Residual disease after concurrent chemoradiation in locally advanced Head and Neck cancer is typically contained in involved lymph nodes (LNs), with primary tumors (PTs) showing complete response to treatment. This resistant phenotype in LNs is not well characterized. Clonal genomic evolution in node metastases may explain this phenotype. **Methods:** PTs and matched LNs from consecutive patients who underwent trans-oral robotic surgery with modified neck dissections as primary therapy were tested using NextGen sequencing using the Oncomine Comprehensive Assay run on the Ion Torrent S5 system. This platform detects genetic mutations in 143 known cancer related genes. Tumors from patients treated with primary surgery were used given the need for sufficient tumor content to run the assay. Results were interpreted using the Ion Reporter Software. **Results:** A total of 21 patients had sufficient tumor content in FFPE samples that passed QC testing. Eight (38%) matched sets of PTs and LNs displayed the same mutation profile. LNs from four patients (19%) showed loss of mutations detected in primary tumors. Nine patients (43%) showed gain of mutations in neck LNs compared to PTs. Genes showing gain of mutation in LNs included: TP53 (4), PIK3CA (3), FBXW7 (3), VHL (1), PTEN (1), JAK3 (1), and MAPK1 (1). **Conclusions:** Gain of mutations in regional LNs was detected in almost half of all HPV-positive oropharynx patients. Gain of mutations in genes such as TP53 and PIK3CA may define a resistant genotype when such patients are treated with primary chemoradiation.

6079 Poster Session (Board #67), Sat, 1:15 PM-4:45 PM

Post-treatment evaluation of head and neck cancer patients in the era of advanced imaging and value-based care. *First Author: Thomas Hirsch, Medical College of Wisconsin, Milwaukee, WI*

Background: Current guidelines recommend imaging (CT and/or PET) to evaluate treatment response and detect residual disease after nonsurgical management of head and neck cancers squamous cell cancers (HNSCC). To objectively evaluate the utility of these diagnostic tests, we reviewed our institutional cohort to better understand the value of these interventions compared to routine history and physical examination (PE). **Methods:** After IRB approval, we retrospectively reviewed an institutional cohort of 160 HNC patients who underwent definitive radiation +/- chemotherapy from 2003 - 2014. All patients had post-treatment history, PE, and imaging data, including a 4-month PET scan. The sensitivity, specificity, negative-predictive and positive-predictive values were calculated, along with Kaplan-Meier survival analyses for each symptom, PE, and imaging finding. **Results:** PE and symptoms had higher specificity than imaging but had lower sensitivity (see table). While imaging had good sensitivity and NPV, excess false positives led to poor specificity and PPV. When PE and symptoms were evaluated together, performance was similar to CT and PET. On KM analysis, all PE/symptom factors and PET response correlated with outcome, while baseline CT did not. There were no early interventions resulting from baseline CT scans. **Conclusions:** In an era of value-based care, a renewed emphasis on patient symptoms and PE findings may allow for improved resource utilization and cost of care. These are strong predictors of residual disease in the immediate post-treatment setting, suggesting a need to reevaluate current imaging paradigms, particularly the utility of post-treatment CT scans.

	Palpable nodes	Persistent Primary	Pain	Odynophagia	Dysphagia	Post-Treatment CT	4-month PET	Combination symptoms and PE
Locoregional Control								
Sensitivity	0.17	0.27	0.53	0.17	0.42	0.61	0.81	0.67
Specificity	0.98	0.92	0.74	0.92	0.70	0.58	0.61	0.54
NPV	0.80	0.86	0.84	0.79	0.80	0.87	0.92	0.85
PPV	0.67	0.41	0.37	0.38	0.29	0.25	0.38	0.30
Death from Disease								
Sensitivity	0.18	0.20	0.53	0.20	0.53	0.52	0.80	0.80
Specificity	0.99	0.93	0.76	0.94	0.76	0.57	0.64	0.60
NPV	0.75	0.74	0.80	0.74	0.80	0.75	0.89	0.88
PPV	0.89	0.53	0.47	0.56	0.47	0.32	0.47	0.43

6080 Poster Session (Board #68), Sat, 1:15 PM-4:45 PM

Prevention of surgical site infection after oral cancer surgery by topical tetracycline: Results of a multicenter randomized control trial. *First Author: Madoka Funahara, Kyushu Dental University School of Oral Health Sciences, Faculty of Dentistry, Kitakyushu, Japan*

Background: In a pilot study, we showed that topical administration of a tetracycline could decrease oral bacteria levels for 6 hours in patients who underwent oral cancer surgery combined with tracheotomy and flap reconstruction. This multicenter, randomized control trial aimed to investigate the effectiveness of topical application of tetracycline ointment for prevention of surgical site infection (SSI) associated with major oral cancer surgery. **Methods:** One hundred and seventeen patients who underwent oral cancer resection combined with neck dissection, flap reconstruction, and tracheotomy were divided randomly into an intervention group (n = 56) and a control group (n = 61). The intervention consisted of topical administration of tetracycline ointment on the dorsum of the tongue every 6 hours for 48 hours postoperatively. Factors relating to the occurrence of SSI in both groups were subjected to logistic regression analysis. **Results:** SSI occurred in 11 patients (19.6%) in the intervention group and 22 patients (36.1%) in the control group. Multivariate analysis showed that a longer operating time and not receiving topical tetracycline were independent risk factors for development of SSI. **Conclusions:** Administration of topical tetracycline for 48 hours postoperatively is an effective way of preventing SSI after oral cancer surgery. Clinical trial information: 000018318.

6081 Poster Session (Board #69), Sat, 1:15 PM-4:45 PM

Second interim analysis of RIFTOS MKI, a global non-interventional study assessing the use of multikinase inhibitors (MKIs) in the treatment of patients with asymptomatic radioactive iodine-refractory differentiated thyroid cancer (RAI-R DTC). *First Author: Marcia S. Brose, Department of Otorhinolaryngology, Head and Neck Surgery and the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Sorafenib and lenvatinib are oral MKIs approved for the treatment of RAI-R DTC; however, there is no consensus on when patients with asymptomatic RAI-R DTC should start treatment with a MKI. **Methods:** RIFTOS MKI is an ongoing, global, non-interventional study, enrolling patients with asymptomatic RAI-R DTC, designed to compare the time to symptomatic progression from study entry in the real-life setting between two cohorts. The classification into one of the two cohorts is based on the treating physician's decision to initiate a MKI at study entry (yes or no). Here, we report the results from a planned second interim analysis; no comparisons between cohorts were made. **Results:** Of 551 patients enrolled, and valid for analysis, 44% were male and the median age was 68 years; the median duration of observation was 9.0 months. Most patients had an ECOG performance status of 0 or 1 (95%) and distant metastases (87%) at study entry, and the most frequent histology was papillary (74%). The median time from initial diagnosis of DTC to study entry was 7 years, and RAI refractoriness was mainly due to a lack of RAI uptake (65%). The average dose per RAI treatment and median cumulative activity of RAI were 4.63 GBq and 8.51 GBq, respectively. A total of 28% of patients were treated with sorafenib at any time during the study. The median duration of sorafenib exposure was 6.7 months, and most patients (66%) received an initial dose of 800 mg/day. Of 113 patients included in the sorafenib safety analysis, 106 (94%) had $\geq$1 adverse event (AE), and 28 (25%) had $\geq$1 serious AE; hand–foot skin reaction (HFSR) was reported in 54 patients (48%), and grade $\geq$3 HSFR in 11 patients (10%). **Conclusions:** The RIFTOS MKI study is the largest non-interventional study in RAI-R DTC. Safety data from patients treated with sorafenib is consistent with the known safety profile of sorafenib. Of note, HFSR appears to be reported less frequently in real-life practice compared with phase 3 clinical studies. Clinical trial information: NCT02303444.

6082 Poster Session (Board #70), Sat, 1:15 PM-4:45 PM

An open-label, randomized phase III trial of gemcitabine and carboplatin (GC) followed by Epstein-Barr virus-specific autologous cytotoxic t lymphocytes (EBV-CTLs) versus GC as front-line therapy for patients (pts) with advanced nasopharyngeal carcinoma (NPC). *First Author: Han Chong Toh, Tessa Therapeutics Pte Ltd, Singapore, Singapore*

Background: Median overall survival (OS) and prognosis in patients with advanced EBV-positive NPC remain poor and treatment options are limited. In a small phase II trial (38 Asian pts), EBV-CTLs following chemotherapy (GC) as a first line setting for pts with metastatic and/or recurrent NPC has shown promising efficacy and acceptable toxicity: median OS and overall progression free survival (PFS) was 29.9 and 7.6 months respectively, with 2-year OS rate of 62.9% (Chia et al., Mol Ther., 2014). A Phase III trial has been initiated to evaluate the antitumor efficacy of GC-CTL versus GC in these pts (NCT02578641). **Methods:** This multicenter, randomized, open-label, two arm study is ongoing across 30 sites in Malaysia, Singapore, Taiwan, Thailand and USA. Eligible pts have a histologically confirmed metastatic or locally recurrent EBV-positive, non-keratinizing and/or undifferentiated NPC (not amenable to curative treatment with surgery and/or chemoradiation therapy), with measurable disease (RECIST v1.1) at screening, ECOG PS$\leq$2 and NCI CTCAE $<$ 2. Pts with CNS metastasis, autoimmune disease or prior immunotherapy are excluded. Prior chemotherapy or radiation with curative intent is allowed. 330 pts will be randomized 1:1 to receive either four cycles of GC followed by six cycles of EBV-CTLs (Arm A) or six cycles of GC alone (Arm B). Stratification factors include country and disease stage (metastatic versus locally recurrent). Analysis of the primary endpoint is based on the hazard ratio calculated using the Cox Proportional Hazard model. Secondary endpoints include PFS, overall response rate, clinical benefit rate and quality of life. Safety assessments will consist of monitoring and recording all adverse events (graded by NCI CTCAE v 4.0). **Results:** As of 31 Jan 2018, 226 of the planned 330 pts are enrolled. **Conclusions:** An Independent Data Monitoring Committee has reviewed the trial on 29 Aug 2017 and concluded that trial accrual continue as planned. Clinical trial information: NCT02578641.

6083 Poster Session (Board #71), Sat, 1:15 PM-4:45 PM

Integrative whole-genome analysis of salivary duct carcinoma. *First Author: Sehhoon Park, Seoul National University Hospital, Seoul, Korea South*

Background: Salivary duct carcinoma (SDC) is one of the most aggressive histological subtypes of salivary gland cancers. Conventional chemotherapy and radiation have shown only limited efficacy in metastatic SDC. Currently, clinically approved targeted-therapeutics are not available for treatment of this disease, mainly due to its rarity and limited understanding of the molecular mechanisms underlying its pathogenesis. Thus, we conducted multi-level genomic profiling of the SDC to delineate the genomic alterations prevalent in this disease. **Methods:** Whole-genome sequencing, whole exome-sequencing and transcriptome sequencing were performed on 10 discovery cohort of SDC samples. Genomic profiling was performed in additional 32 SDC samples to corroborate the findings obtained from the initial discovery cohort. **Results:** The cancer cohort is characterized by an average mutation burden of 85 somatic non-silent exonic mutations per tumor. The cohort displayed a mutational signature of BRCAness and APOBEC/AID. Several genes, including *TP53, RB1, SMAD4, HRAS, APC, PIK3CA* and *GNAQ* were recurrently mutated in SDC. A novel fusion gene, generated by genomic rearrangement, *MYB-NHSL1*, was identified. **Conclusions:** These findings represent an important layer in the systematic understanding of clinically meaningful genomic targets for precision medicine in SDC, a disease with a significant unmet clinical need.

6084 Poster Session (Board #72), Sat, 1:15 PM-4:45 PM

Novel approach for unresectable salivary duct carcinoma: Targeting HER2 and androgen receptor. *First Author: Daisuke Kawakita, Department of Otolaryngology Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan*

Background: Salivary duct carcinoma (SDC) is highly aggressive and rare cancer, often expressing androgen receptor (AR) and/or HER2. While chemotherapy has been failed to show significant efficacy on SDC, we have demonstrated efficacy and safety of AR- or HER2-targeted therapy in patients with unresectable locally advanced or recurrent/metastatic (LA/RM) SDC in a single-arm phase II trial. However, data regarding whether these targeted therapies prolong survival compared with conventional therapy is lacking. **Methods:** We conducted a multi-institutional retrospective cohort study of SDC patients in Japan. The survival impact of molecular-targeted therapy was compared with conventional therapy, including chemotherapy and/or cetuximab by multivariate proportional hazard models. **Results:** A total of 152 LA/RM patients were enrolled, of whom 65 received conventional therapy, 55 received HER2-targeted therapy, and 32 received AR-targeted therapy. Median follow-up time was 1.8 years (range: 0.1-9.5 years). The 2-year overall survival (OS) were 38.7% for conventional therapy, 69.3% for HER2-targeted therapy, and 57.9% for AR-targeted therapy. After adjustment by potential confounders, HER2-targeted therapy significantly improved OS compared with conventional therapy among HER2-positive patients (hazard ratio [HR]: 0.34; 95% confidence interval [CI], 0.16-0.71). AR-targeted therapy did not significantly improve OS compared with conventional therapy among AR-positive patients (HR: 0.63; 95% CI, 0.32-1.26). No other biomarker predicting efficacy of targeted therapies was found. **Conclusions:** Although this study was retrospective, this was the first study to demonstrate that novel therapy targeting HER2 prolonged OS compared with conventional therapy in patients with LA/RM SDC.

6085 Poster Session (Board #73), Sat, 1:15 PM-4:45 PM

A novel prognostic risk classification model for NUT midline carcinoma: a largest cohort analysis from the NMC registry. *First Author: Nicole Grace Chau, Dana-Farber Cancer Institute, Boston, MA*

Background: NUT midline carcinoma (NMC) is a rare subtype of squamous cancer defined by rearrangement of the *NUT* gene. Due to its rarity and under-diagnosis, there are no existing models to classify patients (pts) into risk groups based on baseline clinicopathologic factors. We aim to develop a prognostic risk classification model for NMC survival outcomes based on the largest cohort of NMC pts analyzed to date. **Methods:** Clinicopathologic variables and survival outcomes were extracted for N = 143 pts registered between 1990-2017 from the International NMC Registry. We performed survival tree regression to determine pt subgroups with statistically distinct risk factors and overall survival (OS) outcomes. Briefly, we performed Cox proportional-hazards regression for each potential factor. We dichotomized pts into two subgroups using the significant factor with the highest hazard ratio. We repeated this process within each subgroup until no further significant factors were found. **Results:** For N = 143 pts, median diagnosis age was 24 y (range = 18d-80y) and 48% were male. About half (54%) of tumors were without squamous cell differentiation; 54% had thoracic origin, 40% head/neck, and 6% other primary site. Most patients had the *BRD4-NUT* fusion (71%), followed by *BRD3-NUT* (13%), and *NSD3-NUT* (5%). At diagnosis, 78% had lymph node or organ metastases (mets). Median follow-up time was 2.9y (1d-19.1y). For N = 134 with survival data, median OS was 6.8m (95% CI = 5.8-9.7); 2-year OS was only 23% ($\pm$SE = $\pm$4%). Survival tree regression identified 3 distinct risk groups: (A) no mets [2-yr OS = 39.5$\pm$ 10%; N = 24]; (B) with mets, non-thoracic origin [2-yr OS = 38.7$\pm$10%; N = 27]; (C) with mets, thoracic origin [2-yr OS = 6$\pm$4%, N = 55]. **Conclusions:** This is the first risk classification model for NMC. Metastatic pts with thoracic primary tumors have markedly poorer prognosis compared to other subgroups.

6086 Poster Session (Board #74), Sat, 1:15 PM-4:45 PM

Phase II study on lenvatinib (LEN) in recurrent and/or metastatic (R/M) adenoid cystic carcinomas (ACC) of the salivary glands (SG) of the upper aereodigestive tract (NCT02860936). *First Author: Laura Locati, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Systemic chemotherapy and targeted therapies (TT) are almost ineffective in R/M ACC patients (pts). Sorafenib and axitinib showed some activity, possibly through their antiangiogenic effect. LEN is a stronger second-generation antiangiogenic inhibitor. Here we report the activity of LEN in R/M ACC pts. **Methods:** Pts with R/M disease, 1 previous line of chemotherapy and/or TT, received oral LEN 24 mg/day. Progression within 6 months at study entry was required. Primary endpoint was objective response rate (ORR) according to RECIST 1.1; secondary endpoints were progression free survival (PFS), overall survival (OS), toxicities (CTC 4.0) and assessment of quality of life (QoL) with EORTC QLQ C-30, EORTC QLQ-H&N35, EQ-5D. A 2-stage Simon design was applied, to test the null hypothesis of response $\leq$ 5% versus the alternative response $\geq$ 20%; 3 responses were required to reject the null hypothesis. **Results:** Twenty-eight pts were enrolled, F 16/M 12, median age 55 years (range: 22-73), 14 ACC of major and 14 of minor SGs, 96% metastatic. PS was 0 in 14 cases, 1 in 12 and 2 in 2 pts. Treatment related adverse events (AEs) were frequent (all grades 96%): asthenia 79%, hypertension 75%, stomatitis and weight loss 71%, TSH elevation 68%, were the most common. Grade $\geq$ 3 occurred in 50% of pts (asthenia 25%, hypertension 18%). No G5 toxicities occurred neither bleeding. Nine SAEs were reported, 6 of them drug-related. Dose was reduced in 21 pts within 12 weeks from therapy start, only 4 pts maintained the full dose throughout treatment. Among 26 evaluable pts, partial responses were 3 (11.5%) (3/26). Target lesions reduction between 23% and 28% was observed in 4 out 20 pts with stable disease. At a median follow up of 21.9 months (95% CI, 13.8-27.8), 6 pts are still on LEN and 12 died due to progression. Median PFS and DoR were 9 (95%CI 5.5-14.2) and 3.1 (1.8-21.7+) months, respectively. Median OS was 26.1 months (95% CI, 11.1-NR). QoL analysis is ongoing. **Conclusions:** Tumor size reduction was seen in 27% of pts suggesting activity of LEN in ACC. Toxicity was common but manageable. QoL has been studied for the first time. A randomized study is needed to confirm efficacy. Clinical trial information: NCT02860936.

6087 **Poster Session (Board #75), Sat, 1:15 PM-4:45 PM**

Combination of dabrafenib (DAB) and lapatinib (LAP) for the treatment of *BRAF*-mutant thyroid cancer. *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: mutations (BRAFm) are the most common mutations in thyroid cancer. BRAF inhibitors (DAB) are active in BRAFm melanoma, but there is less activity noted in BRAFm thyroid cancer. Preclinically, BRAF inhibitors inhibit BRAFm thyroid cancers only transiently due to activation of HER2/HER3, driven by a neuregulin-dependent autocrine loop. The addition of LAP, a HER2/HER3 kinase inhibitor, sensitizes the cell to growth suppression by BRAF inhibitors (Cancer Discov 5(3):520, 2013). This study evaluates the safety and efficacy of the combination of DAB and LAP. **Methods:** Eligibility included thyroid cancers with the presence of a BRAFV600E mutation. Any prior treatment was allowed. All patients received DAB 150 mg bid starting 2 weeks prior to LAP. Doses of daily lapatinib were escalated in a standard 3+3 design at (1) 750 mg; (2) 1250 mg; (3) 1500 mg. Patients removed before the start of LAP were not included in the analysis. An additional 6 patients were added at the MTD. Responses were defined using RECIST 1.1. **Results:** 21 evaluable patients were enrolled on the phase I portion of the study. Gender – 14/21 (67%) male; median age – 63 years; histology – differentiated thyroid cancer (DTC) 19 (90%), anaplastic thyroid cancer (ATC) 2 (10%); brain metastases – 5 (24%); prior BRAF inhibitor – 5 (24%); prior BRAF or tyrosine kinase inhibitor – 13 (62%). There was one DLT - Grade 5 event unlikely related to drugs in a patient with ATC. Grade 4 toxicities – 0. Grade 3 toxicities – lymphocytes (1); uveitis (1). Median progression-free survival (PFS) and overall response rate (RR) of the subsets in the DTC only group are listed in the table. Clinical trial information: NCT01947023. **Conclusions:** The combination of DAB 150 mg bid and LAP 1500 mg daily was safe and well-tolerated. Despite the number of subjects with prior treatment (including with BRAF inhibitors) and brain metastases, excellent activity was found with this combination in DTC. Further investigation with this regimen is warranted.

	#	RR	PFS (months)
DTC	19	58%	18
Dose Level 1 (LAP 750 mg)	5	60%	11
Dose Level 2 (LAP 1250 mg)	2	50%	16
Dose Level 3 (LAP 1500 mg)	12	58%	18
No prior BRAF inhibitor	14	64%	20
No brain metastases	14	57%	20
No prior BRAF inhibitor or brain metastases	11	64%	29

6088 **Poster Session (Board #76), Sat, 1:15 PM-4:45 PM**

A phase II trial of cabozantinib (CABO) for the treatment of radioiodine (RAI)-refractory differentiated thyroid carcinoma (DTC) in the first-line setting. *First Author: Marcia S. Brose, Department of Otorhinolaryngology, Head and Neck Surgery and the Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: CABO is a multi-tyrosine kinase inhibitor targeting VEGF receptor kinase, RET, MET and AXL. We previously participated in a Phase I study which suggested activity in the RAI-refractory DTC patients that had had one or more prior therapies. To further study the activity of CABO in differentiated thyroid cancer, we conducted a single-arm open-label phase II study of CABO in patients with metastatic, RAI-refractory DTC in the first-line setting (clinicaltirals.gov: NCT02041260). **Methods:** Thirty-five patients with metastatic, RAI-refractory, unresectable or locally-advanced DTC were administered CABO 60 mg orally QD. Responses were monitored by CT scan every 2 months. The primary outcome was response rate (RR) and secondary outcomes included progression-free survival (PFS), time to progression (TTP), duration of response and clinical benefit rate and safety. **Results:** Our study completed accrual in August 2017. As of Feb 2018, the median time on study is 35 wks (range 3-197). Median age is 65 yrs (range 45 to 84); 17 pts (49%) are male. Of the 35 total patients, 22 (63%) have papillary, 3 (9%) have Hürthle cell and 10 (29%) patients have poorly differentiated histology. Partial response (PR) was achieved in 19 (54%) patients with a median duration of response of 40 wks (range 10 to 198+). Fifteen (43%) had stable disease (SD) with a median duration of 25 wks (range 8 to 143+), and 9 (26%) maintained their SD $>$ 6 mos for a clinical benefit rate (CR+PR+SD $>$ 6mos) of 80% (n = 28). Median PFS has not been reached and updated PFS data will be presented. Among the six patients who progressed, the median TTP was 35 weeks. Sixteen patients remain on study as of February 2018. CABO was well tolerated with dose interruptions and dose adjustments as needed; the most common treatment-related adverse events included hyperglycemia, diarrhea, fatigue/malaise, weight loss. **Conclusions:** This is the first study to document CABO anti-tumor activity in patients with RAI-refractory DTC in the first-line setting. The 54% RR is comparable to currently approved agents and warrants further investigation in this patient population. Clinical trial information: NCT02041260.

6089 **Poster Session (Board #77), Sat, 1:15 PM-4:45 PM**

Comprehensive genomic profiling of anaplastic thyroid carcinoma. *First Author: Daniel W. Bowles, University of Colorado, Aurora, CO*

Background: Anaplastic thyroid carcinoma (ATC) is a rare malignancy with a poor prognosis. We queried whether comprehensive genomic profiling (CGP) could uncover biomarkers that could enable targeted and immunotherapies. **Methods:** CGP was performed on 180 FFPE ATC samples using hybridization-captured, adaptor ligation based libraries to a mean coverage depth of $>$ 500X for up to 315 cancer-related genes. The results were analyzed for all classes of genomic alterations (GA) including short variant (SV) base substitutions and insertions and deletions; select rearrangements; and copy number changes. 408 consecutively sequenced papillary thyroid carcinomas (PTC) were included as a comparison group. Total mutational burden (TMB) was determined on 1.1 megabases of sequenced DNA. MSI status was determined by a proprietary algorithm. **Results:** There were 88 female (49%) and 92 (51%) male ATC patients with a median age of 64 years (range 25-86 yrs). All ATC cases were submitted as *de novo* ATC. ATC had significantly higher mean frequency of genomic alterations (GA) per sample and higher frequency of *TP53* mutations (Table). In contrast, PTC had significantly higher frequencies of *RET* and *BRAF* SV mutations and gene rearrangements in *BRAF*, *RET*, *ALK* and *NTRK*. TMB levels were similarly low in both groups and no cases featured a MSI-High status. Examples of ATC with responses to targeted therapies will be presented. **Conclusions:** ATC differs significantly in genomic alterations from classic PTC. Advanced stage PTC and ATC are frequently driven by *BRAF* GA or oncogenic rearrangements, suggesting ATC might result from dedifferentiation of *BRAF* mutated PTC. TMB appears to be low for both ATC and PTC.

	PTC	ATC	Significance
No. Patients	408	180	
Median age (years)	59	64	
Gender (F/M)	215/193	88/92	
GA/tumor	2.75	4.34	
Significant genes altered	*BRAF* *TERT* *TP53* *RET*	*TP53* *TERT* *BRAF* *NRAS* *PIK3CA* *NF1* *NF2* *PTEN*	
***TP53* GA Frequency**	11%	66%	P $<$ 0.0001
***RET* GA Frequency**	9%	2%	P = 0.002
***hTERT* Frequency**	58%	61%	NS
***BRAF* GA Frequency**	73%	39%	P $<$ 0.0001
***BRAF, RET, ALK*, or *NTRK* rearrangements**	13%	3%	P $<$ 0.0001
Total Mutational Burden ≥10 mut/Mb	2%	3%	NS
Opportunity for Targeted Therapies	High (BRAF, oncogenic fusions)	Moderate (BRAF, *NF1*, *NF2*, oncogenic fusions)	

TPS6090 **Poster Session (Board #78a), Sat, 1:15 PM-4:45 PM**

A phase 3, randomized, open-label study of epacadostat plus pembrolizumab, pembrolizumab monotherapy, and the EXTREME regimen as first-line treatment for recurrent/metastatic head and neck squamous cell carcinoma (R/M SCCHN): ECHO-304/KEYNOTE-669. *First Author: Ezra E.W. Cohen, University of California, San Diego, La Jolla, CA*

Background: Although the EXTREME regimen is a Category 1 evidence-supported combination recommended by NCCN guidelines as first-line (1L) treatment for patients with R/M SCCHN, it is associated with limited survival benefit and burdensome toxicities. There remains a high unmet need for more effective and well tolerated treatment strategies. Both the programmed cell death 1 (PD-1) receptor and indoleamine 2,3-dioxygenase 1 (IDO1) enzyme have been identified as key mechanisms that suppress T-cell–mediated antitumor immunity and induce tumor escape. Pembrolizumab (P) is a potent, highly selective humanized monoclonal antibody that directly blocks the interaction of PD-1 and its ligands. Epacadostat (E) is a potent, highly selective oral inhibitor of IDO1. Preliminary phase 1/2 data from the ECHO-202/KEYNOTE-037 study showed encouraging efficacy results and a tolerable safety profile with E + P in SCCHN. This randomized, open-label, phase 3 global study (NCT03358472) evaluates the efficacy and safety of E + P, P, and EXTREME as 1L treatment in patients with R/M SCCHN. **Methods:** Key eligibility criteria: histologically or cytologically confirmed R/M SCCHN considered incurable by local therapies, ECOG PS $\leq$1, no prior systemic therapy for R/M disease, and no prior IDO1 inhibitors or immune checkpoint therapies. Approximately 625 patients will be randomized 2:1:2 to E 100 mg BID + P 200 mg Q3W, P 200 mg Q3W, or EXTREME (cetuximab 400 mg/m^2 Cycle 1 Day 1, then 250 mg/m^2 QW + cisplatin 100 mg/m^2 or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m^2/day continuously over Days 1–4 Q3W). Stratification includes ECOG PS, p16 status, and prior definitive systemic treatment for locally advanced disease. Patients receive $\leq$35 cycles of E + P or P, or $\leq$6 cycles of EXTREME followed by cetuximab maintenance; and are treated until disease progression, intolerable toxicity, or investigator/patient decision to withdraw. Primary endpoints are OS and PFS (per RECIST v1.1 assessed by central radiologist review). Secondary endpoints include ORR, safety and tolerability, and patient-reported outcomes. Clinical trial information: NCT03358472.

TPS6091 **Poster Session (Board #78b), Sat, 1:15 PM-4:45 PM**

A phase 2, multicenter, open-label study to evaluate the efficacy and safety of CDX-3379 in combination with cetuximab in patients with advanced head and neck squamous cell carcinoma (HNSCC). *First Author: Julie E. Bauman, Department of Medicine, Division of Hematology/Oncology, University of Arizona Cancer Center, Tucson, AZ*

Background: ErbB3 (HER3) and its ligand, neuregulin-1 (NRG1), are widely expressed in HNSCC and associated with tumor progression. ErbB3 may provide a key mechanism of resistance to therapies targeting EGFR and HER2. HPV− tumors, typified by poorer prognosis, have shown favorable response to ErbB3-targeted therapy. CDX-3379, an anti-ErbB3 monoclonal antibody with a half-life-extending Fc region YTE mutation, binds a unique epitope, locks ErbB3 in an inactive form, and blocks all ErbB3-dependent downstream signaling. CDX-3379 enhances antitumor activity of targeted therapies in preclinical models (Falchook ASCO 2016). In a phase (ph) 1 trial, CDX-3379 was well-tolerated alone and in combination with targeted agents. A patient (pt) with cetuximab-refractory HNSCC experienced a durable complete response to CDX-3379 + cetuximab, while 2 pts with BRAF-mutant non-small cell lung cancer, one dabrafenib-resistant, experienced partial responses to CDX-3379 + vemurafenib (Falchook ASCO 2016). A newly-initiated trial evaluates CDX-3379 + cetuximab in pts with HPV− cetuximab-resistant advanced HNSCC. **Methods:** A ph 2, multicenter, open-label clinical trial (NCT03254927) is enrolling ≤30 pts with advanced refractory HNSCC. Eligibility requires: screening biopsy; HPV−; RECIST 1.1 measurable disease; cetuximab resistance (progression within 6 months); prior PD-1-targeted check-point inhibition (if a candidate); no active brain metastases; and no nasal, paranasal sinus, or nasopharyngeal WHO Type III carcinoma. Pts receive CDX-3379 (initial dose 12 mg/kg IV q 21 days) + cetuximab (loading dose 400 mg/m^2; 250 mg/m^2 IV weekly) until progression/toxicity. Tumor assessments occur at 6-week intervals. Endpoints include objective response rate (ORR; primary), progression-free and overall survival, safety, pharmacokinetics, immunogenicity, and biomarkers (NRG, EGFR ligands). It is hypothesized that CDX-3379 + cetuximab will achieve ORR of 20%, with 80% power and a null hypothesis of ORR ≤5% and $\alpha = 0.05$ based on a Simon's 2-stage design. Three US sites are actively recruiting pts, with additional sites planned. Clinical trial information: NCT03254927.

TPS6092 **Poster Session (Board #79a), Sat, 1:15 PM-4:45 PM**

ECHO-310: A phase 3, randomized trial of epacadostat + nivolumab + chemo vs EXTREME as first-line treatment of recurrent/metastatic SCCHN. *First Author: Ezra E.W. Cohen, University of California, San Diego, La Jolla, CA*

Background: Novel combination treatments targeting broad immunosuppression in the tumor microenvironment (TME) may improve patient (pt) survival. Nivolumab (N) is a PD-1 inhibitor that was shown to significantly prolong overall survival (OS) in pts with platinum-refractory r/m SCCHN. Epacadostat (E) is a potent, highly selective oral inhibitor of indoleamine 2,3-dioxygenase 1 (IDO1), a tryptophan-catabolizing enzyme that contributes to immunosuppression in the TME. Preliminary phase 2 findings from the ECHO-204 study suggest encouraging efficacy with E + N in pts with r/m SCCHN. The ECHO-310 study (NCT03342352) compares E + N + chemo vs the EXTREME regimen as first-line treatment for r/m SCCHN. **Methods:** Eligible pts are ≥18 years old with treatment-naive r/m SCCHN (oral cavity, oropharynx, hypopharynx, and larynx), ECOG PS ≤1, and no prior IDO inhibitors or immune checkpoint therapies. Approximately 550 pts will be randomized (2:2:1) into 3 arms: Arm A receives blinded E 100 mg BID + N 360 mg Q3W + 6 cycles of chemo (cisplatin 100 mg/m^2 in Cycle 1, then 75 mg/m^2 Q3W in Cycles 2–6 or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m^2 on Days 1–4 of each cycle); Arm B (EXTREME) receives cisplatin 100 mg/m^2 Q3W or carboplatin AUC 5 Q3W + 5-FU 1000 mg/m^2 on Days 1–4 of each cycle + cetuximab 400 mg/m^2 on Cycle 1 Day 1, then 250 mg/m^2 QW (starting Cycle 1 Day 8); and Arm C receives E-matched placebo BID + N 360 mg Q3W + 6 cycles of chemo (same as Arm A). Randomization will be stratified by PD-L1 status (expressing [≥1%] vs nonexpressing [< 1%]/nonevaluable), HPV status (oropharyngeal p16 positive vs oropharyngeal p16 negative/nonoropharyngeal SCC), and investigator's choice of cisplatin vs carboplatin. E and placebo treatment continue for up to 2 years or until permanent discontinuation of N, disease progression, unacceptable adverse event (AE), or consent withdrawal. Primary endpoints: OS and PFS in Arms A and B. Secondary endpoints: ORR and duration of response (DOR) in Arms A and B; ORR, PFS, and DOR in Arm C; and quality of life in Arms A and B. Tumor assessments (RECIST v1.1) are performed Q6W for 48 weeks and Q12W thereafter. AEs, graded per CTCAE v4.0, are evaluated for at least 100 days after end of treatment. Clinical trial information: NCT03342352.

TPS6093 **Poster Session (Board #79b), Sat, 1:15 PM-4:45 PM**

A phase 1b/2a, multi-center, open-label study to evaluate the safety and efficacy of combination treatment with MEDI0457 (INO-3112) and durvalumab (MEDI4736) in patients with recurrent/metastatic human papilloma virus–associated head and neck squamous cell cancer. *First Author: Charu Aggarwal, Hospital of the University of Pennsylvania, Medical Oncology, Philadelphia, PA*

Background: Anti–PD-1 immunotherapy has significantly changed outcomes for patients (pts) with recurrent/metastatic (RM) head and neck squamous cell cancer (HNSCC). However, only ≈20% of pts respond, so more effective therapies are needed. MEDI0457 (INO-3112), a plasmid DNA vaccine, comprises 3 plasmids expressing HPV-16 and HPV-18 E6 and E7 proteins along with IL-12. A pilot study in pts with locally advanced HPV-associated HNSCC found MEDI0457 to be safe and well tolerated; it was associated with induction of HPV-16/18 E6/E7–specific humoral and cellular immune responses and showed synergistic activity with anti–PD-1 therapy in immune correlative studies.[1] Durvalumab (MEDI4736) is a human IgG1 mAb that blocks programmed death-ligand 1 (PD-L1) binding to PD-1, stimulating anti-tumor immune response. 60-70% of HPV+ HNSCC can be PD-L1 positive.[2,3] We hypothesize that MEDI0457 administered with durvalumab may enhance anti-tumor effects against HPV-associated HNSCC and improve outcomes for pts with RM disease. **Methods:** This phase 1b/2a, open-label, multi-center study is evaluating MEDI0457 plus durvalumab in pts with confirmed HPV-16 or HPV-18–associated RM HNSCC after treatment with ≥1 platinum-based chemotherapy or platinum-ineligible pts in whom an approved treatment failed. Key exclusion criteria are nasopharyngeal cancer and prior immunotherapy. As this is the first study of MEDI0457 combined with durvalumab, a safety analysis run-in phase will assess the first 3-12 pts with a limit of 4 vaccine doses; this will be followed by the planned recommended dosing schedule in ≈50 pts until disease progression or unacceptable toxicity. Primary objectives are safety and objective response rate. Secondary objectives are disease control rate at 16 weeks, overall survival, progression-free survival, and pharmacokinetics and immunogenicity of durvalumab. Recruitment is ongoing (NCT03162224). [1] Aggarwal, *et al.* SITC 2017 [P125]. 2 Badoual, *et al. Cancer Res* 2013 [128]. 3 Lyford-Pike, *et al. Cancer Res* 2013 [1733]. Clinical trial information: NCT03162224.

TPS6094 **Poster Session (Board #80a), Sat, 1:15 PM-4:45 PM**

Pembrolizumab plus chemoradiation vs chemoradiation alone for locally advanced head and neck squamous cell carcinoma: The phase 3 KEYNOTE-412 study. *First Author: Jean-Pascal H. Machiels, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Background: Preclinical data in murine cancer models show improved tumor growth control and survival when radiation therapy (RT) is combined with a PD-1 inhibitor. Pembrolizumab is effective for treatment of recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), and initial results from a phase 1b study suggest that pembrolizumab plus chemoradiation therapy (CRT) is tolerable in patients with locally advanced (LA) HNSCC. KEYNOTE-412 (NCT03040999) is a phase 3, randomized, placebo-controlled, double-blind trial to determine efficacy and safety of pembrolizumab given with CRT and as maintenance therapy vs placebo plus CRT in LA-HNSCC. **Methods:** Patients will be randomly assigned (1:1) to receive pembrolizumab 200 mg every 3 weeks plus cisplatin-based CRT or placebo plus cisplatin-based CRT. Treatment will be stratified by RT regimen (accelerated RT [56-70 Gy, 6 fractions/week for 6 weeks] or standard RT [56-70 Gy, 5 fractions/week for 7 weeks]), tumor site/p16 status (oropharynx p16 positive vs p16 negative or larynx/hypopharynx/oral cavity), and disease stage (III vs IV). Priming dose of pembrolizumab or placebo will be given 1 week before CRT, followed by 2 doses during CRT, and an additional 14 doses after CRT, for a total of 17 pembrolizumab or placebo infusions. Eligibility criteria include age ≥18 years; newly diagnosed, treatment-naive, oropharyngeal p16–positive (any T4 or N3), oropharyngeal p16–negative (any T3-T4 or N2a-N3), or larynx/hypopharynx/oral cavity (any T3-T4 or N2a-N3) SCC; evaluable tumor burden (RECIST v1.1); and ECOG performance status 0-1. Treatment will be discontinued at the time of centrally confirmed disease progression, unacceptable toxicity, or patient/physician decision to withdraw. Patients will be evaluated to determine the necessity of neck dissection 12 weeks after completion of CRT. The primary end point is event-free survival. Secondary end points are overall survival, safety, and patient-reported outcomes. Relationship between biomarkers and clinical activity will be included as an exploratory end point. Recruitment is ongoing in 21 countries and will continue until ~780 patients are enrolled. Clinical trial information: NCT03040999.

TPS6095 **Poster Session (Board #80b), Sat, 1:15 PM-4:45 PM**

EORTC 1559-HNCG: A pilot study of personalized biomarker-based treatment strategy or immunotherapy in patients with recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN)—"UPSTREAM". *First Author: Rachel Galot, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

Background: The treatment of R/M SCCHN includes platinum-based chemotherapy, cetuximab, and anti-PD-1 compounds. Some genetic alterations have been identified, making SCCHN attractive for molecular targeted therapies. However, when these agents are given to unselected SCCHN patients (pts), only limited activity is observed. EORTC 1559 is a biomarker-driven umbrella trial for R/M SCCHN that investigates the activity of immunotherapy or targeted agents in tumors harboring pre-defined biomarker(s). **Methods:** Pts with R/M SCCHN progressing after platinum-based chemotherapy are enrolled. Inclusion criteria are: ECOG 0-1 and measurable disease by RECISTv1.1. Previous treatment with anti-PD(L)1 is allowed. Before inclusion, a fresh tumor biopsy is taken and analyzed in a certified central laboratory (OncoDNA, Belgium). We designed a custom theranostic test that includes IHC, NGS and gene fusions. Based on a pre-defined algorithm, pts are allocated to different treatment cohorts: afatinib (one cohort for p16- cases with either EGFR or HER2 mutation/amplification or PTEN H-score $>$ 150 and another cohort for p16- cetuximab naïve pts), palbociclib (p16- and cyclin D1 amplification), niraparib (one cohort for p16+ oropharyngeal cancer and another cohort for p16- platinum sensitive disease) and entrectinib (NTRK1/NTRK3 or ROS1 fusions). Pts not eligible for the biomarker-driven cohorts are included in 1 of the immunotherapy cohorts (monalizumab monotherapy or monalizumab + durvalumab). Each cohort is designed as a phase II trial with its own statistical hypothesis. The 1^0 endpoint is either PFS or ORR depending on the investigated drug, cohort sizes range from 32 to 76 pts. The study is designed to allow the addition of new treatment cohorts based on new biomarker hypotheses. We are currently working on adding FGFR inhibitors cohorts. The EORTC HN1559 Upstream trial is the 1st international umbrella trial with a personalized treatment strategy or immunotherapy for pts with SCCHN. The study is open since November 2017 in Belgium and France with 12 first patients enrolled. We plan to open Italy, UK and Germany. Clinical trial information: NCT03088059.

TPS6096 **Poster Session (Board #81a), Sat, 1:15 PM-4:45 PM**

A phase 2, multicenter study to evaluate the efficacy and safety of autologous tumor infiltrating lymphocytes (LN-145) for the treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (HNSCC). *First Author: Rom S. Leidner, Earle A. Chiles Research Institute at Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR*

Background: Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TIL) has demonstrated efficacy in the treatment of immunogenic tumors with high mutation loads, such as melanoma. Despite the heterogeneity of HNSCC tumors, most tumors are either virally-associated or carry high mutation loads that increase the potential antigens targeted by TIL ACT. Since outcomes for patients with recurrent and/or metastatic HNSCC remain poor despite existing approved therapies, a clear rationale exists for the potential application of ACT with TIL in patients with HNSCC. **Methods:** Clinical trial C-145-03 (NCT03083873) is a prospective phase 2 multicenter, open-label study evaluating the efficacy of a single autologous TIL infusion (LN-145) followed by IL-2 after a non-myeloablative lymphodepletion (NMA-LD) regimen in patients with recurrent and/or metastatic HNSCC. Patients undergo a surgical resection of a tumor lesion from which TIL are extracted and expanded at a central GMP manufacturing facility that prepares a cryo-preserved TIL (LN-145) product ready for shipment and infusion. One week prior to LN-145 infusion, patients undergo NMA-LD consisting of cyclophosphamide (60 mg/kg) daily x 2 days followed by fludarabine (25 mg/m^2) daily x 5 days. LN-145 is infused 24 hours after NMA-LD followed by up to 6 doses of IL-2 (600,000 IU/kg) every 8-12 hours. The primary efficacy endpoint is the objective response rate per RECIST v1.1. Secondary endpoints include an assessment of safety & other efficacy parameters such as progression free and overall survival. Patients must have been treated with at least one systemic therapy for recurrent and/or metastatic HNSCC and, in addition to the tumor resected for TIL manufacture, must have an additional measurable lesion for assessment of response. Additional eligibility criteria include amongst others: adequate bone marrow, liver, pulmonary, cardiac, and renal function; and ECOG performance status of 0 or 1. Clinical trial information: NCT03083873.

TPS6097 **Poster Session (Board #81b), Sat, 1:15 PM-4:45 PM**

PATHOS: A phase II/III trial of risk-stratified, reduced intensity adjuvant treatment in patients undergoing transoral surgery for human papillomavirus (HPV)-positive oropharyngeal cancer. *First Author: Mererid Evans, Velindre NHS Trust, Cardiff, United Kingdom*

Background: Incidence of Oropharyngeal squamous cell carcinoma (OPSCC) is rapidly increasing as a result of Human Papillomavirus (HPV), genotype 16 infection. Existing treatments for HPV+ OPSCC have high survival rates but often result in significant long-term toxicities, particularly affecting swallowing function, impacting on quality of life (QoL). PATHOS is a UK phase II-III randomized, multi-centre study. Patients undergo Transoral Surgery (Transoral Laser Microsurgery or Transoral Robotic Surgery) prior to post-operative stratification, according to pathological risk factors. Aim: To determine whether reducing intensity of adjuvant treatment; by lowering radiotherapy (RT) dose or, in patients with positive margins and/or Extracapsular Spread (ECS), omitting concurrent chemotherapy, will result in better long-term swallowing function whilst maintaining high Overall Survival rates. **Methods:** Patients are eligible if requiring primary resection and neck dissection, fit for surgery/treatment, histologically confirmed OPSCC (TNM T1-T3, N0-N2b), and $\geq$ 18 years. Following informed consent, patients are confirmed as HPV+. Baseline swallowing panel (including QoL) is carried out prior to surgery and during follow-up. Post-op group allocation: Clinical trial information: NCT02215265. PATHOS has recruited 152 patients across 18 UK sites to date, clearly demonstrating feasibility of recruitment. PATHOS will proceed to an international Phase III in collaboration with the European Organization for Research and Treatment of Cancer (EORTC) subject to funding being awarded. *Funded by Cancer Research UK (A17161). Coordinated by the Centre for Trials Research, Cardiff University.*

A	no pathological risk factors	No adjuvant treatment
B	close (1-5mm) primary tumour margins (-ve marginal biopsies), T3 tumours, N2, perineural invasion, vascular invasion	Post op: Randomised 1:1 B1: RT 60Gy in 30# over 6 wks (Control) B2: RT 50Gy in 25# over 5 wks (Test)
C	positive ($<$ 1mm) margins (-ve marginal biopsies), ECS	Post-op: Randomised 1:1 C1: RT 60Gy in 30# over 6 wks with concurrent Cisplatin chemotherapy (CT) (Control) C2: RT 60Gy in 30# over 6 wks without CT (Test)

TPS6098 **Poster Session (Board #82a), Sat, 1:15 PM-4:45 PM**

BEST OF: A phase III study assessing the best of radiotherapy (Intensity Modulated RadioTherapy, IMRT) compared to the best of surgery (Trans-Oral Surgery, TOS) in patients with T1-T2, N0 oropharyngeal squamous cell carcinoma (OPSCC). *First Author: Christian Simon, CHUV - Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

Background: The incidence of OPSCC has increased dramatically in the last 15 years. The standard treatment for early stage disease is either surgery or radiotherapy, both with comparable high tumor control rates but with different side effect profiles and technical constraints. Treatment choice is generally based on expert or center experience. It is still unclear whether they differ in terms of functional outcome. To clarify this, we proposed a randomised trial with the primary objective to assess and compare the patient-reported swallowing function over the first year after randomisation to either IMRT or TOS among patients with early stage OPSCC. Clinician and patient-reported outcomes will be used to assess treatment. **Methods:** This is a phase III randomised trial (NCT02984410) that will primarily assess the MD Anderson Dysphagia Inventory (MDADI) score reported by the patients at months 4.5, 6, 9, and 12 after randomisation. MDADI is composed of 19 questions on emotional, functional, and physical aspects, all related to swallowing, wherein scores range between 20 (poorest function) and 100 (best function). BEST OF is powered to detect a clinically significant difference in MDADI score at each of these time points: 4.5, 6, 9, and 12 months with a planned sample size of 170 patients. Key secondary endpoints include treatment response at 6 months after randomization, oncologic outcomes at year 1 and 5, toxicities based on CTCAE, quality of life (QOL) based on QLQ-C30 and HN43 and out-of-pocket costs. QOL domains will be ranked based on patient's priorities. Eligible cases are resectable T1 or T2, N0, M0 OPSCC assessed by a multidisciplinary team. The EORTC quality assurance program (QA) for surgery and pathology (SURCARE) and radiotherapy (RTQA) was implemented in the study. This integrated QA will be the model for future EORTC Head and Neck Cancer trials. BEST OF was opened for recruitment since December 2017 in Belgium and Switzerland and will soon open in France, UK, Germany, Poland, Italy and Portugal through a collaboration with EORTC HNCG and ROG, SAKK, NCRI, GORTEC, and IAG-KHT. Clinical trial information: NCT02984410.

TPS6099 Poster Session (Board #82b), Sat, 1:15 PM-4:45 PM

Hope for salivary gland cancer (SGC): EORTC HNCG/UKCRN 1206 randomized phase II study to evaluate the efficacy and safety of chemotherapy (CT) vs androgen deprivation therapy (ADT) inpatients with recurrent and/or metastatic androgen receptor (AR) expressing SGC (NCT01969578). *First Author: Laura Locati, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: SGCs are rare and heterogeneous tumors (< 1% of all malignancies in Europe). Among more than 20 histotypes, only salivary duct carcinoma (SDC) and adenocarcinoma NOS express AR. These variants are aggressive and associated with poor prognosis. Surgery is the main curative treatment but upon relapse, patients are left with very few options. This study (NCT01969578) aims to evaluate the efficacy and safety of ADT (experimental arm) vs chemotherapy (standard arm) in patients with recurrent and/or metastatic, AR overexpressing SDC and adenocarcinoma, NOS by demonstrating a 15% improvement in Progression Free Survival (PFS) rate at 6 months in favor of ADT. **Methods:** Trial design: In this multicenter, randomized, phase II intergroup study a total of 76 treatment patients (Cohort A) are planned to be randomized to receive ADT or platinum-based chemotherapy. Patients previously treated with chemotherapy will be enrolled in a separate Cohort B to receive ADT. Patients from Cohort A randomized to chemotherapy can also enter in Cohort B at disease progression. The primary endpoint is PFS for Cohort A and best overall response for Cohort B. AR overexpression is mandatory at study entry. Mechanisms of AR activation and resistance will be studied. This study is led by EORTC Head and Neck Cancer Group with UNICANCER/REFCOR, International Rare Cancer Initiative UK Salivary Gland Cancer Group and RARECARENet. It will run in 35 sites in 10 countries: Austria, Belgium, France, Germany, Greece, Hungary, Italy, Portugal, The Netherlands, and United Kingdom. Sites from the EURACAN European Reference Network are participating. On 9 th February 2018, 54 patients are registered; 27 have been enrolled, of which 17 have been randomized in Cohort A. Identification of AR as a treatment target in SGC can be practice changing. Clinical trial information: NCT01969578.

6500 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Randomized trial comparing a web-mediated follow-up via patient-reported outcomes (PRO) vs. routine surveillance in lung cancer patients: Final results. *First Author: Fabrice Denis, Institut Inter-regional de Cancérologie Jean Bernard, Le Mans, France*

Background: In a previous interim analysis, we found a 7-month median overall survival (OS) benefit (p = 0.002) associated with web-based monitoring to detect recurrence in lung cancer patients after initial treatment, vs. scheduled imaging. We hypothesized that benefit was due to earlier detection of symptoms and relapses, prompting earlier treatment and supportive care. Final results with 2-year follow-up is presented. **Methods:** Advanced-stage lung cancer patients without evidence of disease progression after initial treatment were randomly assigned to compare a web-mediated follow-up (experimental arm) based on weekly self-scoring of 13 common patient symptoms with a routine follow-up (control arm) with 3-6 months repeated CT-scans. In the experimental arm, an alert email was sent to the oncologist when self-scored symptoms matched predefined criteria. The IRB protocol-specified primary outcome was OS. After a pre-planned interim analysis in which OS improvement was observed, the IDMC suggested a cessation of further recruitment in 1-2016 and recommended to offer eligible patients in the control arm to cross over to the intervention. **Results:** From 6-2014 to 1-2016, 121 patients were included in the intent-to-test survival (ITT) analysis. Ten out of 34 living patients in the control arm were eligible to cross over following the interim analysis. With 2 years of follow-up and 70 deaths observed, the median OS was 23.0 months in the experimental arm and 14.8 months without adjustment for crossover in the control arm (HR 0.62, 95% CI 0.39 to 0.995, p= 0.048). Censoring crossover resulted in a hazard ratio of 0.53 (95% CI 0.33 to 0.85, p = 0.009) with consistent results also observed based on a rank-preserving structural failure time model (psi = -0.55, 95% CI -1.09 to -0.03). **Conclusions:** With a longer follow-up and although eligible patients from the control arm crossed over to receive intervention after the preplanned interim analysis, the OS remained significantly larger with the web-mediated follow-up based on PRO than with routine disease follow-up by CT scans alone. This is the first study to show the benefits of PROs during surveillance in cancer patients. Clinical trial information: NCT02361099.

6501 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Patient-reported outcomes, emoji, and activity measured on the Apple Watch in cancer patients. *First Author: Carrie A. Thompson, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Patient-reported outcomes (PROs) are important measures in patients with cancer, but may be burdensome to collect. We aimed to measure PROs via mobile technology, using novel emoji PRO scales and associations between PROs and wearable data. **Methods:** Adult patients (pts) with diagnosis ($<$ 5 years) of lymphoma, myeloma, brain, pancreatic, breast, and ovarian cancer, life expectancy of $>$ 6 months, and ownership of an iPhone $\geq$5.0 were recruited and provided with an Apple Watch. Pts completed baseline and weekly PROs for 12 weeks: PROMIS physical function, fatigue, sleep, social/role function short forms; single-item linear analog self-assessment (LASA) of quality of life (QOL), fatigue, and physical function. Pts were randomized into 3 groups for mode of survey response: paper, iPhone, and Watch. Watch and iPhone groups completed an emoji mood scale and an emoji ordinal scale for physical, emotional, and overall QOL. Activity levels were analyzed using the square root of the average daily values to minimize the effects of outliers. Associations between PROs and activity levels were assessed using Spearman correlations for univariate analyses, stepwise linear regression models for multivariate associations, and mixed models for longitudinal associations. **Results:** From 2/2017-8/2017, 296 pts were recruited. Pts wore the watch for an average of 9.8 hours/day and did 4590 mean steps/day (SD 3724). Weekly survey response rates ranged from 60% (Watch group) to 77% (iPhone group). Logging more steps/day was associated with less fatigue and sleep disturbance, better global physical QOL, physical function, and social function, while more minutes of exercise/day was associated with better global mental QOL and sleep. Spearman correlations showed very strong associations between the emoji ordinal scale and LASAs: -0.80 for fatigue, 0.70 for physical well-being, 0.68 for emotional well-being, and 0.75 for overall QOL (all p $<$ 0.001). The baseline emoji mood scale was strongly related to all baseline PROMIS PROs (all p $<$ 0.001). **Conclusions:** Collecting PROs in cancer patients via mobile technology is feasible. Apple Watch activity data is significantly associated with PROs, and emoji scales are a promising tool.

6502 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

The effect of a lay health worker-led symptom assessment intervention for patients on patient-reported outcomes, healthcare use, and total costs. *First Author: Manali I. Patel, Division of Oncology; Clinical Excellence Research Center; Stanford University School of Medicine, Stanford, CA*

Background: Rising cancer costs demand models that safely lower expenditures and improve patients' experiences and outcomes. In response, we developed a risk-stratified proactive symptom assessment intervention which consisted of a lay health worker, supervised by a nurse practitioner, who telephonically assessed symptoms weekly for high-risk patients and monthly for low-risk patients. We implemented the intervention in an oncology group with collaboration from a health plan to test the effect on patient-reported outcomes, healthcare use and cost. **Methods:** We enrolled all newly diagnosed health plan beneficiaries with Stage 3 and 4 cancer from 11/2014 through 9/2015. We evaluated patient-reported satisfaction, emotional and mental health with validated assessments at enrollment and 5-months post-enrollment. We compared healthcare use and costs to all patients with Stage 3 and 4 cancer diagnosed from 11/1/2013-10/31/2014 (control). We assessed differences in demographic and clinical factors using chi-square and t-tests. To evaluate differences in healthcare use and costs we used generalized linear models adjusted for age, stage, co-morbidity, cancer diagnosis, and length of follow-up. **Results:** There were 186 patients in the intervention and 102 in the control. In both arms, median age was 78 years, 55% were female, and gastrointestinal malignancies were the highest proportion of diagnoses. There were statistically significant improvements in mental and emotional health (p $<$ 0.05) and satisfaction with care (p $<$ 0.05) at 5-months follow-up compared with baseline. Patients in the intervention had significantly lower mean number of inpatient admissions per quarter (0.72 vs. 1.02, p = 0.03); mean number of emergency department visits per quarter (0.61 vs. 0.92, p = 0.04), and lower median total healthcare costs ($22344 vs $28414, p = 0.03) as compared to the control. **Conclusions:** A lay health worker-led symptom assessment intervention significantly improved patient satisfaction and reduced healthcare use and costs and may represent one solution to improve care for patients.

6503 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Frequency of post-treatment surveillance and survival in localized prostate cancer: AFT-30 a national study. *First Author: Ronald C. Chen, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: The optimal frequency of post-treatment PSA surveillance is undefined, and different existing guidelines based on expert opinions recommend frequencies ranging from 1x/year to 4x/year. Whether more frequent surveillance improves survival is unknown. **Methods:** Using the backbone of the National Cancer Data Base (NCDB), medical records of 10,477 randomly sampled patients diagnosed with localized prostate cancer from 2005-2010 were abstracted from 1007 sites throughout the US to provide additional data for this study. 53% of the cohort received primary radiotherapy; 47% received radical prostatectomy. Primary exposure is number of post-treatment PSA tests in the first 2 years, and primary outcome is overall survival. **Results:** There were 4,088 low-risk, 3,241 intermediate, and 3,148 high-risk patients. Median age at diagnosis was 64 years, and median follow-up was 8 years. At last follow-up, 17% (low-risk), 33% (intermediate), and 50% (high-risk) patients had died. Median numbers (IQR) of PSA tests in the first 2 post-treatment years were: 4 (2-5)(low-risk), 4 (2-5) (intermediate), and 4 (2-5)(high-risk). Cox multivariable models showed no significant association between frequency of PSA surveillance and overall survival in any risk group (Table). **Conclusions:** More frequent PSA surveillance after definitive treatment for localized prostate cancer is not associated with improved survival. This is the first large-scale study to provide data to inform guidelines and patient/physician decisions. Based on these results, surveillance guidelines recommending PSA tests every 3-6 months likely represent overutilization of care.

Cox multivariable analysis for overall survival.

	Low risk HR (p-value)	Intermediate risk HR (p-value)	High risk HR (p-value)
PSA frequency (REF: lowest third)			
Middle third	1.15 (0.50)	1.11 (0.49)	1.04 (0.73)
Highest third	1.14 (0.55)	1.13 (0.43)	1.01 (0.94)

Model adjusted for age, race, treatment, comorbidity score, facility type, census track education and income.

6504 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Lung cancer screening rates: Data from the lung cancer screening registry. *First Author: Danh Pham, James Graham Brown Cancer Center, University of Louisville, Louisville, KY*

Background: Lung cancer is the leading cause of cancer related mortality in the United States. Since 2013, the United States Preventive Services Task Force (USPSTF) recommended annual screening for lung cancer with low-dose computed tomography (LDCT) for those aged 55-80 years for those who have smoked at least 30 pack years who currently smoke or have quit within the past 15 years. Current literature has provided only estimates of lung cancer screening since implementation. Our study aims to present the number of screening LDCTs being performed across the United States. **Methods:** Using data from the Lung Cancer Screening Registry (LCSR) provided by the American College of Radiology (ACR) in 2016, we collected the total number of LDCT from all 1,796 accredited radiographic screening sites. We used the 2015 National Health Interview Survey (NHIS) to estimate screening eligible smokers per USPSTF criteria and compared them with the 2016 LCSR reported screens. Analyses excluded respondents with missing data and history of lung cancer. **Results:** In 2016, 1.9% of 7.6 million eligible smokers were screened. These rates varied by region from 1.0% in the West to 3.5% in the Northeast (Table). The majority of eligible smokers were populated in the South and had the most accredited screening sites, but were still amongst the lowest in screening rate. Approximately 85% of the screened current smokers were offered smoking cessation. **Conclusions:** Annual LDCT screening remains inadequate following USPSTF recommendations despite the time since implementation and potential to prevent thousands of lung cancer deaths each year. It remains unclear why the lung cancer screening rate is dramatically lower than other cancer screening modalities such as mammography and colonoscopy. Further initiatives are needed including awareness programs and mandating lung cancer screening as a national quality measure.

LDCT screens performed in 2016 compared to eligible smokers per USPSTF criteria.

U.S. Census Region	No. of Accredited Centers	Estimated Eligible Smokers	LDCT Screens	Rate (%)
Northeast	404	1,152,141	40,105	3.5
Midwest	497	2,020,045	38,931	1.9
South	663	3,072,095	47,966	1.6
West	232	1,368,694	14,080	1.0
Total	**1796**	**7,612,975**	**141,260**	**1.9**

6505 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Integrating tobacco treatment into cancer care: A first snapshot of RCT findings. *First Author: Elyse R. Park, Massachusetts General Hospital, Boston, MA*

Background: Despite ASCO recommendations that tobacco use be assessed and managed, most cancer patients who smoke do not receive tobacco treatment. Evidence-based tobacco treatment has not yet been integrated into routine oncology care, and the optimal tobacco treatment strategy in this context is unknown. **Methods:** We conducted a two-arm, two-site RCT to compare sustained counseling plus medication (Intervention Group; IG) to standard tobacco counseling (comparison group; CG) to assist newly diagnosed cancer patients to quit smoking. Both treatment groups received 4 weekly telephone-delivered motivational counseling sessions. The IG additionally received 4 biweekly plus 3 monthly counseling sessions (total 11) and 12-weeks of free FDA-approved cessation medication (nicotine replacement therapy (NRT; patch/lozenge), varenicline, or bupropion). Eligibility criteria included a recent cancer diagnosis (breast, GI/GU, gyn, head & neck, lymphoma, lung, melanoma), cigarette use in the past 30 days, and English/Spanish speaking. The primary outcome was 6-month biochemically verified abstinence. **Results:** 303 (70% of confirmed eligibles) patients were enrolled and randomized to a treatment group. Participants were 56% female; 82% white non-Hispanic and 10% black; mean age = 58.3 (sd = 9.7); 40% had a non-smoking related tumor. 86% completed the 6-month surveys. 80% of IG patients used a smoking cessation medication, among which 83% selected NRT. Using intention-to-treat, 6-month quit rates were 33% in the IG group vs. 19% in the CG group ($p < .02$). Using intention-to-treat, 57% of IG patients were adherent to sustained counseling (≥7 sessions), which was associated with increased 6-month quit rates ($p < .0001$). Cost per patient was $1,273 (IG) vs. $838 (CG). **Conclusions:** Among newly-diagnosed cancer patients, a treatment program of sustained telephone-delivered counseling and free medication produced a higher 6-month quit rate vs. a briefer counseling program. The cost-per-quit compared favorably to other cessation interventions. Findings provide strong support for the benefit of sustained tobacco treatment and a model for effective implementation of tobacco treatment into oncology care settings nationwide. Clinical trial information: NCT01871506.

6506 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Uptake of genetic testing and outcomes in a randomized study of remote genetic services as compared to usual care in community practices without genetic providers. *First Author: Angela R. Bradbury, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Providing remote genetic services by phone or videoconference for patients at community practices without access to genetic providers could increase access to genetic testing. How uptake of testing compares to usual care options for genetic testing has not been reported. **Methods:** To date, 106 patients at 6 community practices were randomized to remote genetic counseling (35 phone; 31 videoconferencing) and 40 to usual care (recruitment to end 3/2018). Primary outcomes were uptake of genetic counseling and testing at 6 months. Secondary outcomes include knowledge, state and general anxiety, depression, and cancer-specific distress in phone versus videoconferencing arms. We used Fisher's exact tests, T-tests, and logistic regressions for analyses. **Results:** 92% of participants are female, 17% are non-white, 33% are college graduates and 65% have a history of cancer. 86% had multigene panel testing. At 6 months, 79% (52/66) of participants in the remote services arms had pre-test genetic counseling as compared to 5% (2/40) in the usual care arm ($p < 0.001$). 56% (37/66) in the remote services arm completed genetic testing and 4 genetic carriers were identified (*ATM, MUTYH* and 2 with *BRCA2*) as compared to 12.5% (5/40) and 0 carriers in the usual care arm ($p < 0.001$ for genetic testing uptake). Highest income levels ($p < 0.05$), older age ($p = 0.07$) and being married ($p = 0.06$) were associated with uptake of testing. In secondary analyses comparing the videoconference and phone arms, we have found greater knowledge gains (phone: +7.4, SD 10.5 v. VC: 17.8, SD 16.5, $p < 0.01$) and reductions in depression (phone +0.1, SD 2.3 v. VC: -1.1, SD 2.0, $p = 0.07$) from baseline to post-disclosure with videoconferencing as compared to phone. **Conclusions:** These data suggest that offering remote genetic services by phone or real-time videoconference may increase the uptake of testing and identification of genetic carriers in community practices without access to genetic services. Continued evaluation of the relative benefits of videoconferencing over telephone counseling in patients at community practices is critical to understanding how to optimize patient outcomes. Clinical trial information: NCT02517554.

6507 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

PRECISE: A clinical-grade automated molecular eligibility screening and just-in-time (JIT) physician decision support solution for molecularly-selected oncology trials. *First Author: Jessica Tao, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clinical informatic systems that aid in identifying and matching actionable molecular alterations to the appropriate targeted therapies are critical for ensuring both the delivery of optimal routine care and the successful implementation of precision oncology research programs. We developed DARWIN PRECISE (PRECision Insight Support Engine), a clinical-grade informatics solution that identifies and dynamically tracks patients based on molecular and clinical data. PRECISE also provides JIT notifications to study teams and treating oncologists, facilitating patients' seamless matching and enrollment to molecularly-selected trials. **Methods:** Under an IRB-approved study, we prospectively followed all patients identified by PRECISE and subsequently enrolled to molecularly-selected clinical trials at MSKCC between 16-April-2014 and 31-January-2017. Demographic, clinical, and molecular data were abstracted from the institutional data warehouse. Characteristics of therapeutic accruals facilitated by PRECISE were measured using descriptive statistics. **Results:** Patients treated by 150 unique oncologists and all accruals to 42 therapeutic trials that used PRECISE were included in the analysis. During the study period, a total of 742 patient-accruals occurred across the 42 trials. Of these, PRECISE prospectively identified 327 (44%) of accrued patients. Patients identified and subsequently enrolled by PRECISE harbored a wide variety (n = 32) of molecular alterations; with SNVs, CNAs, or fusions in *ERBB2* (23.5%), *PIK3CA* (18.2%), *BRAF* (9.3%), and *FGFR1/2/3* (6%) occurring most frequently. The median time from initial identification by PRECISE to trial consent was 82 days (IQR: 35-166), and the median time from tumor sequencing to consent was 161 days (IQR: 64-350). **Conclusions:** PRECISE facilitated the identification and enrollment of 44% (n = 327) of all patients accrued to molecularly-matched studies using this informatic platform. Automated JIT decision-support tools like PRECISE represent a novel and effective method for enhancing patient accrual to molecularly-selected therapies.

6508 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

A cloud-based virtual tumor board to facilitate treatment recommendations for patients with advanced cancers. *First Author: Subha Madhavan, Innovation Center for Biomedical Informatics, Georgetown University Medical Center, Washington, DC*

Background: A deficiency in current approaches in Precision Oncology is the sole focus on gene mutations while overlooking the patient context, including medical and treatment history, as well as other multi-omic data, such as proteomics, germline, and phosphoprotein assays. Optimally every patient facing a molecular treatment decision will benefit from an expert tumor board, but it is impossible to convene this for every patient. **Methods:** We developed a cloud-based, asynchronous virtual tumor board (VTB) that integrates multi-modal patient data to formulate, discuss, and rank treatments. The VTB utilizes 8 linked databases, a treatment scoring model based on the AMP/ASCO variant interpretation guidelines and an AI-based treatment recommender. Molecular and clinical data including past medical history, molecular and pathology reports were aggregated from 1342 cases from $>$ 300 community and academic hospitals. A preliminary list of therapy options and trials were prepared by the VTB which integrates variant annotations, biomarker implications, trial eligibility criteria, outcomes, and literature. Medical and scientific experts reviewed each case, discussed through an asynchronous chat room, modified, and ranked treatment options delivered as a report to the treating oncologist. **Results:** Automation through VTB, increased the volume of cases reviewed per month by twofold. The VTB also led to a larger set of options compared to a lab report alone. Across 642 patients, the VTB enabled genomic-based therapy options in 503 (78.6%) patients. Additionally, proteomic data strengthened on-label treatment recommendations in 229 (36%), and off-label treatment recommendations in 80 (12%) patients. Importantly, by considering patients' previous treatment histories, the VTB omitted treatment options in 64% of patients to which patients had developed resistance. **Conclusions:** The VTB provides a scalable platform for integration and asynchronous team communication for facilitating case review with no geographical and time/attendance restrictions. We anticipate that further development of such decision support tools will be important for widespread adoption of cancer precision medicine.

6509 Poster Discussion Session; Displayed in Poster Session (Board #335), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Clinical trajectory modeling to predict hospitalization or death after palliative chemotherapy. *First Author: Kenneth L. Kehl, Dana-Farber Cancer Institute, Boston, MA*

Background: Hospitalization or death within 30 days of palliative-intent chemotherapy for metastatic cancer represent undesirable outcomes. An automated framework for predicting the risk of hospitalization or death within 30 days of chemotherapy could inform clinical decision-making, research, and quality improvement efforts. **Methods:** We piloted a machine learning framework for time-dependent clinical trajectory modeling using administrative data and applied it to prediction of hospitalization or death within 30 days of palliative cytotoxic chemotherapy. Patients with stage IV non-small cell lung cancer (NSCLC) diagnosed 2008-2013 were identified in SEER-Medicare. Inpatient, outpatient, durable medical equipment, prescription, home health, and hospice claims were extracted. The sequence of claims for the 60 days, or "clinical trajectory," prior to each date of chemotherapy was embedded into a feature space based on context similarity, and the sequence was fed into a stacked ensemble model to predict hospitalization or death within 30 days of each chemotherapy date. These administration dates were divided into 80% training and 20% validation sets. Discrimination was measured with the c-statistic (AUC). No manual feature engineering was performed. **Results:** 43,250 dates of chemotherapy administration were identified for 6,067 patients with stage IV NSCLC. 8,057 chemotherapy dates (19%) were followed by hospitalization (N = 7,629) and/or death (N = 1,688) within 30 days. In the validation set, our framework predicted the composite of hospitalization or death with an AUC of 0.83. Among 42,823 chemotherapy dates that were not followed by death without hospitalization within 30 days, our framework predicted hospitalization with an AUC of 0.84. **Conclusions:** Clinical trajectory modeling predicts hospitalization or death within 30 days of palliative-intent cytotoxic chemotherapy for stage IV NSCLC with good discrimination. These results could inform clinical decision-making and targeted cancer care delivery interventions.

6511 Poster Discussion Session; Displayed in Poster Session (Board #337), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

End of life spending among cancer patients in an ACO vs. non-ACO. *First Author: Miranda Lam, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: Nearly 25% of the annual Medicare budget is devoted to care of beneficiaries who die in a given year. Therefore, there has been increased policy and provider focus on understanding the care provided to patients at the end of life. Of the many initiatives aimed at improving the value of healthcare services in the United States, Accountable Care Organizations (ACOs) are receiving substantial policy attention. Early evidence shows modest reductions in total healthcare costs for Medicare beneficiaries. However, we are unaware of any data looking specifically at the impact of ACOs on spending for cancer patients at the end of life. **Methods:** We analyzed a 20% sample of Medicare beneficiaries age 66 years or older. We followed CMS guidelines to attribute patients to an ACO or non-ACO practice. Using ICD-9 codes, we identified patients with cancer. We matched ACO and non-ACO practices within the same HRR and narrowed to patients who died in 2013 or 2014. We calculated mean annual standardized total costs in the 180 days prior to death and stratified by inpatient, outpatient, physician, skilled nursing facility, home health, hospice, radiation oncology, and chemotherapy spending. Spending was adjusted for patient characteristics and by chronic conditions. **Results:** 36% of patients were in an ACO. ACO and non-ACO patients were similar in terms of patient characteristics (age, race, sex, dual eligibility, comorbidities). ACO beneficiaries had modest but significantly higher total annual standardized costs compared to beneficiaries not in an ACO ($47,629 vs. $45,582; p = 0.02). The ACO and non-ACO patients had similar spending by categories: inpatient ($23,908 vs. $22,843; p = 0.06), outpatient ($4,939 vs. $4,403; p = 0.09), physician services ($13,412 vs. $12,975; p = 0.26), SNF ($2,164 vs. $1,952; p = 0.18), HHA ($2,009 vs. $2,027; p = 0.82), hospice ($683 vs. $793; p = 0.07), radiation oncology ($449 vs. $422; p = 0.62), and chemotherapy ($1,927 vs. $1,813; p = 0.57). **Conclusions:** Spending in the last 6 months of life among cancer patients treated in an ACO was slightly higher compared to those not treated in an ACO. This study suggests that ACOs have not had a meaningful impact in reducing costs at the end of life for cancer patients.

6512 Poster Discussion Session; Displayed in Poster Session (Board #338), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Are National Comprehensive Cancer Network (NCCN) Evidence Blocks (EB) Affordability Ratings (AR) representative of real-world costs? An evaluation of advanced non small cell lung cancer (aNSCLC). *First Author: Scott David Ramsey, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The NCCN EB are designed to provide AR on the overall cost of drug treatments (tx), including medication, administration, supportive care, side effect management and hospitalization. This study characterized the relationship between real-world costs of aNSCLC tx and NCCN AR. **Methods:** We used the Truven MarketScan claims database to identify patients (pts) treated with aNSCLC tx evaluated by the NCCN EB from 2006-2011. We estimated mean per patient per month (PPPM) cost (including inpatient, outpatient, and pharmacy costs) for each regimen, adjusted for patient characteristics using generalized linear models with log-link gamma. Tx regimens were grouped into their respective NCCN EB AR. Weighted linear regression was used to examine the correlation between adjusted mean PPPM costs per regimen and NCCN AR. **Results:** The study identified 15,574 pts (mean age: 65 [SD = 11], 53% male). The mean PPPM cost per regimen ranged from $12,188 to $66,996 (mean $22,782, median $16,412). EGFR and ALK tx and generic chemotherapy had different AR despite having similar mean PPPM costs (EGFR/ALK: $13,665-$27,782, AR 2; chemo: $16,175-$28,195, AR 3-4). The mean PPPM costs per regimen by AR had low correlation (R^2= -0.34) and was not statistically significant (p = 0.13). Pairwise comparisons show a significant difference in mean PPPM costs between AR 1 and other groups; there were no significant differences in mean PPPM costs among AR 2, 3, and 4. **Conclusions:** Real-world costs are often inconsistent with the NCCN AR. Given the intended use of NCCN EB to inform tx decisions and value discussions between providers and pts, our results suggest that the NCCN AR need to be further refined and validated.

NCCN AR	Mean PPPM (95% CI)	Difference vs. AR = 2	Difference vs. AR = 3	Difference vs. AR = 4
AR 1: Very Expensive (n = 860)	$40,084 ($31,123, $49,044)	-$19,230*	-$15,226*	-$19,734*
AR 2: Expensive (n = 2177)	$20,854 ($17,755, $23,953)	–	$4,003	-$505
AR 3: Moderately expensive (n = 3155)	$24,857 ($21,349, $28,365)	–	–	-$4,508
AR 4: Inexpensive (n = 9307)	$20,349 ($18,517, $22,182)	–	–	–
AR 5: Very inexpensive (n = 0)	–	–	–	–

* $p < 0.01$

6513 Poster Discussion Session; Displayed in Poster Session (Board #339), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Cost-effectiveness of multi-gene panel sequencing (MGPS) for advanced non-small cell lung cancer (aNSCLC) patients. *First Author: Lotte Maria Gertruda Steuten, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: MGPS, compared to single-marker genetic testing (SMGT), has the potential to identify more patients who could benefit from targeted therapies, but the impact on outcomes and total costs of care is uncertain. Our goal was to estimate the cost-effectiveness of MGPS vs SMGT in aNSCLC. **Methods:** aNSCLC patients (stage IIIB or metastatic) diagnosed between 2011-2016 were identified from the Flatiron Health database, representing curated electronic health record-derived clinical information from > 250 oncology practices nationwide. After stratifying patients in MGPS or SMGT cohorts, we analyzed the percentage of patients that receive targeted treatment; survival; and total costs of care. SMGT included *EGFR* and *ALK* testing; MGPS also allowed detection of *BRAF, RET, ROS1, HER2* and *MET* mutations. Cost data sources were the CMS Fee Schedule and 2017 ASP drug cost. We estimated the incremental cost-effectiveness ratio (ICER) and performed sensitivity analyses from a US payer perspective over a lifetime horizon, using a decision model. **Results:** We identified 5688 aNSCLC patients receiving MGPS (n = 875) or SMGT (n = 4813), of which 22% tested positive for *EGFR* (18.5% MGPS, 17.3SMGT) or *ALK* (3.59% MGPS, 3.78% SMGT). Among MGPS tested patients, an additional 8% were found to have *BRAF, RET, ROS1, HER2* or *MET* mutations. Of MGPS tested patients, 21% received targeted treatments vs 19% with SMGT. Model-projected survival was 1.14 life years (LYs) in SMGT vs 1.20 LYs in MGPS. Lifetime total costs were $8,814 higher per patient for MGPS. The ICER of MGPS vs SMGT was $148,478 per LY gained. If all patients with actionable mutations would receive targeted treatment in MGPS-guided care vs the proportion currently receiving targeted treatments under SMGT, the ICER would be $110K/LY gained. Sensitivity analyses shows widely varying ICERs ($139/LY to $661,625/LY). **Conclusions:** Based on data from a nationwide oncology patient database, MGPS has moderate cost-effectiveness compared to SMGT in aNSCLC patients. Efforts to increase the proportion of patients who receive targeted therapies would improve the cost-effectiveness of MGPS, assuming incremental costs and outcomes of targeted treatments remain unchanged.

6514 Poster Discussion Session; Displayed in Poster Session (Board #340), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Cost-effectiveness analysis of abiraterone acetate (AA) versus docetaxel (D) for the management of metastatic hormone naïve prostate cancer (mHNPC). *First Author: Chethan Ramamurthy, Fox Chase Cancer Center, Philadelphia, PA*

Background: Therapies previously reserved for castration resistant prostate cancer (CRPC) have demonstrated improved progression-free (PFS) and overall survival (OS) in mHNPC. Four randomized trials have provided level 1 evidence for using either D or AA in addition to androgen deprivation therapy (ADT) for mHNPC, but the cost-effectiveness of these options has not been compared. **Methods:** A Markov cohort model was developed to project cost-effectiveness of each treatment until disease progression. Survival curves for progression/death were abstracted and digitized from the CHAARTED and LATITUDE studies. Clinically or financially significant adverse events (AEs) were modeled (neutropenia, neutropenic fever, and severe fatigue); utility values were obtained from the literature. Drug costs were obtained from a range of sources (Average Wholesale Price; VA costs). Effectiveness was measured in PFS quality adjusted life years (PFS QALYs) and cost-effectiveness was calculated using incremental cost-effectiveness ratios (ICER). **Results:** Adding D or AA to ADT improved PFS QALYs by 0.26 and 0.54, and increased cost by $12,185 and $208,684, respectively. Resulting ICERs were $46,519/QALY (D vs ADT) and $705,323/QALY (AA vs D). Results were highly sensitive to AA price, although even under lowest prices, the ICER was $404,451/QALY (AA vs DC) (Table 1). AA cost must be reduced by 76% for it to fall below a willingness-to-pay threshold of $150,000/QALY. **Conclusions:** Addition of AA modestly increases PFS QALYs compared with D, but substantially increases costs. While therapy subsequent to progression will impact the overall cost-effectiveness of the respective frontline options, the relative durations of treatment for CRPC are shorter. Thus, cost-effectiveness of mHNPC therapy is an important consideration given that OS is similar between studies for D and AA.

Effect of varying medication costs on ICERs.

	Cost ($)	ICER (AA vs D) ($)	ICER (D vs ADT) ($)
Base case		705,323	46,519
Abiraterone (cost/30d supply)	9358*		
LB	5,550	404,450	46,519
UB	11,275	856,743	46,519
Docetaxel (cost/mg)	10*		
LB	1.6	726,302	24,206
UB	12	700,210	51,958

*Base case; LB = lower bound, UB = upper bound

6515 Poster Discussion Session; Displayed in Poster Session (Board #341), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Potential life-years lost: The impact of the cancer drug regulatory process in Canada. *First Author: Joanna Gotfrit, Ottawa Hospital, Ottawa, ON, Canada*

Background: Canada has an established publicly-funded healthcare system but a complex drug approval and funding process. After proof of efficacy (POE; key publication/presentation), before becoming publicly accessible each drug undergoes a Health Canada approval process, a health technology assessment (HTA), a pricing negotiation and finally individual provincial funding agreements. We quantified potential life-years lost due to delays in this process. **Methods:** We analyzed drugs for advanced lung, breast and colorectal cancer that underwent the HTA process between 2011-2017. Life-years lost were calculated by: (documented PFS/OS improvement) x (number of eligible patients) x (time from POE to first public funding). For conservative calculation, we assumed all eligible patients in Canada had access at the time of first public funding, while in reality provinces fund at different time-points. **Results:** We analyzed 21 drugs. Of these, 15 have been funded publicly. See Table 1 for time delays and life-years lost for select publicly funded drugs. The time from POE to first public funding ranged from 1.2-7.5 years (median 2.1 years). Total progression-free life-years lost from POE to first public funding were 36,854 (lung 9,015; breast 4,134; colorectal 23,706 years). Total overall life-years lost from POE to first public funding were 48,366 (lung 32,388; breast 5,823; colorectal 10,155 years). **Conclusions:** The number of potential life-years lost during the drug regulatory and funding process in Canada is substantial. Recognizing that inter-provincial differences exist and that eligible patients may not all receive a given drug, if even a fraction does so, the impact of delays remains substantive. Other countries with similar systems likely experience similar delays. Collaborative national initiatives are required to address this major barrier to treatment access.

Tumour Site	Drug Name	Indication	Time from efficacy to first public funding (years)	Progression-free life-years lost	Overall life-years lost
Lung	Pembrolizumab	1st line, expressing PD-L1 > 50%	1.2	2240	8229
Breast	Pertuzumab	Her2/neu(+), in combination with a taxane/trastuzumab	1.9	1001	2494
Colorectal	Cetuximab	1st line, KRAS wild type	6.4	4352	10154

6516 Poster Discussion Session; Displayed in Poster Session (Board #342), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Trends of new cancer drug approvals from the perspective of a publicly funded healthcare system: Analyses of the pan-Canadian Oncology Drug Review (pCODR) recommendations. *First Author: Saroj Niraula, CancerCare Manitoba and Univ of Manitoba, Winnipeg, MB, Canada*

Background: United States Food and Drug Administration (FDA) primarily takes into account the therapeutic index before approval of a new cancer drug whereas in countries with public funding of healthcare cost-effectiveness, utility, and adoption feasibility are also considered rigorously. **Methods:** Data from the pan-Canadian Oncology Drug Review (pCODR) – a national drug review system that makes evidence-based funding recommendations to Canada's provinces and territories - were collected. Analyses based on rationale of the pCODR recommendations and any conditions thereof, pCODR timelines compared to FDA approvals, published results of the pivotal clinical trials used to support the pCODR recommendations, cost/Quality Adjusted Life Years (QALY), and Incremental Cost Effectiveness Ratio (ICER)/QALY of the new drugs compared to controls were performed using established methods. **Results:** From inception to January 31, 2018, 60 new cancer drugs for 91 indications were reviewed by pCODR. There was a median of 15 months' time lag between FDA approval and final pCODR recommendation. Eighteen of the 91 pCODR reviews (approved previously by FDA for public use) received negative recommendation on the grounds of inadequate clinical benefits. Of the 73 that received positive pCODR recommendation, 90% were approved conditional on improvement in cost-effectiveness to an acceptable level. Surrogate outcomes were used as the primary basis for approval in 83% of the reviews, of which 4 drugs subsequently led to a compromise in overall survival compared to respective controls by a median of 1.5 months. Median ICER/QALY of new drugs, compared to the controls was $186,403 (range 7.2k to 4 millions). **Conclusions:** Close to a quarter of cancer drugs approved for public use by FDA do not meet Canadian standards for efficacy, and some may have detrimental effect on survival. A vast majority of the pCODR approved drugs are cost-ineffective at presented price. With finite resources to share among multiple societal priorities like education and preventative health, incremental cost of new cancer drugs is unsustainable even in the wealthiest of nations.

6517 Poster Discussion Session; Displayed in Poster Session (Board #343), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

FDA acceptance of surrogate endpoints in later lines of therapy. *First Author: Emerson Yu-sheng Chen, Oregon Health and Sciences University, Portland, OR*

Background: U.S. Food and Drug Administration (FDA) utilizes surrogate endpoints in order to speed drugs to market. Surrogates reduce development time, though they do so to a larger extent in the front line rather than in later line settings. **Methods:** We examined all adult cancer drugs approved by the FDA from 01/2006 to 12/2017. Data regarding the approval type (regular or accelerated), cancer type, treatment indication, and basis for approval were extracted from the FDA website and any relevant publications. Basis for approval was categorized into response rate (RR), progression-free or relapse-free survival (PFS/RFS), and overall survival or quality-of-life (OS/QoF) endpoints. Drugs for mainly pediatric cancers and cancers limited to genetic syndromes were not included in this study. Statistical analysis was performed using SAS 9.4 version. **Results:** 182 drug indications among 108 cancer drugs were identified. 67 (36.8%) drug indications were approved for first-line setting, 75 (41.2%) for second-line setting, 24 (13.2%) for third-or-later-line setting, and 16 (8.8%) for adjuvant or maintenance settings. 49 (26.9%) were approved based on OS/QoF endpoints. 133 (73.1%) were approved based on surrogate endpoints: 69 (37.9%) being RR and 64 (35.2%) being PFS/RFS. Accelerated instead of regular approval was more likely to be sought in subsequent lines of therapy (19.4% in first-line, 30.7% in second-line, 62.5% in third line, $p < 0.01$). Surrogate endpoints had a trend toward being used in subsequent lines of therapy (68.7% in first-line, 70.7% in second-line, and 87.5% in third-line approvals, $p = 0.18$). However, RR specifically was used more frequently in subsequent lines of therapy compared to PFS/RFS or OS/QoF (22.4% in first-line, 45.3% in second-line, and 79.2% in third-line approvals, $p < 0.01$). **Conclusions:** Surrogate endpoints are increasingly used in oncology trials with the intention of speeding drugs to market. They are used most often in later lines of therapy, when definite endpoints like OS or QoF can be expeditiously evaluated, and the 'acceleration' of approval is actually limited. Accelerated approval based on surrogate endpoints is thus granted preferentially in later lines of therapy, when the impact is likely modest.

6518 Poster Discussion Session; Displayed in Poster Session (Board #344), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Internet- and mobile-based lifestyle intervention for prostate cancer patients on androgen deprivation therapy: Prospective, multicenter, randomized trial. *First Author: Yong Hyun Park, Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of (South)*

Background: Androgen deprivation therapy (ADT) has several adverse effects including loss of libido, osteoporosis, and metabolic complications. We aimed to examine whether the Smart After-Care service (internet- and mobile-based lifestyle intervention) has an effect on clinical outcomes in patients with prostate cancer (PCa) on ADT. **Methods:** Two hundred patients with PCa on ADT were randomly assigned to the Smart After-Care or control group. The Smart After-Care group received a mobile application and wearable device, providing general health information, nutritional and medication care and exercise program (aerobic exercise at least 90 or 150 minutes every week for 12 weeks depending on patients' aerobic fitness and strengthening exercise at least 2 times a week for 12 weeks) while the control group was imparted brief education for the exercise program. Primary endpoint was an increase in patients' physical function as assessed using 2 minutes' walk test. Secondary endpoints included improvement in muscle strength (30 seconds chair stand test, grip strength test), short physical performance battery, body composition, and health-related quality of life (EORTC-QLQ-C30, and PR 25). **Results:** In the aspect of physical performance, both groups showed significant improvement in 2 minutes' walk test and 30 seconds chair stand test after 12 weeks of intervention, whereas a repeat measures ANOVA showed a significant improvement in 2 minutes' walk test ($P = 0.042$) over time in the Smart After-Care group as compared to the control group. The Smart After-Care group had additional improvement in right hand grip strength ($P = 0.038$) and reduction in body fat percentage ($P = 0.022$) compared to the controls. Also, the Smart After-Care group showed significant improvement in social functioning ($P = 0.016$) as well as in appetite loss ($P = 0.048$). Both groups showed significant improvement in urinary symptom, whereas the Smart After-Care group showed significant improvement in sexual functioning ($P = 0.032$). **Conclusions:** The Smart After-Care service is an effective method in PCa patients on ADT in improving exercise capacity and general health related quality of life. Clinical trial information: NCT03264209.

6519 Poster Discussion Session; Displayed in Poster Session (Board #345), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Objective metrics of patient activity: Use of wearable trackers and patient reported outcomes in predicting unexpected healthcare events in cancer patients undergoing highly emetogenic chemotherapy. *First Author: Alexander S. Martin, University of Southern California, Los Angeles, CA*

Background: Functional status and predictors that identify those cancer patients at risk for unplanned hospitalization can have broad implications for the health care system and clinical trials. We evaluated the feasibility of monitoring physical activity (PA) using wearable activity trackers in cancer patients on highly emetogenic chemo as well as potential correlations between PA and unplanned healthcare events (UHE) and ECOG scores. **Methods:** This study was conducted as a multi-institutional single arm observational clinical trial of 65 patients with solid tumors undergoing highly emetogenic chemo based on Hesketh classification. We measured PA by analyzing daytime hourly metabolic equivalents (1 MET = resting metabolic rate) from 10 AM - 7 PM over 60 days via Microsoft band 2. Patient reported outcome data was collected using smartphone apps. UHE were collected by review of medical records over the 60 days of band wear plus 90 days of clinical follow up. **Results:** Data was successfully captured from 41 of the 65 activity trackers. Patients were compliant with wearing the activity trackers for $>$ 7 of 9 total hrs on 67.7% of study days. Only 9 out of 41 patients exhibited $>$ 60 hours of non-sedentary activity, defined as $>$ 1.5 METs, over the 60-day band wear period. Mean step counts/day were similar between higher and lower PA groups at 2564 steps/d and 2261 steps/d respectively. 9 patients with $>$ 60 hrs of 1.5 METs had significantly fewer UHE compared to the 32 patients with $<$ 60 hrs of 1.5 METs ($p = 0.02$). The physician reported ECOG scores had no correlation with PA or UHE. **Conclusions:** In solid tumor patients undergoing highly emetogenic chemo regimens, activity trackers are feasible and identify those patients with a profile of lower activity that predicts UHE. Incorporation of activity trackers has the potential to identify patients who are at need for interventions to prevent hospitalization and may also predict the subset of patients enrolled in clinical trials who are more likely to record serious adverse events.

6520 Poster Discussion Session; Displayed in Poster Session (Board #346), Sat, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Sat, 4:45 PM-6:00 PM

Opioid use in long term cancer survivors. *First Author: Lisa Catherine Barbera, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada*

Background: Our research team previously found that the rate of opioid use in cancer patients surviving at least 5 years beyond diagnosis was 1.2 times higher compared with age-sex matched controls without cancer. The purpose of this study was to evaluate the factors associated with opioid use after 5 years of survival from cancer diagnosis. **Methods:** We conducted a retrospective cohort study using linked provincial administrative data. Patients were aged 24-70 and economically disadvantaged, making them eligible for government funded pharmacare. The index date was defined as the 5 year anniversary from the diagnosis date. Patients were accrued continuously between April 1, 2010 and March 31, 2015 on their index date. Those with any evidence of recurrence (resuming anti-cancer therapy, palliative care) were excluded. Patients were observed until death, relapse or end of data accrual. The main outcome was opioid prescription rate after index date. The main exposures were opioid use prior to diagnosis date, opioid use between diagnosis date and index date (none, continuous, at diagnosis only, other), certain cancer surgeries (e.g. thoracotomy) and chemotherapy agents known to cause neuropathy. A negative binomial regression model was used to estimate the relative rates of opioid use after index date. **Results:** Our cohort included 7,431 individuals. The factors most strongly associated with a higher rate of opioid use after index date was continuous opioid use between diagnosis and index date. The RR was 63.4 (95% CI 39.4-102.1) for those with no pre-diagnosis opioid use and 76.6 (95% CI 40.7-144.0) for those with pre-diagnosis opioid use. The only group with no increased risk used opioids only at diagnosis and had no prior use. Surgery was not significant. Chemotherapy was not significant with the exception of those who used opioids initially. A history of depression, comorbidity and more than 2 years of diabetes were also associated with higher risk. **Conclusions:** Cancer patients who use opioids continuously after diagnosis are at increased risk of continued use after 5 years of survival. Further work is needed to understand the reasons for ongoing use after diagnosis. Increased attention is needed to ensure safe prescribing for this group to minimize issues with dependence.

6521 Poster Session (Board #347), Sat, 1:15 PM-4:45 PM

Implementation of breast cancer pathway for genetic counseling and testing in multi-state health system. *First Author: Stephanie L. Graff, Sarah Cannon Cancer Institutes HCA Midwest Health, Overland Park, KS*

Background: Genetic counseling and/or testing (GC/T) are important aspects of breast cancer care. The National Comprehensive Cancer Network has guidelines for GC/T but reports demonstrate variable compliance. Across the Sarah Cannon Cancer Network (SCCN), pathways were developed and implemented by physician leadership teams to select patients (pts) who meet criteria for GC/T. Participating physicians receive pathways training. Adherence metrics are tracked in real time. This study evaluates compliance with GC/T for pts treated on and off pathway in the SCCN. **Methods:** Data was collected from seven SCCN markets in six states to create 3 data sets. 1. Pre-pathway: treated prior to implementation of pathways. 2. Off pathway: treated off pathway by physicians not yet trained on pathways after pathways implementation. 3. On pathway: treated by at least one physician trained on pathways. Pathway criteria for GC/T include: age $<$ 50 years, male breast cancer, $\geq$ 2 affected relatives, ovarian cancer (family or self), triple negative biology $<$ 60 years of age, 2 primary breast cancers, Ashkenazi Jewish ancestry. All pts were navigated by nurse navigators who entered the data into iNavigate, SCCN's proprietary software. Data represents all breast cancer pts in iNavigate between December 2012 and November 2017. Pathways were implemented March 2016. Chi-squared tests were performed without continuity correction, using Bonferroni correction methods to account for multiple comparisons **Results:** Summarized in Table 1. **Conclusions:** Following implementation of pathways guiding genetic counseling and/or testing (GC/T), patient referral improved by 61.3% (95% CI: 56.1%, 66.4%; $p < 0.0001$). For pts not managed on pathway, GC/T improved by 15.7% (95% CI: 10.9%, 20.6%; $p < 0.0001$), possibly due to increased navigator or system awareness. These findings support pathways as one way to ensure best practice and guidelines based care across a large, multi-state health system.

	Total Patients	Eligible GC/T	GC/T Offered
Pre-Pathway	4321	1151	245 (21.3%; 95% CI: 19.0%, 23.7%)
Off Pathway	2711	889	329 (37.0%; 95% CI: 33.9%, 40.2%)
On Pathway	1277	453	374 (82.6%; 95% CI: 78.8%, 85.8%)

6522 Poster Session (Board #348), Sat, 1:15 PM-4:45 PM

Trends and disparities in place of death for cancer patients in the United States, 1999-2015. *First Author: Fumiko Ladd Chino, Duke University Radiation Oncology, Durham, NC*

Background: Dying in a preferred place is an essential component of high quality cancer care. Comprehensive national trends and disparities in place of death are unknown as prior research is limited in scope and to patients $\geq$65. **Methods:** CDC WONDER contains death certificate data for all US counties and is maintained by the National Center for Health Statistics. Place of death was obtained for all cancer deaths from 1999- 2015, as well as year of death, age, sex, race, ethnicity, marital status, and education. Place of death was dichotomized to death at home or hospice facility vs other location. Using data from the most recent year (2015), univariate (UVA) and multivariate (MVA) logistic regression were used to test for disparities in place of death associated with sociodemographic variables. **Results:** In the study period, 9,646,498 cancer deaths occurred, with 45.5% dying at home or hospice facility. 30.3% of deaths occurred in patients $<$ 65. From 1999-2015, inpatient deaths decreased from 36.6% to 24.6%, while home deaths (38.4 to 42.6%) and hospice facility deaths (0 to 14.0%) increased (all $p < 0.001$). On UVA, older age, female sex, white race, Hispanic ethnicity, marriage, higher education, and pancreatic or colorectal cancer were associated with death at home or in a hospice facility. On MVA, all assessed factors were associated ($p < 0.05$) except education and ethnicity. In particular, being married (OR 2.04, 95% CI 1.98-2.10) and having pancreatic cancer (OR 1.36, 95% CI 1.33-1.40) were associated with death at home or hospice, while being black (OR 0.74, 95% 0.73-0.76) or Asian (OR 0.65, 95% CI 0.62-0.68) and having breast cancer (OR 0.90, 95% CI 0.88-0.92) had decreased odds of dying at home or hospice. Despite improvements over time, in 2015 black patients remained 42% more likely to die in hospital (32.8% black vs 23.1% white) and 21% less likely to die at home (34.6% black vs 43.7% white) (both $p < 0.001$). **Conclusions:** Inpatient cancer deaths decreased by one third with commensurate rise in home and hospice facility deaths over the study period. Multiple sociodemographic factors were associated with place of death; targeted efforts to increase utilization of palliative care and hospice services may decrease these disparities.

6523 Poster Session (Board #349), Sat, 1:15 PM-4:45 PM

Methodologic challenges of defining oncology provider networks from administrative claims data. *First Author: Karyn Beth Stitzenberg, Univ of North Carolina, Chapel Hill, NC*

Background: Provider characteristics measured from administrative claims data are increasingly used to study health care organization/delivery and to measure quality of care. Most studies use claims from a single large payer to calculate provider statistics and examine networks. This study compares and contrasts findings generated from claims of different but overlapping payer populations. **Methods:** Outpatient claims data from 2003-13 Medicare and a large private payer were used to construct colorectal cancer provider networks where edges between providers correspond to the number of shared patients. Payer-specific network and provider statistics were compared. Network metrics on the private network were compared to distributions of subsampled Medicare networks to identify statistical differences controlling for patient numbers. The study was IRB approved. **Results:** 1735 surgeons and medical oncologists were identified from Medicare and 1321 from private claims with 1163 appearing in both. Across networks, there were 33164 pairs of providers connected by at least one patient. 4835 (14.6%) pairs appeared only in the private network, while 18218 (54.9%) appeared only in Medicare. Average volume for surgeons and medical oncologists was similar between networks (R^2 = .85), but 24.5% of providers' volume rank differed by at least one quintile group between payers. Likewise, average clustering coefficients were similar in magnitude across payers (.51 vs .53), but many providers had vastly different values in the two networks. Most of the same clusters/communities of providers were detected in both networks. However, there were two cases in which the combined network detected distinct communities of providers that Medicare alone missed. **Conclusions:** Provider networks constructed from Medicare claims alone differ from networks constructed from other large payers. Researchers should be cautious extrapolating findings from networks constructed from a single payer to other contexts. For example, this study brings into question whether Medicare data alone can be used to accurately quantify patient volume of any individual provider.

6524 Poster Session (Board #350), Sat, 1:15 PM-4:45 PM

Trends related to program participation, implementation, best practices, challenges and resource requests among oncology care model (OCM) participants. *First Author: Daniel Gutkin, Amgen, Thousand Oaks, CA*

Background: The OCM is an alternative payment model (APM), developed by the Center for Medicare & Medicaid Innovation (CMMI) to improve the quality of oncology care. The Patient Outcomes & Policy Regional Executive (POPRE) team was tasked with engaging OCM participants to understand their unique challenges and develop appropriate resources to address their concerns. We examined trends related to participation, implementation, best practices, and resource requests among OCM participants. **Methods:** Between May and October 2017, the POPRE team conducted interviews at 57 OCM sites, including 30 community, 24 academic, and 3 payer-based accounts. Participants answered questions pertaining to their OCM processes, challenges and needs. **Results:** The top OCM provider challenges identified were data extraction/analysis, electronic medical record (EMR) integration, and cost of care estimates. Common data extraction/analysis difficulties included labor intensive data collection, entry, and abstraction. EMR integration gaps centered on risk adjustment factors, tumor staging, triage processes, supportive care/pain care plans, among others. Patient & provider education materials, tech/IT tools, and EMR integration tools were the three most common requests from OCM providers. Care coordination solutions, including utilization of pathways, innovative software tools for symptom monitoring, and triage/virtual consults, were among the top OCM Best Practices shared. EMR integration solutions included the adoption of well-known pathways, care and survivorship plans, and symptom screening/risk stratification tools. **Conclusions:** The majority of participants interviewed experienced difficulties with OCM requirements. Most of those challenges were related to data extraction/analysis and EMR integration issues; however many practices utilized those gaps to innovate, adapt, and request appropriate resources to address these concerns. Resolving common data and solving EMR integration challenges may help improve other critical OCM practice transformations, thus enhancing patient care, providers' engagement and overall program's viability.

6525 Poster Session (Board #351), Sat, 1:15 PM-4:45 PM

Value-based healthcare delivery models in oncology: A systematic review. *First Author: Emeline Aviki, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: With the rising cost of health care in the US has come increasing emphasis on optimizing value. Value-based healthcare delivery models are designed to maximize outcomes and minimize costs through changes in care delivery. Little is known about the impact of value-based interventions in cancer care. We performed a systematic review to describe the landscape of value-based interventions in cancer. **Methods:** This review included peer-reviewed and non peer-reviewed articles describing value-based interventions in cancer care. We identified articles through structured searches of PubMed/MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Clinical Trials since passage of the Affordable Care Act. We used the Effective Public Health Practice Project Quality Assessment Tool to evaluate the quality of studies reporting results. **Results:** Twenty-three articles describing 22 unique value-based interventions in cancer met inclusion criteria. Of the 23 articles, 12 were published in the peer-reviewed literature, and 13 reported outcomes and were assessed for quality. All were of moderate (n = 6, 46%) or weak (n = 7, 54%) quality. The 22 value-based interventions included 6 (27%) bundled payments, 4 (18%) accountable care organizations (ACOs), 9 (41%) patient-centered medical homes, and 3 (14%) other interventions. Most interventions were conducted in community settings (n = 16 of 21, 76%) and performed through commercial insurance contracts (n = 13 of 15, 87%), including all bundled payments and all cancer-specific ACOs. Of the 12 interventions with outcomes reported, the majority (n = 7, 58%) improved value, 4 had no impact on value, and 1 reduced value, though this effect was no longer significant after 2-3 years. **Conclusions:** This systematic review of value-based healthcare delivery models in cancer care found that reports of outcomes are often lacking and are of variable quality when available. Despite promising early signs, the efficacy of these interventions in cancer remains unclear. Moving forward, rigorous evaluations and increased outcome reporting will enable continued innovation to achieve the highest value of care for cancer patients.

6526 Poster Session (Board #352), Sat, 1:15 PM-4:45 PM

Treatment patterns among patients diagnosed with stage IV cancers who died within one month of diagnosis. *First Author: Helmneh M. Sineshaw, American Cancer Society, Atlanta, GA*

Background: Little is known about the factors associated with treatment in patients diagnosed with metastatic cancers and who die soon after diagnosis. We examined patterns of treatment in patients diagnosed with metastatic lung, colorectal, breast, and pancreatic cancer who died within one month of diagnosis. **Methods:** Using the National Cancer Data Base, we identified de novo stage IV lung, colorectal, breast, and pancreatic cancer patients ages $\geq$18 years and diagnosed between 2004-2014 who died within one month of diagnosis. We used descriptive analyses to calculate percentages and multivariable logistic regression analyses to generate adjusted odds ratios for receipt of specific types of treatment. **Results:** Among 97,884 patients, 66% had lung, 18% pancreatic, 12% colorectal, and 3.7% breast cancer. Surgery was least common in pancreatic (0.4%) and most common in colorectal (28.8%) cancer. Rates of chemotherapy ranged from 5.8% in colorectal to 11.3% in lung and breast cancer. Rates of radiation ranged from 1.2% in pancreatic to 18.7% in lung cancer. Endocrine therapy was initiated for 23.7% of patients with hormone receptor-positive breast cancer. Over the study period, surgery for colorectal and breast cancer, chemotherapy and radiation treatment for lung cancer, and chemotherapy for breast and pancreatic cancer progressively declined (P trend < 0.01). Age, insurance, and facility type were strongly associated with receipt of treatment across most cancer types. Uninsured patients had 43% lower odds of receiving surgery for colorectal cancer, 34% lower odds of initiating chemotherapy for lung cancer, and 47% lower odds of initiating chemotherapy for breast cancer compared with their privately insured counterparts. Compared with patients with lung cancer treated at NCI-designated cancer centers, those treated at community cancer centers had 48% lower odds of initiating radiation. **Conclusions:** Treatment of patients diagnosed with imminently fatal metastatic cancer (death within one month of diagnosis) varied markedly by cancer type and patient/facility characteristics. More research is needed to identify patients with imminently fatal metastatic cancer who would benefit from early treatment.

6527 Poster Session (Board #353), Sat, 1:15 PM-4:45 PM

Results from a pilot of an innovative 4R Cancer Care Delivery Model: Impact on patient self-management. *First Author: Julia Rachel Trosman, Center for Business Models in Healthcare, Chicago, IL*

Background: Under the "NCI ASCO Teams" Project, we proposed a 4R Model of teamwork and patient self-management (pSM) (Trosman JOP '16). 4R is Right Info / Care / Patient / Time. It enables patient (pt) and care team to manage interdependent care along the care continuum with an innovative multimodality personalized 4R Care Project Plan. We piloted 4R at 3 centers (academic, community, safety net) and assessed its impact on pSM. **Methods:** 4R Plans were administered to breast cancer pts stage 0-III Sep '16 – Aug '17 (4R cohort). We surveyed the 4R cohort and a comparable historical cohort of pts who received care pre-4R, Jun '15 – May '16 (control). We used simple frequencies and Fisher's exact test in analyses. **Results:** Survey response rates: 68%, 185/271 (4R cohort); 47%, 241/410 (control). 75% of 4R respondents reported 4R Plans very useful / useful in overall understanding and organizing their care; 68% found 4R's novel "project" component, very useful / useful in managing timing & sequencing of interdependent care. Care complexity impacted 4R usefulness: 67% of pts who received $>$ 6 care services found 4R very useful / useful vs. 47% of pts who received $<$ = 6 services, p = .01. Pts with lower care complexity suggested how to make 4R more useful to them, eg focus on endocrine therapy. Table compares pSM metrics in the 4R and control cohort. Care complexity was a significant factor of feeling overwhelmed for pts in the control cohort (51% of pts receiving $>$ 6 care services felt overwhelmed vs. 31% of pts receiving $<$ = 6 services, p = .02), but not a significant factor for pts in the 4R cohort (30% vs. 28%, p = .9). **Conclusions:** The 4R model significantly improved pt self-management in early breast cancer and reduced the impact of care complexity on pts, but provider factors of pSM need improvement. A 4R pilot at additional 12 cancer centers across the U.S. is in progress.

Aspect of pSM	%, 4R cohort, N = 185	%, Historical control cohort, N = 241	P value
Know stage of your cancer	93	80	.0001
Care plan clear / very clear	84	67	.0001
Able to manage own care well / very well	78	69	.05
During care, seldom / never overwhelmed, not in control of your care	71	58	.008
Care coordination by providers to support the patient	72%	69%	.5
Having a "go to" clinician to support the patient	76%	78%	.7

6528 Poster Session (Board #354), Sat, 1:15 PM-4:45 PM

Defining survivorship and surveillance with evidence. *First Author: Robert Dood, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Survivorship involves a multidisciplinary approach to surveillance and management of comorbidities and secondary cancers, however timing is based on arbitrary 5 year cutoffs. Here, we used a novel method analyzing annualized mortality rates to systematically define these cut-offs for transitions of care. **Methods:** The SEER database was queried for survival data on patients aged 18-100 years with any incident diagnosis of any cancer, grouped by ICD-O-3 tumor type. Excess mortality hazard, calculated as an annualized mortality risk above the baseline population was plotted over time. The time this hazard took to stabilize defined a high-risk period. The % morality elevation above age/sex-matched controls in the latter low-risk stable period was reported as the mortality gap. **Results:** Over 2.3 million patients with 68 different primary tumor types were evaluated. High risk surveillance periods ranged from 1 month to 21 years. High risk period durations ranged from under 1 year (breast, prostate, lip, ocular, and parathyroid cancers) up to 19 years (unspecified gastrointestinal cancers). Cluster analysis produced 6 groups. Subanalyses of selected tumor types revealed that stratifying on stage and histologic type can change the risk cluster and guidance for care. **Conclusions:** These findings indicate that a standardized 5 year surveillance period is both inadequate for some cancers while excessive for others. High risk cancers require the most resources with the longest high-risk period, highest persistent baseline mortality risk, and longest period of primary cancer mortality, all arguing for longer follow-up with an oncologist.

Medians by cluster (5-95 %ile).

Cluster	High-risk period, yrs	Mortality gap, %	Cancer types
1	2.5 (0.0-5.0)	1.4% (0.3-2.4)	Prostate, Breast, Cervix, Skin, Uterine corpus, Thyroid
2	7.5 (5.0-12.6)	2.9% (1.4-4.8)	Hematologic, Ovary, Gum/mouth, Tongue, Oropharynx
3	5.0 (4.0-8.0)	2.4% (0.9-4.5)	Colon, Bladder, Lymph node, Kidney, Rectum, Larynx
4	6.5 (5.3-10.8)	3.4% (2.0-8.5)	Hypopharynx, Pharynx, Ill-defined, Uterine NOS
5	9.0 (6.4-16.9)	2.4% (1.1-6.0)	Lung/bronchus, stomach, Brain/CNS, Esophagus
6	12.0 (9.3-12.9)	3.0% (1.1-4.2)	Intrahepatic bile ducts, Pleura, Pancreas

6529 Poster Session (Board #355), Sat, 1:15 PM-4:45 PM

Use of next-generation sequencing tests to guide cancer treatment: Results from a survey of U.S. oncologists. *First Author: Andrew N. Freedman, NCI, Rockville, MD*

Background: The proliferation of next-generation sequencing (NGS) tests provides an opportunity to advance oncology care. However, there are limited data about when and how NGS tests are used and the extent to which test results inform clinical care. **Methods:** Between February and May 2017, a survey developed by the National Cancer Institute and American Cancer Society was mailed to a nationally-representative sample of oncologists; 1281 responded, reflecting a 38% participation rate. Oncologists reported their use of NGS tests over the past year, including their use in different clinical scenarios. We restricted our analysis to the 1123 respondents who treated patients with solid tumors. Weighted percentages were used to describe NGS test use and its association with oncologists' demographic and practice characteristics. **Results:** Overall, 63% of oncologists reported using NGS tests to guide treatment decisions. Among these oncologists, 36% used them "often" to guide treatment decisions for patients with advanced refractory disease, 29% to determine eligibility for clinical trials and 19% to decide whether to use FDA-approved drugs off-label. For 28% of oncologists, NGS test results informed treatment recommendations "often," 53% reported "sometimes," and 19% of oncologists reported that results "never" or "rarely" informed treatment recommendations. Oncologists $<$ 50 years of age, practicing in an urban or suburban setting, treating patients at an academic center, holding a faculty appointment or receiving genomics training were more likely to use NGS tests. Over 50% of all oncologists reported that one or more patients presented with NGS test results from a commercially-available company they had not ordered. **Conclusions:** Most U.S. oncologists use NGS tests for their patients with solid tumors to inform treatment options for those with advanced cancer, and to identify clinical trials and/or approved drugs for off-label use. Among oncologist using NGS tests, over 80% reported that results informed their treatment recommendations either sometimes or often. Research is needed to more clearly establish the clinical utility of NGS tests and to inform clinical guidelines for their use in practice.

6530 Poster Session (Board #356), Sat, 1:15 PM-4:45 PM

Patient predictive factors for clinical trial participation. *First Author: Adrianne Rose Mallen, University of South Florida/Moffitt Cancer Center Gynecologic Oncology Fellowshi, Tampa, FL*

Background: Clinical trials (CT) in cancer research are considered the gold standard in evaluating efficacy of a new treatment and quite, literally, save lives. On average, only 3% of adult patients with cancer enroll in CT. Our primary aim was to assess patient predictive factors for CT participation. Our secondary aim was to assess overall survival for patients enrolled in CT versus no CT (NCT). Methods: A 14-year retrospective chart review was conducted for analysis of sociodemographic, clinicopathologic and treatment characteristics of 558 advanced stage epithelial ovarian cancer patients who were treated at a single-institution NCI-CCC at some point in their treatment course. **Results:** A total of 399/558 patients (71.5%) did not participate (NCT) versus 160/558 (28.5%) who did at some point in their treatment course (CT). Overall, 238/558 (43%) had CT discussion with their provider. The majority, 126/160 (78.75%) participated in CT at time of recurrence, 20/160 (12.5%) at time of adjuvant chemotherapy only and 14/160 (8.75%) for both adjuvant therapy and recurrence. Patients were well-matched in terms of disease characteristics. Younger age (58.04 in CT vs 63.07 in NCT, $p < 0.0001$), type of insurance ($p < 0.0001$), receipt of neoadjuvant chemo ($p = 0.014$), receipt of intraperitoneal chemo ($p = 0.00024$) and gynecologic oncologist as adjuvant chemo provider ($p = 0.005$) were also statistically significant patient factors associated with greater CT participation. Race ($p = 0.02$), educational level ($p = 0.095$), religion ($p = 0.39$), marital status ($p = 0.66$), distanced traveled for care ($p = 0.99$), debulking status ($p = 0.72$) and platinum sensitivity ($p = 0.13$) were not statistically significant patient factors. After adjusting for clinical factors associated with OS, women who participation in a clinical trial had significantly better OS (HR = 0.698, 95% CI (.544, 0.896), $p = 0.005$). **Conclusions:** Encouragement for clinical trials appears to be warranted. Improved survival was significant for CT patients and is further justification for offering the gold standard of treatment at our NCI-CCC. Understanding of patient predictive factors warrants further exploration so we can overcome barriers to patient enrollment in CT.

6531 Poster Session (Board #357), Sat, 1:15 PM-4:45 PM

Factors associated with follow-up physician visits among women with early stage breast cancer. *First Author: Farah Quyyumi, Columbia University Medical Center, New York, NY*

Background: In patients with early stage breast cancer (BC), follow-up guidelines vary widely among national organizations. ASCO recommends clinical examination every 3-6 months for 3 years, every 6-12 months for the next 2 years, and then annually. We sought to evaluate patterns and predictors of provider follow-up care within the first five years following diagnosis. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked dataset, we evaluated patients diagnosed with stage I-II BC who underwent lumpectomy from 2002-2007 with follow-up to 2012. Patients who died in the 5 years following diagnosis were excluded. We defined discontinuation of follow-up care as $>$ 12 months without a visit claim from either a surgeon, medical oncologist (MO) or radiation oncologist (RO). We performed a multivariate logistic regression analysis to determine factors associated with discontinuation. Patients were censored if a new cancer was diagnosed. **Results:** A total of 30,053 BC patients were included in the analysis. In addition to the surgeon, 85.8% saw a MO, 71.9% saw a RO, and 65.8% saw all 3 providers in the first year. The mean number of total visit claims for years 2-5 were 4.2, 3.1, 2.5 and 2.1, respectively. During the 5 years, 6,302 (21.0%) patients discontinued follow-up visits. Discontinuation increased with increasing age. Women with a higher stage cancer were less likely to discontinue follow-up (OR 0.78, 95% CI 0.73-0.83). Patients with a low grade tumor were more likely to discontinue follow-up compared to those with a high grade cancer (OR 1.09, 95% CI 1.02-1.18). For every year of diagnosis, patients were 3% less likely to discontinue seeing all three physicians. Hormone status, race, SES and marital status were not associated with discontinuation of follow-up visits. **Conclusions:** Clinical practice guidelines for surveillance of BC after diagnosis are based on expert opinion and have an unclear effect on outcomes. Coordination of follow-up care between oncology specialists may reduce discontinuation rates and increase clinical efficiency. More research is needed to determine the optimal follow-up for maintaining adherence to therapy, reducing over-testing and decreasing cost.

6532 Poster Session (Board #358), Sat, 1:15 PM-4:45 PM

Early discharge after induction chemotherapy for acute myeloid leukemia: Safety outcomes and hospital readmissions. *First Author: Nikita V. Baclig, University of Washington, Seattle, WA*

Background: Adults with acute myeloid leukemia (AML) typically remain hospitalized after induction chemotherapy for the duration of pancytopenia. Several studies have suggested that outpatient management following completion of chemotherapy is safe and associated with lower resource utilization. This has become standard practice at our institution if logistics allow. Here, we examine outcomes of adults $\geq$18 years of age with newly-diagnosed AML (acute promyelocytic leukemia excluded) or high-grade myeloid neoplasms (i.e. $\geq$10% blasts) who received AML-like induction chemotherapy with a regimen as or more intense than 7+3 between 8/2014 and 7/2017 and who were discharged early (ED) or remained hospitalized based on individual provider assessment. **Methods:** Patients were identified via institutional electronic medical records. Clinical information was collected through manual patient record review from the day after chemotherapy until count recovery (absolute neutrophil count $\geq 0.5\times10^9$/L and self-sustained platelet count $\geq 20\times10^9$/L), receipt of further chemotherapy, transfer to a different institution, or completion of 45 days on study. Patients were considered ED if discharge occurred within 3 calendar days of study start and control if not. **Results:** 260 patients (median: 61 [range 20-90] years) underwent induction chemotherapy, 168 of whom (64.6%) were ED. Age and gender distribution were similar between ED and control patients. Mean time on study was similar between ED and controls (25.6 vs. 25.2 days; $p = 0.73$). There was no difference in death rate (5.6% vs. 4.3%; $p = 0.59$), rate of febrile neutropenia (69.6% vs. 67.4%; $p = 0.71$), or proportion of patients requiring ICU-level care (8.9% vs. 15.2%, $p = 0.12$) between groups during the study period. In the ED group, 71.4% were readmitted with 0.95 readmissions on average per patient. Mean length of time between discharge and readmission among ED patients was 7.2 days. Overall, ED patients spent fewer days in the hospital than control patients (7.1 vs. 16.0; $p < 0.0001$). **Conclusions:** ED appears safe outside a clinical trial setting. Despite high readmission rates among ED patients, total hospital stay was shorter than for controls.

6533 Poster Session (Board #359), Sat, 1:15 PM-4:45 PM

Financial toxicity in patients with colorectal cancer and neuroendocrine tumors. *First Author: Leonidas Apostolidis, Department of Medical Oncology, National Center for Tumor Diseases, Heidelberg University Hospital, Heidelberg, Germany*

Background: Financial toxicity of cancer has so far been discussed primarily in the US health care system and has been shown to be associated with higher morbidity and mortality. In Germany with its third-party paid health care system the socio-economic impact of cancer is poorly understood. This study aims to provide data on financial consequences of a colorectal cancer (CRC) or neuroendocrine tumor (NET) diagnosis on patients' economic situation and psychosocial outcomes. **Methods:** This prospective study recruited 247 patients (n = 125 CRC / n = 122 NET) from November 2016 to March 2017 at the National Center for Tumor Diseases, Heidelberg University Hospital. They completed a survey on income, cancer-related out-of-pocket costs, distress (DT) and quality of life (EORTC-LQ). **Results:** Overall, 80.6 % (n = 199) stated to have higher out-of-pocket costs, and 37.2 % (n = 92) reported income loss as a sequel to their disease. While monthly out-of-pocket costs did not exceed 200 € in 76.9 % of affected patients, 44.6 % of those with income losses report losing more than 800 € per month. A multiple regression analysis showed effects of economic deteriorations on patient's quality of life and distress depending on the type of health insurance: high financial loss relative to income was significantly associated with a lower estimation of patient's quality of life (p = 0.0009) and more distress (p = 0.0037). Patients with private health insurance indicate better quality of life (p = 0.0134) and less distress (p = 0.0005) compared to those with statutory health insurance. **Conclusions:** Distress and reduced quality of life due to financial problems intensify the burden that already results from a cancer diagnosis. As many patients have to face financial loss and most are insured under the statutory health insurance scheme, there is a need for targeted support measures at the individual and system level in Germany.

6534 Poster Session (Board #360), Sat, 1:15 PM-4:45 PM

Burdensome end-of-life (EOL) transitions among frail older adults with advanced cancer. *First Author: Daniel E Lage, Massachusetts General Hospital, Boston, MA*

Background: Older adults with advanced cancer residing in nursing homes (NHs) are a vulnerable population that has not been well studied in terms of clinical needs and health care utilization. We sought to describe the clinical characteristics of these patients and examine their burdensome care transitions at the EOL. **Methods:** We conducted a retrospective analysis of deceased older adults (> 65 yrs) with advanced solid tumors (defined using Medicare claims, per prior literature) who resided in U.S. NHs and enrolled in Medicare fee-for-service (2008-2009). Medicare claims data were linked with geriatric assessments as part of the Minimum Data Set. Clinical characteristics, including comorbidities, pain scores, activities of daily living (ADLs) and cognition, were measured within 90 days of death. Using Medicare claims and per prior studies on end of life health care utilization, we defined a burdensome transition as two or more hospitalizations or an intensive care unit (ICU) admission in the last 90 days of life. **Results:** We included 34,670 patients with advanced solid tumors. Many residents had comorbid congestive heart failure (CHF) (29.3%), chronic obstructive pulmonary disease (COPD) (34.1%), and diabetes (35.0%). Over half (53.8%) had moderate or severe cognitive impairment; 66.5% were dependent in all ADLs, and 21.1% experienced daily pain. Only 55.4% of patients used hospice. 36.0% of patients experienced a burdensome transition at the EOL, and burdensome transitions were more common for patients who did not receive hospice (45.3% vs. 28.6%, $p < 0.01$). In adjusted analyses, the following characteristics were associated with a higher risk of a burdensome transition at the EOL: female sex (OR 1.2, $P < 0.001$), CHF (OR 1.56, $P < 0.001$), COPD (OR 1.3, $P < 0.001$), diabetes (OR 1.3, $P < 0.001$), full dependence in ADLs (OR 1.9, $P < 0.001$), and receipt of chemotherapy in the last 90 days of life (OR 1.7, $P < 0.001$). **Conclusions:** Although NH residents with advanced cancer have substantial comorbidities, cognitive deficits, and functional impairments, over a third experienced a burdensome care transition at the EOL. Interventions are critically needed to reduce burdensome transitions at EOL in this vulnerable population.

6535 Poster Session (Board #361), Sat, 1:15 PM-4:45 PM

Patient-reported satisfaction with multidisciplinary (MD) v serial care (SC) for lung cancer. *First Author: Kenneth Daniel Ward, Division of Social and Behavioral Sciences, School of Public Health, University of Memphis, Memphis, TN*

Background: Coordinated MD lung cancer care, with all key specialists concurrently providing input to develop a consensus care plan with patients and their caregivers, is much-advocated over the usual SC model but lacks rigorous evaluation. **Methods:** Prospective comparative effectiveness trial enrolled newly-diagnosed lung cancer patients receiving MD or SC within the same US healthcare system. At baseline, 3 and 6 months, patients completed several satisfaction measures from the Consumer Assessment of Healthcare Providers and Systems, and the National Health Interview Survey 'Perceived Financial Burden of Care' instrument. All Group (MD v SC), time (baseline, 3, 6 months), and group by time interactions were analyzed in mixed linear models. Associations were adjusted for insurance, race, clinical stage, and ECOG performance status. **Results:** The 456 patients (159 MD, 297 SC) were similar in sex and health insurance. The MD cohort was slightly older (69 vs. 66) and had more racial minorities (37% vs. 29%). Statistically significant group by time interactions, indicating greater improvement over time for MD, were observed for satisfaction with treatment plan (p = .0036) and quality of care received from the whole care team (p = .0377). However, perceived financial burden of care increased slightly over time for MD but decreased slightly for SC (p = .0352). Collapsed across time, MD patients were more likely to perceive their cancer care to be better than that received by other patients (p = .0025). Collapsed across treatment group, depression increased significantly from baseline to 3 months (p = .0118), and improvements over time occurred for satisfaction with length of time to diagnosis, length of time to complete treatment, and communication from physicians, nurses, and about disease-specific information. **Conclusions:** Compared with SC, MD patients perceived their care to be better than that received by other lung cancer patients, and had greater improvements over the course of treatment in satisfaction with their treatment plan and care team. These positive patient-reported outcomes occurred despite slightly greater perceived financial burden of care. Clinical trial information: NCT02123797.

6536 Poster Session (Board #362), Sat, 1:15 PM-4:45 PM

Outcomes of embedded palliative care outpatients consults on timing of palliative care access, symptoms, and end-of-life quality indicators among advanced non-small cell lung cancer patients. *First Author: Sriram Yennu, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are no studies comparing the outcomes of embedded consults (EPC) as compared to independent outpatient palliative care consults (PC).Our aim was to determine the timing of palliative care access, symptoms and EOL outcomes of advanced non-small cell lung cancer patients referred to EPC as compared to those referred to PC. **Methods:** We retrospectively reviewed a random sample of EPC (Aug, 2012 - Jun, 2013) and PC consults (Jan, 2009 –Jul, 2012) at MD Anderson Cancer Center. Baseline features, symptoms (ESAS), EOL quality outcomes (intensive care unit deaths, admissions, emergency center visits , and hospitalizations and length of stay in the last 30 days before death; cancer treatments 14 days before death; hospice discussions and referrals; do not resuscitate order at first follow-up; advanced care planning (ACP) discussions, and completion of advanced directives), time from referral to first consult, ACP date to death, and overall survival from consult to death were retrieved. **Results:** 340 were evaluable (EPC = 147). At baseline, mean ECOG (2.2 vs 1.9, $p < .001$), and median pain (6 vs 5, p = .038) were higher in EPC. Time from referral to first consult was shorter (median 0 vs 7 days, $p < .001$) and dyspnea was better in EPC at follow-up (-1 vs 0, p = .039). A higher proportion in EPC (77% vs 58%, $p < .001$) had ACP discussions and these occurred earlier (median 4 vs 1 month before death, $p < .001$). No other significant differences in symptoms or EOL outcomes were found. **Conclusions:** EPC consults at referral had earlier access and worse pain and performance status. EPC was not associated with significant improvement in symptoms or EOL outcomes except for better dyspnea control, and more frequent as well as earlier ACP discussions. Further research is needed.

6537 Poster Session (Board #363), Sat, 1:15 PM-4:45 PM

Diffusion of innovation in oncology: A case study of immuno-oncology (IO) adoption for advanced non-small lung cancer (aNSCLC) patients across practices in the US. *First Author: Caroline Savage Bennette, Flatiron Health, New York, NY*

Background: IO agents are being adopted rapidly into clinical care; however, variation in speed and breadth of adoption across oncology practices remains unknown. Our objective was to evaluate adoption patterns in the treatment of aNSCLC and identify practice characteristics associated with adoption trajectories. **Methods:** 43,697 patients diagnosed with aNSCLC from Jan'11-Dec'17 were obtained from the Flatiron Health electronic health record-derived database, a national sample of academic and community practices. We estimated the proportion treated each month with IO (nivolumab, pembrolizumab or atezolizumab) versus other therapies from time of first IO approval (Mar'15) through Dec'17 in 123 practices that treated aNSCLC patients during this time. We used k-means clustering to identify patterns of IO adoption. Multivariable logistic regression models were used to adjust for differences in case-mix and evaluate association of practice size, location, and Quality Oncology Practice Initiative (QOPI) certification program with IO adoption. **Results:** We identified 4 distinct groups of practices based on trajectories that differed in speed and extent of IO adoption (Table). 17% of practices adopted IO rapidly and extensively; 28% were slower and more limited in their adoption; 24% initially had limited IO use, but adoption accelerated rapidly after 18 months; 32% initially adopted rapidly, but slowed markedly after 1 year. In multivariable analyses, we found no significant association between a practice's size, location, or QOPI certification and IO adoption trajectory. **Conclusions:** There is significant variability in adoption of IO therapy by oncology practices. Further research is needed to characterize drivers of this variation at the physician level and its impact on patient outcomes. Understanding variability in the diffusion of new innovations could guide development of targeted educational interventions to optimize use of new effective therapies.

	Rapid & extensive adopters, N = 21	Slower & limited adopters, N = 34	Later adopters, N = 29	Decelerating adopters, N = 39
% IO use in Dec'15	19.8	10.0	10.0	20.8
% IO use in Dec'17	50.7	30.8	48.0	36.6

6538 Poster Session (Board #364), Sat, 1:15 PM-4:45 PM

A multidisciplinary toxicity team for cancer immunotherapy-related adverse events. *First Author: Jarushka Naidoo, Johns Hopkins Kimmel Comprehensive Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy, Baltimore, MD*

Background: Immune checkpoint inhibitors (ICI) cause immune-related adverse events (irAEs). The spectrum of irAEs requiring referral to non-oncology specialists has not been well described. We established an immune-related toxicity (IR-Tox) team of oncology (n = 8) and medical subspecialists (n = 20), to support multidisciplinary irAE diagnosis and management. **Methods:** Patients (pts) treated with ICIs were electronically referred to the IR-Tox team between 01/2017-03/2018. IR-Tox team met monthly to discuss complex irAEs, and identify areas of clinical need. Pt demographics, treatment, and irAE details were collected. Pt features and irAE associations were analyzed using Chi-square tests. **Results:** The IR-Tox Team received 92 referrals for 80 pts (outpt: 61%, inpt: 39%). Median age was 65 years (range: 21-91), 55% were male, and 14% had prior autoimmune disease. Pts most commonly had non-small cell lung cancer (35%), melanoma (19%), or gynecologic malignancies (10%). Pts received ICI monotherapy (56%) or combination immunotherapy (44%), as standard-of-care (46%) or on clinical trials (54%). Referrals related to diagnosis (32%), management (11%), or both (51%) were received from faculty (68%), fellows (12%), and nurses (20%). Referrals were for suspected irAE (90%), pre-ICI assessment in known autoimmune disease (9%), or ICI re-challenge (1%). Sixty-three irAEs were confirmed (CTCAE grade 1 = 19%; 2 = 43%; 3+ = 38%), and 26 patients developed $>$ 1 irAE (2 irAEs = 19, 3 irAEs = 7). IrAEs included pneumonitis (22%), arthritis (17%), dermatitis (13%), colitis/diarrhea (13%), idiopathic thrombocytopenia purpura (5%) hepatitis (5%) and thyroid dysfunction (5%). A new irAE of bony inflammation was identified (n = 2). Grade 3+ irAEs (p = 0.04) and colitis/diarrhea (p = 0.01) were more likely with combination immunotherapy. Medical specialty input was obtained in 85% of pts, and 35% required an invasive procedure for irAE diagnosis or management. **Conclusions:** Creation of an IR-Tox Team facilitated identification and management of complex irAEs. This new model provides a valuable forum to identify educational/service needs, manage multi-system irAEs, identify new irAEs, stratify irAE risk, and establish research collaborations.

6539 Poster Session (Board #365), Sat, 1:15 PM-4:45 PM

Reportable actionability versus pragmatic actionability: Implementing precision medicine at three large health systems. *First Author: Michael A. Thompson, Aurora Health Care, Delafield, WI*

Background: Precision medicine (PM) molecular panel (MP) testing report actionable findings with associated targeted therapies (including immunotherapies). However, these actionable findings "reported actionability" by molecular testing companies are often not realized as "pragmatic actionability" in the real world setting. We explored the concordance among PM MP therapy recommendations and subsequent drug treatment orders by clinicians at Aurora Health Care (AHC), Henry Ford Health System (HFHS), and Hoag Memorial Hospital Presbyterian (HMHP). **Methods:** Structured clinical, genomic report data, and treatment orders were obtained from the Syapse database. At AHC, HFHS, and HMHP, we identified 996 MP reports from 748 patients who received testing between 2014 and 2018. **Results:** 713 MP reports had "reported actionable" (positive) treatment recommendations and a subsequent treatment order across all 3 health systems. 24.4% (174/713) of MP reports were followed by a treatment order that matched to at least one reported actionable treatment. The translation from a MP-reported actionable finding to a prescribed treatment order was 28.1% (105/374) at AHC, 20.9% (9/43) at HFHS, and 20.3% (60/296) at HMHP, which has borderline statistical significance (p = 0.0563). Of the 713 MP reports analyzed, there was an average of 7.8 therapy recommendations per MP report. There were no significant rate differences in actionability of individual drug recommendations between the two molecular testing vendors examined. We did not examine the actionability of MP report recommendations for investigational agents. **Conclusions:** Of all 996 MP reports in the initial sample, only 17.5% resulted in a treatment order which matched a MP report recommendation. The translation of reported actionability to pragmatic actionability was consistent across all 3 health systems. This may reflect different definitions of "actionable" between molecular testing companies and clinicians as well as patient performance status changes over time, insurance coverage for off-label use, or referral to a clinical trial. Further research is warranted to understand the issues involved.

6540 Poster Session (Board #366), Sat, 1:15 PM-4:45 PM

Patient comorbid conditions and cancer clinical trial participation. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The American Society of Clinical Oncology (ASCO) recently recommended modernizing criteria related to comorbid conditions routinely used to exclude patients from clinical trials. We investigated how baseline comorbid conditions influence clinical-trial decision making and trial participation. We also modeled how reducing major trial comorbidity exclusion criteria might impact participation, to provide a benchmark for evaluation of the ASCO recommendations. **Methods:** Data were from a large national web-based survey of 5,499 cancer patients in the cancer treatment-decision-making process. Self-reported data on 18 comorbid conditions were collected. We examined how individual and combinations of comorbidities – using the "best" subset method – influenced patterns of trial discussions, offers, and participation. We also simulated how trial participation rates would change if individual and combinations of comorbidity exclusion criteria were removed. Logistic regression was used. Multivariable regression included adjustment for important demographic and socioeconomic variables. **Results:** Most patients (66%) had $\geq$1 baseline comorbidities. The most common comorbid condition was hypertension (35%). Hypertension, prior cancer, and hearing loss were most strongly and uniformly associated with outcomes; each increase in the number of these conditions (0 vs. 1 vs. $\geq$2) was associated with a decreased risk of trial discussions (11% lower, p = .02), trial offers (18% lower, p = .004), and trial participation (22% lower, p = .006). The removal of all comorbidity restrictions would generate an 18% relative increase in trial participation, or (if the overall participation rate is 5%) a 1% absolute increase. **Conclusions:** The presence of baseline comorbid conditions adversely impacts trial discussions, trial offers, and trial participation itself. Although the modernization of trial eligibility criteria will benefit many patients, this effort alone is unlikely to substantially increase trial participation rates overall.

6541 Poster Session (Board #367), Sat, 1:15 PM-4:45 PM

Cancer pain in the emergency department: A multicenter study of the Comprehensive Oncologic Emergencies Research Network. *First Author: Christopher John Coyne, University of California San Diego, San Diego, CA*

Background: Despite initiatives to improve cancer analgesia, patients with cancer frequently present to the emergency department (ED) with pain related issues. To our knowledge, no previous studies have investigated how the presence and severity of pain in cancer patients presenting to the ED may relate to morbidity and mortality. This study aims to investigate these associations. **Methods:** We conducted a multicenter prospective cohort study of patients with active cancer presenting to 18 EDs within the Comprehensive Oncologic Emergencies Research Network (CONCERN) between December 1st, 2016 and June 1st, 2017. We recorded initial, final and highest ED pain scores and used logistic regression to estimate their association with the following outcomes: 30-day mortality, 30-day ED revisits, and 30-day hospital readmissions. Pain was recoded into none (0), mild (1-3), moderate (4-6) and high (7-10). We also recorded demographics and ECOG scores. **Results:** We enrolled 1075 patients. The cohort was 52% female with a median age of 64. Approximately 70% of patients had pain, while only 48% of patients received an analgesic. 62% reported having home pain medications. The median highest pain score was 5, while the initial and final were 4 and 1, respectively. Of the patients who presented with pain, 64.8% reported improvement prior to discharge, 28.7% reported no change and 6.5% worsened. A high initial pain score was associated with increased 30-day mortality (OR 2.3, 95%CI 1.11-4.87). An ECOG score of 2 was associated with increased 30-day ED revisits (OR 1.7, 95%CI 1.14-2.5) and readmissions (OR 2.2, 95%CI 1.47-3.27). **Conclusions:** Pain remains a significant issue for cancer patients presenting to the ED, and was present in nearly 3/4 of our cohort. While not all patients received pain medications, we did note a low median final pain score. Severe pain on presentation appeared to be associated with increased mortality. This knowledge may aid physicians when determining ED disposition for those patients with high initial pain scores. An ECOG score of 2 appears to be associated with increased ED revisits and readmission, which may reflect a population in need of more aggressive outpatient symptom management.

6542 Poster Session (Board #368), Sat, 1:15 PM-4:45 PM

Practice transformation: Early impact of OCM on hospital admissions. *First Author: Molly Mendenhall, Oncology Hematology Care, Cincinnati, OH*

Background: The purpose of the Oncology Care Model is to improve quality and reduce cost through practice transformation. A foundational tenant is to reduce avoidable ER visits and hospitalizations. In anticipation of being an OCM participant, we instituted a multidimensional campaign designed to meet these objectives. **Methods:** Prior Actions: Established phone triage unit. After-hours and weekend call. Instituted weekend urgent care. Year One: Improved education provided by nurse navigators and APPs prior to start of treatment (OCM Treatment Planning visit). Implemented triage pathways: 38 symptom and 27 follow-up pathways (modified COME HOME, Barbara McAneny, M.D.). Proactive symptoms follow-up calls to help circumvent emergent admissions. Increased APP staffing to provide blocked time slots for same day patient visits w/o schedule disruptions. Initiated "Call Us Early – Call Us First" campaign. Incorporated verbal and/or written instructions at all patient touch points, emphasizing patient's responsibility to call before going to the emergency room. **Results:** Based on data from the Chronic Condition Warehouse, as provided by CMS, we were successful at reducing the acute care admissions rate by 16 percent. OCM patient survey scores improved. Readmissions (4.9 vs 5.6/100 pts), ER utilization (17 vs 18.6/100 pts), and Observation Stays (2.7 vs 3.6/100 pts) remained below Risk Adjusted National averages. **Conclusions:** By implementing a cost efficient, reproducible, and scalable campaign targeting ER avoidance and hospitalizations, we were able to decrease hospital admissions. Reported Medicare savings amounted to nearly $798,000 in inpatient cost per quarter over 1,600 patients.

	Baseline Jan '16 – Mar '16	Year One Jul '16 – Jun '17	Year One Benchmark (Risk Cohort)
Patients per Quarter	1,722	1,600	-
Mean Patient Risk Score	2.999	3.000	> 2.724
Admissions per 100 Patients, per Quarter	27.0	22.6	25.9
Cost per Admission Event	11,122	11,106	-
Inpatient Cost per Patient, per Quarter	3,003	2,505	-

6543 Poster Session (Board #369), Sat, 1:15 PM-4:45 PM

Cancer survival in the context of growing hospital participation in Medicare ACOs. *First Author: Stephen Matthew Schleicher, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Accountable Care Organizations (ACOs) represent one of the main policy-level interventions to improve healthcare quality. We investigated the trend of 1) hospital participation in ACOs over time and 2) cancer survival rates at participating hospitals. **Methods:** We searched public reporting websites of all Pioneer and Medicare Shared Savings Program (MSSP) ACOs. We matched ACO participant lists with the Dartmouth Hospital Atlas to identify participating hospitals. Five year mortality rates of patients with cancer were captured in 100% Medicare fee-for-service claims data from 2011 assessed at the hospital level, as previously described.[1] We calculated unadjusted cancer mortality rates for newly joining ACOs over time, and pooled estimates of survival comparing ACO to non-ACO control hospitals across hospital referral regions. **Results:** We identified 1,059 hospitals that participated in Medicare ACOs that joined through 2017. There was a trend towards increased hospital participation in ACOs, defined as the percentage of ACOs that included hospitals, over time (26.5% in 2012-2014 vs. 57.7% in 2015-2017). The five year overall survival rate for patients with cancer treated at new ACO hospitals was fairly stable over time (53.1% in 2012-2014 vs. 54.4% in 2015-2017). Similarly, there was no significant change in the odds of cancer survival for ACO vs. non-ACO hospitals over time. **Conclusions:** Despite growth in hospital participation within Medicare ACOs over time, the quality of cancer care at hospitals joining MSSP has remained stable.

	2012[2]	2013	2014	2015	2016	2017
New Medicare ACOs	146	106	119	89	100	99
Percent of ACOs including hospitals	22%	28%	28%	69%	59%	45%
Survival rate in new ACO hospitals	52.8%	53.3%	53.5%	54.4%	54.8%	53.9%
Odds ratio (95% confidence interval) for survival (ACO vs. non-ACO)	1.00 (0.98, 1.02)	0.97 (0.92, 1.02)	0.98 (0.94, 1.03)	1.01 (0.97, 1.05)	1.01 (0.98, 1.05)	1.01 (0.97, 1.05)

[1]Pfister DG, et al. JAMA Oncol, 2015; [2]Includes the 32 initial Pioneer ACOs.

6544 Poster Session (Board #370), Sat, 1:15 PM-4:45 PM

24-hour cancer clinic: An approach to same-day care. *First Author: Jonathan Thomas Kapke, Medical College of Wisconsin, Wauwatosa, WI*

Background: Managing healthcare delivery and optimizing the cost of care for cancer patients is a difficult task for healthcare systems. Cancer patients are at risk for complications of their disease and adverse effects of treatment that often require urgent medical care. The inability to access oncology specific care 24-hours a day can lead to increased use of the Emergency Department (ED), which is often associated with unnecessary diagnostic testing, high rates of hospital admission, low patient satisfaction and excessive cost. On 11/1/16, Froedtert & the Medical College of Wisconsin opened the 24-hour Cancer Clinic (24hCC). The 24hCC is staffed by oncology trained providers and offers around the clock access to patients for a variety of urgent care needs. In this study, we evaluated resource utilization, admission rates, patient satisfaction and cost for patients seen in the 24hCC compared to the ED. **Methods:** We analyzed de-identified data for patients seen in the 24hCC and the ED between 1/1/17 and 1/24/18 as part of a quality improvement project. Utilization was defined as the quantity of imaging, ECG and lab studies ordered. Cost was measured based on hospital charges. Patient satisfaction surveys were reviewed. **Results:** Prior to the 24hCC, oncology patients seeking urgent, same-day care were often directed to the ED. There were an average of 250 ED visits per month with an admission rate of 55%. During the time period analyzed, 897 patient visits were completed in the 24hCC and 1621 in the ED. There was 56%, 32% and 11% less imaging, ECG and lab utilization respectively for patients seen and discharged from the 24hCC compared to the ED. The admission rate from the 24hCC was 18% compared to 42% from the ED. The mean overall rating of care for the 24hCC was 97.5%, with a 89.7% top box score (9 or 10 on 1-10 scale). When comparing diagnostic charges in the 24hCC to the ED during the first six months of data collection, the median charge was $1554 less for discharged patients and $2269 less for admitted patients. **Conclusion:** Our data demonstrates that a 24-hour oncology specific clinic can provide same-day care that is associated with decreased utilization, less hospital admission, improved patient satisfaction and lower cost for selected non-emergent cancer patients.

6545 Poster Session (Board #371), Sat, 1:15 PM-4:45 PM

ECHO palliative care in Africa (ECHO-PACA): Improving access to quality palliative care. *First Author: Sriram Yennu, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There is limited access to quality Palliative Care (PC) for advanced cancer patients being treated in Sub Saharan Africa due to limited PC knowledge among health care providers in the region. The goal of this innovative project was to improve access by offering cost-effective training to these providers using Project ECHO (Extension for Community Healthcare Outcomes), an established telementoring and support program.Our aim was to evaluate feasibility, attitudes, knowledge, and efficacy of participants of ECHO-PACA to deliver PC. **Methods:** An interdisciplinary team at the UT MD Anderson Cancer Center, guided by PC providers in Sub Saharan Africa, developed a standardized curriculum based on PC needs in the region. Participants were then recruited and monthly telementoring sessions consisting of case presentations, discussions, and didactic lectures began in July 2016. Program participants included 14 clinics and teaching hospitals from Ghana, Kenya, Nigeria, South Africa, and Zambia, with sessions offering participants the ability to interact and learn new skills in PC. Participants were surveyed at the beginning, mid-point and end of the 16 month program to evaluate changes in self-perceived efficacy in pain assessment and management, Identification of signs/symptoms of imminent death, Identifying and addressing challenging communication issues related to end of life. **Results:** Median participation per session was 30. Median duration of monthly meetings was 90 minutes. 33 of 40 initial participants (83%) completed the survey. There was significant improvement in appropriate use of non-opioid analgesics for persistent pain ($p = .03$), titrating opioids to optimize pain control ($p = .03$), Identification of signs/symptoms of imminent death ($p = .05$), and Identifying and addressing challenging communication issues related to end of life ($p = .02$). **Conclusions:** ECHO-PACA was a feasible, cost effective, pragmatic approach to disseminate PC knowledge without the need for travel, which has the potential to increase access to quality PC through enhancing the skills of providers in resource challenged areas of Sub Saharan Africa. Further studies are needed to evaluate ECHO-PACA impact on patient outcomes.

6546 Poster Session (Board #372), Sat, 1:15 PM-4:45 PM

Do accountable care organizations impact prostate cancer screening? *First Author: Quoc-Dien Trinh, Brigham and Women's Hospital/ Harvard Medical School, Boston, MA*

Background: Accountable care organizations (ACO) are an alternative payment model designed to incentivize efficient, high value care. In this model, groups of providers are reimbursed together, with incentives for high-value, coordinated care. Prostate cancer screening is a service with large variations in use and questionable value—especially in men over 70. We analyzed trends in PSA screening and biopsies of American men depending on whether their providers joined ACOs. **Methods:** We relied on Medicare claims data to identify men whose primary care providers joined ACOs between 2010 and 2014. We examined whether trends in PSA and biopsy rates were different in men with ACO-affiliated providers versus those with non-ACO affiliated providers. Inverse-probability weighting and difference-in-differences analyses were utilized to compare utilization of both screening tests. Analyses were stratified by age groups: 1) 66-69 and 2) $\geq$70. **Results:** For men whose providers joined ACOs between 2010 and 2014, the prevalence of PSA screening for men aged 66-69 declined from 62.4% to 55.9%. Non-ACO affiliated providers also had a similar decline in rates of PSA screening of 62.4% to 55.9%. Trends in biopsy rates were similar in both groups: 4.7% to 5.3% in ACOs and 4.6% to 5.3% in non-ACOs. The difference-in-differences analyses showed that the change in use of PSA from 2010 to 2014 was not significantly different at ACOs and non-ACOs ($p = 0.3$). The trend in biopsies was not significantly different in ACOs and non-ACOs ($p = 0.7$). Similar non-significant differences were observed in men aged $\geq$70 years old (Table 1). **Conclusions:** Overall, trends in PSA screening and biopsies from 2010 to 2014 were similar at both ACO and non-ACO affiliated providers, regardless of patient age. This suggests that the implementation of ACOs did not impact on the use of PSA screening or biopsy, including in older age ranges where PSA screening is considered lower value.

Biopsy and PSA screening prevalence in 2010 and 2014 with difference in difference analysis comparing ACO and non-ACO patients.

	ACO		Non-ACO		Difference in Difference
	2010	2014	2010	2014	p value
Ages 66-69					
PSA	62.4	55.9	60.5	54.4	0.3
Biopsy	4.7	5.3	4.4	5.2	0.7
Ages 70+					
PSA	54.3	46.0	54.2	46.4	0.2
Biopsy	4.3	4.8	4.1	4.6	0.5

6547 Poster Session (Board #373), Sat, 1:15 PM-4:45 PM

Implementation of individualized care plans in high risk oncology patients: A team based model to decrease unnecessary utilization. *First Author: Girish Chandra Kunapareddy, Cleveland Clinic Foundation, Cleveland, OH*

Background: Due to complexity of disease and treatments, oncology patients (pts) have among the highest hospitalization rate. In our cancer institute, just 6% of all discharged pts accounted for $>$ 40% of all unplanned readmissions (UR), and continue to be of highest risk of future admissions, ICU stay, ED visits, overuse of chemotherapy and underutilization of hospice resources. We hypothesized that developing individualized care plans (ICP) will better provide the complex care necessitated by this group **Methods:** An Interdisciplinary Care Team (ICT) was created consisting of palliative medicine and oncology physicians/social workers/care coordinators/nurse managers. Twice monthly, pts with the highest utilization over a 60-day period with at least two UR were identified. ICPs were created using the team-based approach with parallel input from primary outpatient providers. Communication plans were created to ED and outpatient teams **Results:** A total of 71 pts, 356 hospitalizations, and 260 ED visits were evaluated over a 6-month period, with an avg number of hospitalizations of 0.82 per pt month (ppm). After creation ICT, this decreased to 0.23 ppm. Average ED visits, UR, avg length of stay per admission also decreased (see Table 1). Nearly all solid tumor pts had metastatic disease at ICT review, while pts with hematological malignancies were early in their treatment course receiving myelosuppressive therapy. These results were compared to a historical cohort prior to ICT with the same inclusion criteria, which maintained to show a high relative impact **Conclusions:** Creation of individualized care plans for high-utilizing cancer patients decreased number of hospitalizations, ED visits, unplanned readmissions, and length of stay in all disease groups, but ST patients seemed to have a greater impact than in HM patients

Effect of ICP.

	All Patients N = 71	Solid Tumor N = 40	Malignant Hematology N = 31
Hospitalizations			
Before ICP	0.82	0.79	0.89
After ICP	0.36	0.27	0.49
30-day Readmissions			
Before ICP	0.49	0.48	0.51
After ICP	0.13	0.05	0.29
ED Visits			
Before ICP	0.60	0.61	0.57
After ICP	0.24	0.18	0.42
Average LOS per Admission			
Before ICP	7.17	6.24	8.48
After ICP	4.06	2.55	6.17

6548 Poster Session (Board #374), Sat, 1:15 PM-4:45 PM

Risk stratification and predictive value of the HOSPITAL score for oncology patient readmissions. *First Author: Anu Radha Neerukonda, University of Chicago Medical Center, Chicago, IL*

Background: Hospital readmissions are costly, frequent and harmful. Prediction models such as the HOSPITAL scoring system are reasonably accurate and efficient in predicting the readmission risk after hospital discharge in a general medicine population. However, their utility remains unknown for cancer patients. HOSPITAL is the acronym for 7 variables included in the score: Hemoglobin before discharge (positive if $<$ 12 g/dl), discharge from an Oncology service, Sodium level before discharge (positive if $<$ 135 mmol/L), Procedure performed during hospitalization, Index admission Type, number of Admissions in the previous 12 months, and Length of stay (positive if $\geq$ 5 days). **Methods:** We retrospectively calculated HOSPITAL scores at the time of discharge for all oncology discharges at the University of Chicago Medical Center between November 2016 and November 2017 (N=2957). We used SQL, our internal data warehouse and electronic medical records database for data collection. The HOSPITAL score was calculated for each discharge, with each categorized into 1 of 3 risk groups based on number of points: low risk (0-4), intermediate risk (5-6), and high risk ($\geq$7). **Results:** Table 1 reflects number of patients in each readmission risk category. Based on the HOSPITAL point scoring allotment described, 88% of oncology admissions were identified as intermediate or high risk, with very few patients in low risk category. This is in stark contrast to 38% of all general medicine patients who were identified as intermediate or high risk in the original publication externally validating the HOSPITAL score. **Conclusions:** Findings from this study indicate that HOSPITAL score may not be effective in differentiating readmission risk within an oncology specific patient population, and that other variables such as performance status need to be incorporated. Further research needs to be done for developing and validating specific readmission risk prediction models in the oncology population.

Readmission rate by hospital risk group.

Readmission Risk Group	Number of medical oncology discharges	Percentage of all medical oncology discharges	Readmission Rate
Low	352	11.9%	17%
Intermediate	1058	35.8%	15%
High	1547	52.3%	18%

6549 Poster Session (Board #375), Sat, 1:15 PM-4:45 PM

Clinician perspectives on electronic health records, communication, and patient safety across diverse medical oncology practices. *First Author: Minal R Patel, University of Michigan, Ann Arbor, MI*

Background: We know little about clinicians' documentation and communication challenges and how these might affect the safety of ambulatory oncology care. The present study investigated variation in electronic health record (EHR) capability and satisfaction, clinician communication, and clinicians' actions that enable a safety culture. **Methods:** We distributed paper questionnaires to nurses and prescribers (physicians, nurse practitioners, and physician assistants) in 28 practices that participate in a statewide quality improvement collaborative. Previously-validated measures included the Safety Organizing Scale (SOS) that reflects actions consistent with a safety culture, satisfaction with clinic technology, and satisfaction with communication with other clinicians. We constructed an index to reflect EHR capability (1 = all paper to 5 = all electronic). Linear regression models (with robust standard errors to account for clustering) were used to examine the relationship between covariates of interest and the SOS, adjusting for practice size and ownership. **Results:** The survey response rate was 68%. The mean (SD) of the SOS was 5.3(1.1), with a practice-level range of 4.9-5.4 (based on 7-point scale where higher scores reflect increased safety actions). Higher satisfaction with technology and clinician communication was significantly associated with increased SOS scores, while increased EHR capability was associated with lower SOS scores. Prescribers reported lower SOS scores than nurses (see table). **Conclusions:** Practices vary in their performance of patient safety actions. Supporting clinicians to integrate increased technology is a promising target for interventions. The inverse relationship between EHR capability and safety suggests that technology distracts clinicians from attending to patient safety. Improvement strategies may benefit from tailoring by clinician type to account for observed differences.

Variable	β(SE)	95% CI
Technology satisfaction	0.67(0.1)***	0.5,0.8
Clinician communication satisfaction	0.29(0.1)***	0.1,0.4
EHR capability index	-0.14(0.03)***	-0.2,-0.1
Prescriber (vs. nurse)	-0.38 (0.1)***	-0.7,-0.1

*** $p < .001$

6550 Poster Session (Board #376), Sat, 1:15 PM-4:45 PM

Impact of a cognitive computing clinical trial matching system in an ambulatory oncology practice. *First Author: Tufia C. Haddad, Mayo Clinic, Rochester, MN*

Background: Only 3-5% of cancer patients participate in clinical trials even though up to 20% are eligible. Cognitive computing has promising potential to assist trial enrollment efficiency and accuracy by performing background analytics. The Watson for Clinical Trial Matching (CTM) cognitive system utilizes natural language processing to derive patient and tumor attributes from unstructured text in the electronic health record that can be matched to complex eligibility criteria in trial protocols. Screening patients for trials was performed on an ad hoc basis with traditional methods prior to implementation of the CTM system in the Mayo Clinic breast oncology practice. **Methods:** The Watson CTM system was trained by Mayo subject matter experts and implemented in July 2016. Systemic therapy trials enrolling breast cancer patients were included in the system. Clinical research coordinators validated Watson-derived clinical trial matches on the day prior to patient clinic visits. They gave the oncology providers a list of matched trials for each patient to facilitate treatment decision making at point of care. Enrollment and timing metrics were tracked and compared with manual screening methods. **Results:** Watson CTM facilitated screening of all breast cancer patients for systemic therapy trials with matches validated by coordinators in 40% of patients. Over the 18 month (mo) period following implementation, 6.3 patients/mo were enrolled to breast cancer systemic therapy trials compared with 3.5 patients/mo in the period prior. The average monthly enrollment increased by 80%. This was further increased to 8.1 patients/mo when including accruals to breast cancer cohorts of phase I trials within the experimental therapeutics program. Time to match patients to trials with the CTM system was faster than manual methods but variable depending on the role of the screener and the depth of the matching. **Conclusions:** Implementation of the Watson for CTM system with a screening coordinator team was associated with an increase in breast cancer clinical trial enrollment. The system enabled high volume screening in an efficient manner and promoted awareness of clinical trial opportunities within the breast oncology practice.

6551 Poster Session (Board #377), Sat, 1:15 PM-4:45 PM

Statistical significance of bevacizumab trials when considering the portfolio of all studies. *First Author: Derrick L Tao, Oregon Health & Science University School of Medicine, Portland, OR*

Background: Although clinical trials of novel medications have historically been interpreted individually, there is increasing recognition that trials should be considered as part of a broader clinical trials agenda or portfolio. If a single drug is tested in many tumor types, the interpretation of any single trial result must account for the number of times that agent is trialed. We attempted to better understand the effect of the trials portfolio for bevacizumab, an antibody approved in many tumor types. We conducted a systematic review of cancer trials of bevacizumab efficacy when added to a chemotherapy backbone in solid tumors and adjusted results for the number of reported trials. **Methods:** We queried MEDLINE for "solid tumor", "bevacizumab" and "meta-analysis" on 2/2/2018, extracting all included randomized controlled trials, their reported improvement in median progression free survival (PFS), overall survival (OS), and accompanying p values. We investigated 1. What percent of individual studies met traditional nominal statistical significance for PFS and OS and 2. What percent retained this significance after adjusting for multiplicity using the Bonferroni correction, a commonly used method. **Results:** Our search identified 3 meta-analyses, including 48 randomized trials, 47 reported PFS and OS data. Of the 48 trials, 8 (17%) were phase II and 40 (83%) were phase III. Most common tumor types among the 48 trials included colorectal (14; 29%) and breast (9; 19%). A statistically significant PFS benefit (using a $p < .05$ cutoff) was reported in 30 of 47 trials (64%). After adjusting the p-value for multiplicity using the Bonferroni correction ($P < .00106$), 21 trials reported statistically significant improvements (45%). A statistically significant OS benefit (using $P < .05$) was reported in 7 of 47 (15%) trials. After adjusting p-value for multiplicity using the Bonferroni correction ($P < .00106$), 1 trial (2%) reported statistically significant improvement. **Conclusions:** The number of statistically significant studies of bevacizumab is reduced when corrected for multiplicity, suggesting that the current analytic plans may overestimate clinical benefit and could benefit from portfolio-based analysis.

6552 Poster Session (Board #378), Sat, 1:15 PM-4:45 PM

Analysis of use of a molecular reporting and treatment decision support tool in more than 1300 cancer cases. *First Author: Gabriel Alejandro Bien-Willner, Molecular Health Inc., The Woodlands, TX*

Background: Comprehensive characterization of the cancer genome has elucidated the molecular determinants driving response and resistance to targeted therapies. Current NGS-based personalized medicine requires a lot of manual work (e.g., publication and database review) to find relevant biomarker information necessary to create an impactful diagnostic report. Molecular Health Guide (MH Guide) allows for rapid and efficient variant interpretation and treatment support using referenced curated data including evaluation of various quality parameters. **Methods:** We constructed an integrated database of biologic and clinical data called Dataome, upon which we have developed a medical device (MH Guide) for medical reporting, wherein content can be used for clinical treatment decision support (registered medical device in Europe). We assess the clinical information provided by MH Guide in a cohort of patients including the number of recommended and contraindicated drugs and available clinical trials. **Results:** 1352 cancer patients with various solid tumor types (n = 107) were analyzed with MH Guide (2014-2017). The system identified 14,000, 4,800 and 2,300 tumor-type specific biomarkers associated with effective therapies, adverse events and ineffective therapies, respectively. These were based on clinical (10,300) as well as pre-clinical (11,400) data. Putative effective therapies were linked to $>$ 4,700 clinical trials. **Conclusions:** Comprehensive characterization of the cancer genome has elucidated pathways that drive cancer, mechanisms of therapy resistance, and provided important insights for the development of new therapies. To benefit from this in routine medical practice, we need tools and technologies that efficiently assist with interpretation of clinico-molecular patient data against the rapidly growing biomedical knowledge. MH Guide can assist clinicians in making informed decisions about the benefits of therapies in an evidence driven manner. Based on its performance, German health insurance companies have agreed to support the clinical use of MH Guide in a study aimed to reduce non-responders and adverse events; thus, lowering the overall cost of care and improve quality of life.

6553 Poster Session (Board #379), Sat, 1:15 PM-4:45 PM

Association of baseline body mass index (BMI) with overall survival (OS) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) treated with nivolumab (N) and pembrolizumab (P). *First Author: Jizu Zhi, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Poor performance status (PS) is associated with worse clinical outcomes for pts with mNSCLC. However, in the real-world PS is not routinely captured in electronic health records (EHRs). Pts with poor PS may also have cachexia and low BMI. As such, underweight BMI may be a proxy for deteriorated real-world PS when PS score is missing. We have shown that female gender and positive EGFR/ALK mutation status predict longer OS, but not age or other factors. We explore the association of baseline BMI with OS in real world mNSCLC pts treated with N or P. **Methods:** We conducted a retrospective analysis of mNSCLC pts treated with N or P using de-identified real-world data (RWD) from the Flatiron Health network. Index date was start of first single agent N or P. Baseline BMI (kg/m2) was calculated from the most recent weight and height recorded within 30 days prior to index date and categorized as: Underweight (< 18.5), Normal (18.5 – 24.99), Overweight (25 – 29.99), and Obese (30+). Association of baseline BMI with OS was assessed using multivariate Cox proportional hazards model adjusted for gender, age, and EGFR/ALK status prior to N or P start. Eligible pts had valid values for all parameters. **Results:** 703 pts met inclusion criteria (Table). For OS, gender was significant overall, EGFR/ALK mutation was significant overall and for women. **Conclusions:** We observed BMI-based differences in OS for real world mNSCLC pts treated with N or P. Underweight BMI is associated with shorter OS and obese BMI is associated with longer OS. In pts with cancer, declining BMI and PS may signal biologic processes indicative of progressive disease that negatively affect OS. Since PS data is commonly missing in EHRs, our results suggest that BMI can potentially be used as a proxy for poor PS in RWD studies. Investigating the impact of changes in BMI on OS and correlation of BMI with PS would further verify this assumption.

		All		Male		Female	
BMI	**N (%)**	**aHR**	**p**	**aHR**	**p**	**aHR**	**p**
Normal	326 (46)	-	-	-	-	-	-
UnderWeight	59 (8)	1.66	0.002	2.09	0.004	1.4	0.111
OverWeight	207 (29)	0.82	0.071	0.9	0.503	0.71	0.048
Obese	111 (16)	0.75	0.039	0.74	0.131	0.75	0.145

- = Reference, aHR = adjusted Hazard Ratio

6554 Poster Session (Board #380), Sat, 1:15 PM-4:45 PM

Trial prospector update: A point of care automated clinical trials matching application. *First Author: David Lawrence Bajor, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH*

Background: Advances in oncological care and patient outcomes are commonly based on clinical trials, however only 3-7% of cancer patients participate. One major barrier to patient enrollment is the physician effort needed to identify clinical trials for which their patients are eligible. As clinical trial eligibility becomes more complex with cohorts defined by specific lines of therapy or genetic data this barrier grows. Health information technology presents an opportunity to develop automated systems capable of matching patients to appropriate clinical trials in real time without impeding clinical workflow. **Methods:** Trial Prospector (TP) is a web-based, point-of-care, automated clinical trials matching application. (Sahoo SS, et al. Trial Prospector: matching patients with cancer research studies using an automated and scalable approach. *Cancer Informatics* 13:157-66, 2014. Corresponding author. PMID: 25506198) In order to enhance its utility, we systematically reviewed eligibility criteria in all lung cancer trials on clinicaltrials.gov, and integrated five new criteria into TP, including the capability to match based on next-generation sequencing data. We then deployed TP in lung cancer clinics, surveyed users for usability, independently verified the accuracy of TP, and measured clinical trial accrual. **Results:** A total of 380 patient visits (282 unique), were included; 10.3% of patients were subsequently accrued to a clinical trial. Among a sample of 25 TP reports, the accuracy of TP, defined as the percentage of correctly matched trials, was 98%. Clinician surveys (n = 38) revealed that 82% found the information provided by TP to be accurate, 71% reported that TP saved them time in identifying potential clinical trials, and 87% would recommend utilizing TP for eligibility screening. **Conclusions:** TP is an adaptable software platform that accurately matches patients to clinical trials in a point-of-care setting. Further testing is warranted to determine the optimal settings for deployment and the impact on physician effort and trial accrual.

6555 Poster Session (Board #381), Sat, 1:15 PM-4:45 PM

Artificial intelligence methods to predict chemotherapy-induced neutropenia in breast cancer patients. *First Author: Peter Abdul DeWan, Precision Health Ai, New York, NY*

Background: While chemotherapy improves outcomes in breast cancer patients, it also increases the risk of neutropenia. There is a need for improved risk prediction models of chemotherapy-induced neutropenia. This study developed an artificial intelligence (AI) model to predict neutropenia risk within six months of chemotherapy and compared it to traditional logistic regression models. **Methods:** We obtained a cohort of 10,288 breast cancer patients from the ASCO CancerLinQ Discovery™ dataset, who were treated with doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with or without pre-chemotherapy WBC growth factor prophylaxis. We created a hierarchy of predictors, then trained and evaluated a neural network algorithm. **Results:** Using only the relevant predictors for this more specific study, we demonstrate an average 27% increase across the scenarios in AUC ROC ($p < 0.001$) compared to existing studies (Lyman, 2011). We improve prediction by an average of 45%, achieving 0.56 positive predictive value (PPV) and 0.92 negative predictive value (NPV) prior to chemotherapy. **Conclusions:** These results demonstrate that this larger dataset combined with an AI algorithm enabled substantial improvement in prediction of chemotherapy-induced neutropenia. In the clinical setting, this would improve decisions, and enable early intervention for patients that would benefit most from prophylaxis, thus reducing neutropenic fever and infections requiring hospitalization.

		Cohort				Predictive Models					
		Statistics				Logistic Regression (Lyman, 2011)		Logistic Regression (Current Study)		PH.AI Neural Net (Current Study)	
Clinical Decision Point		**N**	**Neutropenia incidence within 6 mo.**	**Stage Distribution (I,II,III,IV)**	**Median time to Neutropenia (days)**	**AUC-ROC**	**# Predictors**	**AUC-ROC**	**# Predictors**	**AUC-ROC**	**# Predictors**
Prior to Starting AC	**with Prophylaxis**	7097	.017	.14, .50, .31, .04	18	.58 ± .03	7	.73 ± .02	19	.78 ± .04	704
	no Prophylaxis	1075	.093	.13, .51, .31, .05	22	.59 ± .03	7	.69 ± .02	15	.74 ± .01	2169
Prior to Starting T	**with Prophylaxis**	6753	.084	.14, .50, .31, .04	31	.59 ± .03	7	.76 ± .02	21	.74 ± .01	2130
	no Prophylaxis	1078	.074	.13, .53, .29, .05	15	.57 ± .02	7	.74 ± .02	16	.89 ± .02	873

6556 Poster Session (Board #382), Sat, 1:15 PM-4:45 PM

Factors impacting progression-free survival (PFS) as a predictor of overall survival (OS). *First Author: David J. Stewart, The Ottawa Hospital, Ottawa, ON, Canada*

Background: Unlike OS hazard ratios (HRs), PFS HRs are unaffected by crossover or post-progression survival, but PFS HRs are poor predictors of OS HRs. We hypothesized that absolute PFS gain (ΔPFS) might predict absolute OS gain (ΔOS). **Methods:** We assessed 279 randomized solid tumor drug comparisons with ≥200 incurable patients from J Clin Oncol or New Engl J Med, 2007 to June, 2017. We used nonlinear regression analysis of PFS & OS curves to calculate half-lives ($t_{1/2}$s: time to death or progression in $\frac{1}{2}$ the remaining patients) and to assess if PFS curves fit 2-phase vs only 1-phase decay models. ΔPFS ≥ 1.5 months (m) is a better predictor of ΔOS ≥ 2m if $t_{1/2}$s are used than if medians are used (Stewart, Proc AACR, 2018 #1644). We used $t_{1/2}$s from the 149 studies with ΔPFS $p < 0.05$ to calculate positive and negative predictive value (PPV & NPV) of ΔPFS ≥ 1.5 m as a predictor of ΔOS ≥ 2 m in selected subgroups. PPV = (no. studies with ΔPFS ≥ 1.5 m & ΔOS ≥ 2 m)/ (no. studies with ΔPFS ≥ 1.5 m & any ΔOS). NPV = (no. studies with ΔPFS < 1.5 m & ΔOS < 2 m)/ (no. studies with ΔPFS < 1.5 m & any ΔOS). **Results:** See table. 4 of 14 ICI trials (29%) and 6 of 265 trials with other drugs (2%) had ΔOS that was both ≥ 2 m & significant ($p < 0.05$) despite insignificant ΔPFS ($p > 0.05$). **Conclusions:** With low CO, ΔPFS that is both significant & greater than 1.5 m predicts ΔOS greater than 2 m. with high PPV and NPV across tumor types other than prostate cancer and across drugs other than ICIs. ICIs (most of which had PFS curve 2-phase decay) generally had high ΔOS despite low ΔPFS.

	ΔPFS < 1.5 m/ ΔOS < 2 m No. comparisons	ΔPFS < 1.5 m/ ΔOS ≥2 m	NPV %	ΔPFS ≥1.5 m/ ΔOS < 2 m No. comparisons	ΔPFS ≥1.5 m/ ΔOS ≥2 m	PPV %
All	46	7	87	18	78	81
Proportion of studies with crossover < 20% or unknown (Low CO) vs > 20% (High CO)						
Low CO	31	5	86	10	52	84
High CO	15	2	88	8	26	76
PFS curve for arm with longer PFS:						
2 phase decay	5	3	63[a]	3	17	85
1 phase decay	41	4	91[a]	15	61	80
Drugs:						
Chemo:						
Low CO	7	1	88	4	7	64
High CO	7	1	88	4	7	64
Bevacizumab:						
Low CO	5	0	100	2	8	80
High CO	1	0	100	3	4	57
Oral angiogenesis inhibitors	8	1	89	0	2	100
Immune check-point inhibitors (ICIs)	1	3	25[b]	1	5	83
Hormones	0	0	NA	1	8	89
Other monoclonals	4	1	80	0	9	100
Oral targeted drugs	13	1	93	3	23	88
Tumors:						
Breast	2	1	67	2	19	90
Colon	10	1	91	2	11	85
NSCLC	13	2	87	2	11	85
Melanoma	0	3[c]	0	1	8	89
Prostate	1	0	100	4	5	56[b]

a. P = 0.06
b. P = 0.02 vs all others
c. all with ICIs

6557 Poster Session (Board #383), Sat, 1:15 PM-4:45 PM

The influence of socioeconomic status, tumor characteristics and patterns of breast cancer care on breast cancer specific survival among elderly women. *First Author: Amanda L. Kong, The Medical College of Wisconsin, Milwaukee, WI*

Background: The purpose of this study was to examine the relationship between patient demographic and socioeconomic status (SES), tumor characteristics, initial and follow-up breast cancer care, and 3-year breast cancer mortality among a population-based cohort of elderly women with incident breast cancer. **Methods:** We identified women with newly diagnosed breast cancer in 2006-2009 from the Surveillance and Epidemiology End Result study linked with Medicare claims (SEER-Medicare). A Classification and Regression Tree (CART) model was applied to 15 individual indicators of neo-adjuvant and adjuvant breast cancer treatment, tumor characteristics, and patient demographic and SES variables to identify patterns (i.e. combinations of variables) with the greatest discriminant value in predicting 3-year mortality by cause of death (outcome = breast cancer vs. other causes vs. alive) . **Results:** Nineteen unique patterns were identified as best discriminating 3-year mortality by cause of death. Breast cancer mortality probabilities associated with these patterns ranged from 2.6% to 39.7%. CART identified the number of positive nodes as the best single discriminator between high and lower breast cancer mortality, followed by the use radiation therapy and tumor stage. Patient's SES was a discriminant factor in four of the ten patterns associated with high ($>$ 15%) breast cancer mortality while non-use of adjuvant hormonal therapy was a discriminant factor in six of the ten high breast cancer mortality patterns. Receipt of treatment within 50 days from diagnosis was associated with two of the lowest probabilities of breast cancer mortality (3.1% and 7.7%). **Conclusions:** Greater adoption of certain patterns of care could improve breast cancer survival of elderly women with incident disease overall, and reduce SES disparities therein.

6558 Poster Session (Board #384), Sat, 1:15 PM-4:45 PM

Feasibility of a self-funded model to provide breast cancer services to uninsured women in New York City. *First Author: Janice Zaballero, Breast Treatment Task Force, New York, NY*

Background: Despite access-expanding mandates in the ACA, approximately 30% of New York State residents remain uninsured. Most safety net programs provide services only to patients who qualify for Medicaid, leaving a large percentage of women without access to affordable breast cancer screening and diagnostics. In response, we developed Breast Treatment Task Force (BTTF) to provide these services to uninsured patients earning $23,760 - $47,520 annually (200%-400% FPL). **Methods:** We surveyed imaging centers located in New York City to determine unused imaging capacity. BTTF then negotiated reduced rates for breast imaging services at these sites. We developed referral networks composed of community organizations including Planned Parenthood. We raised nearly $400,000 through philanthropy to fund operations. We collected demographics for all patients, and patient satisfaction was assessed through surveys administered after receiving services. **Results:** We identified 24 imaging centers with unused capacity totaling 20,000 screening exams and diagnostic procedures. In 2017, BTTF facilitated care for 646 patients in the form of 409 screening exams and 832 diagnostic procedures. Average wait time from abnormal mammogram to diagnostic procedure was less than six days. The median age of BTTF patients was 40, and the majority were from minority backgrounds (34% Asian, 32% Hispanic, and 19% African-American). Median annual income per patient was approximately $30,000, and 61% of patients were employed. Attendance rates for diagnostic services and patient satisfaction rates were each 99% (versus industry averages of 60% and 67%, respectively). Nine patients were newly diagnosed with cancer. Since 2007, BTTF has delivered $16 million in medical services with an annual budget of under $400,000. **Conclusions:** BTTF constructed two networks: 1) network of private imaging centers willing to donate a significant portion of unused capacity and 2) network of large community referral partners to identify low-income patients. This model offers an example of how to successfully provide important breast cancer screening and diagnostic services to non-Medicaid-eligible women who cannot afford health insurance.

6559 Poster Session (Board #385), Sat, 1:15 PM-4:45 PM

Cigarette price, smoking behaviors, and lung cancer mortality in Indiana. *First Author: Ryan Nguyen, Indiana University School of Medicine, Indianapolis, IN*

Background: Increasing tobacco costs have been proven to be one of the most effective interventions of decreasing tobacco use. The relationship between tobacco cost and lung cancer mortality has not been as well established. We investigated the relationship of cigarette price with smoking prevalence, cigarette consumption, and lung cancer incidence and mortality in Indiana and nationally. **Methods:** We obtained average cigarette pack prices, cigarette pack sales, smoking prevalence, and lung cancer incidence and mortality rates in Indiana and nationally from 1995-2015. Average cigarette pack prices were inflation adjusted to 2015 then assessed for Pearson correlation coefficient (r) with cigarette pack sales, smoking prevalence, and lung cancer incidence and mortality. Cigarette price was also correlated with smoking prevalence among state-level characteristics that included gender, age, ethnicity, education, and income. **Results:** From 1995 to 2015, average cigarette pack price in Indiana rose from $2.29 to $5.41. Increasing cigarette price in Indiana was associated with decreasing cigarette consumption (r= -0.91, $p < 0.001$) and decreasing overall smoking prevalence (r= -0.72, $p < 0.001$). However, those in the lowest income level had higher smoking prevalence associated with rising cigarette price (r= 0.67, p = 0.001). Increasing cigarette price correlated with decreasing lung cancer mortality both in Indiana (r= -0.79, $p < 0.001$) and nationally (r= 0.96, $p < 0.001$). **Conclusions:** Increasing tobacco taxes and subsequent increasing cigarette prices were associated with decreased smoking prevalence, cigarette consumption, and lung cancer mortality in Indiana. Lower socioeconomic populations in Indiana may not be as price-responsive as similar populations nationally. Policies aimed at increasing tobacco prices should prioritize diverting revenues towards health programs and tobacco-cessation initiatives for lower-income individuals.

6560 Poster Session (Board #386), Sat, 1:15 PM-4:45 PM

Impact of high-deductible insurance on breast cancer care among lower-income women. *First Author: James Frank Wharam, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA*

Background: High-deductible health plans (HDHP) are increasingly common but delay important breast cancer diagnostic tests and treatment. We hypothesized that such delays would be especially pronounced among lower-income HDHP members. **Methods:** We used 2004-2012 data from a large US health insurer and a pre-post controlled survival design. We included 152,155 lower-income HDHP group members age 25-64 without evidence of breast cancer. These women were continuously enrolled for 1 year in a low-deductible ($\leq$\$500) plan followed by up to 4 years in a HDHP ($\geq$\$1000) after an employer-mandated switch. The comparison group included 1,316,548 contemporaneous, coarsened exact-matched lower-income women whose employers offered only low-deductible plans. Measures were times to first diagnostic breast imaging, breast biopsy, incident early-stage breast cancer diagnosis, and breast cancer chemotherapy. Outcomes were analyzed using Cox survival models adjusted for baseline patient characteristics. We also analyzed measures among 120,755 high-income HDHP members and their 1,095,592 high-income matched controls. **Results:** After the index date, lower-income HDHP members experienced delays in receipt of breast cancer diagnostic imaging (adjusted hazard ratio, aHR: 0.93 [0.92,0.95]), biopsy (0.89 [0.86,0.93]), early-stage breast cancer diagnosis (0.89 [0.80,0.98]), and chemotherapy initiation (0.80 [0.71,0.90]) compared with controls. Corresponding hazard ratios among high-income HDHP members (0.96 [0.95,0.98], 0.93 [0.89,0.97], 0.77 [0.69,0.85], and 0.76 [0.68,0.86], respectively) were similar to those of lower-income HDHP members and confidence intervals overlapped. Findings were also similar when analyzing an even lower income HDHP subgroup. **Conclusions:** Both lower-income and high-income women who were switched to HDHPs experienced delays in diagnostic breast imaging, breast biopsy, early-stage breast cancer diagnosis, and chemotherapy initiation. Further research should determine if such delays cause adverse health outcomes. Oncologists, primary care physicians, and population health managers should consider HDHPs a risk factor for delayed breast cancer services.

6561 Poster Session (Board #387), Sat, 1:15 PM-4:45 PM

Increasing access to NGS tests for women and racial minorities to lift barriers to molecular driven clinical trial enrollment. *First Author: Jared Cotta, University of Miami; Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Molecular-driven oncology clinical trials are a rapidly growing category of clinical research. These trials are focused on generating evidence for the relationship between molecular markers and targeted therapies, often requiring patients to have Next-Generation Sequencing (NGS) results before being considered for qualification. This requirement adds another barrier to clinical trial enrollment for populations that already face healthcare disparities. **Methods:** Defining Platforms for Individualized Cancer Treatment (DePICT) is an IRB approved observational trial designed to monitor outcomes of Broward County, FL residents with late-stage refractory cancer who undergo NGS. Rather than requiring NGS results, DePICT subsidized NGS testing to ensure access to all patients. Enrollment demographics were analyzed to see if these conditions improve gender and minority representation. **Results:** DePICT has recruited 176 patients. 70% of the total cohort is female, compared to 39% female in the institute's accrual of Broward residents. Table 1 shows the base line demographic data for DePICT in comparison to the institutional recruitment. DePICT produced a 26% relative increase in minority recruitment.102 DePICT patients had at least one 12 week follow up (65% women; 13% Black, 25% Hispanic). The follow-up determined which patients pursued an MTB recommended targeted treatment or clinical trial. 12 patients continued on to interventional trials; 50% were women, 50% identified as minorities. An additional 10 patients continued on to targeted therapies; 64% were women and 64% identified as a minority. **Conclusions:** By providing access to NGS testing DePICT accrued underrepresented patients who face healthcare disparities. Targeting underrepresented populations for NGS may improve the enrollment of women and racial minorities to oncology clinical trials. Healthcare providers may encourage testing through education or subsidy programs. Employing these methods to reduce disparities will improve generalizability of clinical research.

	Black	Non-Hispanic White	Hispanic	Minority recruitment
DePICT	15%	57%	23%	38%
SCCC	11%	62%	19%	30%

6562 Poster Session (Board #388), Sat, 1:15 PM-4:45 PM

Financial toxicity associated with conflict-induced cross-border travel for cancer care: Experience of Iraqi patients in Lebanon. *First Author: Deborah Mukherji, The American University of Beirut Medical Center, Beirut, Lebanon*

Background: Conflict-induced cross-border travel for cancer care is commonly observed in the Middle East region. There has been very little research conducted on the impact this has on patients or on how cancer centers can adapt their services to meet the needs of this population. This study examines the experience of Iraqi patients with cancer seeking care in Lebanon at the American University of Beirut Medical Center (AUBMC). The aim of this study was to understand the social and financial context of conflict-related cross-border travel for cancer diagnosis and treatment. **Methods:** After IRB approval, 60 Iraqi patients and caregivers were recruited and interviewed. For background epidemiological data regarding the population of patients seeking cancer care at AUBMC, the diagnoses of adult patients with Iraqi nationality were reviewed from January 2013 to December 2016. **Results:** For the retrospective sample, the total number of patients was 1284 with 40% presenting with advanced solid tumors. The prospective data emphasized the difficulties around access to the necessary financial resources for cancer treatment abroad as well as patterns of mobility. Fifty four respondents (90%) reported high levels of financial distress. Patients relied upon the sale of possessions (48%), homes (30%) and vast networks to raise funds for treatment. Thematic analysis revealed several key drivers for undergoing cross-border treatment, including (1) the conflict-driven exodus of Iraqi oncology specialists; (2) destruction of hospitals or road blockages; (3) referrals by Iraqi doctors to Lebanese hospitals (4) geographical proximity of Lebanon and (5) lack of diagnostic equipment, radiotherapy machines, and reliable provision of chemotherapy in Iraqi hospitals. **Conclusions:** As a phenomenon distinct from medical tourism, conflict-related deficiencies in healthcare at home force patients with limited financial resources to undergo treatments in neighboring countries. We highlight the importance of shared decision-making and taking the unique socioeconomic status of this population of patients into account when planning treatment.

6563 Poster Session (Board #389), Sat, 1:15 PM-4:45 PM

Assessing the impact of early Medicaid expansion on insurance, stage at diagnosis, and survival among young adults ineligible for dependent coverage. *First Author: Justin Barnes, Saint Louis University, St. Louis, MO*

Background: Cancer outcomes in young adults have lagged behind other age groups, which may be related to lower rates of insurance. While some data suggest the Affordable Care Act (ACA) may improve outcomes in young adult cancer patients eligible for dependent coverage through the ACA Dependent Coverage Provision, the impact of the ACA on cancer outcomes among young adults ineligible for dependent coverage has not been well-studied. Our objective is to assess changes in insurance rates, stage at diagnosis, and survival that are associated with early (2010-2011) Medicaid expansion. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER) 18 database, we identify young adults aged 27-34 years diagnosed with a first primary malignancy between 2007-2014. We utilize a quasi-experimental design, comparing expansion-related changes in insurance rates, stage at diagnosis, and survival in the intervention group (cases from states that expanded Medicaid early) to the control group (cases from other, non-expanding states) using difference-in-differences analyses applied to linear probability and Cox proportional hazards regression models. **Results:** A total of 47,750 cases were included in the analyses. Relative to young adults in states that did not expand Medicaid early, young adults in early expansion states had increases in Medicaid insurance (1.51 Percentage Points [PP], 95% CI = 0.15 to 2.87, p = 0.030), decreases in uninsurance (-1.99 PP, 95% CI = -3.03 to -0.95, $p < 0.001$), increases in early stage diagnoses (2.72 PP, 95% CI = 1.09 to 4.34, p = 0.001), decreases in late stage diagnoses (-1.34 PP, 95% CI = -2.53 to -0.16, p = 0.027), but no change in cancer-specific survival (HR: 0.95, 95% CI = 0.85 to 1.07, p = 0.41). **Conclusions:** For young adults ineligible for dependent coverage, early Medicaid expansion is associated with increases in Medicaid insurance rates and early stage diagnoses as well as decreases in the uninsured rate and late stage diagnoses, though evidence for a further downstream effect on survival is lacking.

6564 Poster Session (Board #390), Sat, 1:15 PM-4:45 PM

Superior survival in adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL) treated in pediatric vs. adult centers is only partially attributable to inadequate adoption of pediatric protocols: A population-based IMPACT Cohort study. *First Author: Sumit Gupta, Hospital for Sick Children, Toronto, ON, Canada*

Background: Retrospective studies have shown that AYA with ALL have superior survival when treated in pediatric vs. adult centers (locus of care; LOC). Clinical studies showing superior survival using pediatric treatment protocols have led to their adoption by some adult centers. Whether this has narrowed LOC disparities in real world settings is unknown. **Methods:** The IMPACT Cohort is an Ontario population-based cohort that has captured demographic, disease and treatment (treatment protocol, chemotherapy doses) data for all 15-21 year olds diagnosed with ALL between 1992-2011. Cancer outcomes were determined by both chart abstraction and linkage to provincial administrative health care databases. We examined predictors of outcome, including disease biology, treatment exposures, LOC, and time period (1992-98 vs.1999-2005 vs. 2006-11). **Results:** Of 271 patients, 152 (56%) received therapy at an adult center. 5-year event-free survival (EFS $\pm$ standard error) among AYA treated at a pediatric vs adult center was 72%$\pm$4% vs. 56%$\pm$4% (p = 0.03); 5-year overall survival (OS) was 82%$\pm$4% vs. 64%$\pm$4% ($p < 0.001$). No significant interaction was noted between pediatric vs. adult LOC and time period. Neither induction deaths nor dose reductions varied by LOC. In the latest time period, 39/59 (66%) AYA treated at an adult center received a pediatric protocol, as compared to 4/40 (10%) in the middle period. Late period AYA treated at adult centers with pediatric protocols experienced superior outcomes compared to those of contemporaneous AYA treated on an adult protocols, but inferior to those of AYA treated at pediatric centers (EFS 72%$\pm$5% vs. 60%$\pm$9% vs. 82%$\pm$3%; p = 0.02; OS 77%$\pm$7% vs. 65%$\pm$11% vs. 91%$\pm$4%; p = 0.004). **Conclusions:** Survival disparities between AYA treated in pediatric vs. ALL centers have persisted over time, partially attributable to inadequate adoption of pediatric protocols by adult centers. Although use of pediatric protocols has improved survival, residual survival disparities remain and do not seem to be due to excessive toxicity or dose reductions.

6565 Poster Session (Board #391), Sat, 1:15 PM-4:45 PM

Changes in access to care and financial hardship associated with Affordable Care Act (ACA) implementation for cancer survivors aged 19-64 years. *First Author: Amy J. Davidoff, Yale School of Public Health, New Haven, CT*

Background: In 2014, as part of the ACA implementation, Medicaid eligibility was expanded in over half of states and insurance marketplaces were created in all states, with premium subsidies for selected individuals. Our prior research indicated a 38% reduction in the uninsured rate for cancer survivors by 2015. Here we examine subsequent changes in access and financial hardship. **Methods:** We pooled data for cancer survivors aged 19-64 years from the 2012, 2013 & 2015 National Health Interview Survey (N = 2996). We examined perceived access barriers (unmet need, medication cost-related non-adherence (CRN)), ability to pay medical bills, worry about future bills, and food insecurity. Linear probability regressions examined changes between the 2012-2013 and 2015 periods. Models controlled for eligibility for both Medicaid and premium subsidies to purchase insurance, constructed using family structure, income and employment, and linked data on state-specific Medicaid expansion policies. Models also controlled for demographics and comorbidities. **Results:** Prior to ACA implementation, 18% of cancer survivors delayed healthcare due to cost, 13% had unmet need for medical care, 18% reported CRN, 31% reported being highly worried about paying future medical bills and 23% reported food insecurity. Post-ACA there were adjusted decreases of 4.5 percentage points (PPT) in delayed care, 4.8 PPT in any unmet need, 7.4 PPT decline in worry about future bills, all at $p < .01$. No reductions were observed in unmet drug need, medication CRN, or food insecurity. In 2015, 13% still reported delayed healthcare, 14% reported CRN, and 25% worried about ability to pay future medical bills. **Conclusions:** After the ACA implementation, cancer survivors experienced significant reductions in access burden and financial worry. Despite improvements, cancer survivors still experience healthcare access limits, and worry about future financial health. ACA coverage changes, participation, access and health outcomes for cancer survivors need ongoing monitoring, particularly given repeal of the individual mandate.

6566 Poster Session (Board #392), Sat, 1:15 PM-4:45 PM

Addressing financial concerns of cancer clinical trial participants: Longitudinal outcomes of an equity intervention. *First Author: Ryan David Nipp, Massachusetts General Hospital, Boston, MA*

Background: Cancer patients' (pts) financial concerns (FCs) represent a barrier to clinical trial (CT) participation and interventions targeting pts' FCs are needed. We sought to assess the impact of an equity intervention on CT pts' FCs. **Methods:** We developed an equity intervention to reimburse non-clinical expenses related to CTs (e.g. travel, lodging) for low income pts. From 7/2015-7/2017, we surveyed intervention and control pts matched by age, sex, cancer type, specific CT and CT phase. We longitudinally assessed pts' FCs (cost concerns for CT-related travel and lodging), cost-coping strategies (e.g. altering medical care or lifestyle due to costs) and financial wellbeing (FWB; COST measure, scores range 0-44, higher scores = better FWB) at baseline, day 45 and day 90. We used longitudinal models to assess intervention effects over time. **Results:** We enrolled 260 pts (157 intervention, 103 controls); median age = 59.2 (range: 23.8-83.3); 66% female; 72% on phase I CTs. Intervention pts had lower incomes than controls (under $60k: 52% vs 24%, $P < .001$). At baseline, intervention pts were more likely than controls to report FCs for CT-related travel (41% vs 7%, $P < .001$) and lodging (33% vs 2%, $P < .001$). Intervention pts were more likely to report travel to appointments as their most significant FC (23% vs 7%, P = .001). Intervention pts were also more likely to report forgoing needed care (14% vs 1%, P = .001) and using savings to pay for care (84% vs 43%, $P < .001$). At baseline, intervention pts had worse FWB than controls (COST score: 15.3 vs 23.9, $P < .001$). Over time, intervention pts experienced greater improvements in their FCs about CT-related travel (-10% vs +1%, P = .02) and lodging (-4% vs +4%, P = .03) compared with controls. Intervention pts also reported travel to appointments as their most significant FC less often (+2% vs +11%, P = .08) and had improvements in their COST scores (+1.1 vs -0.3, P = .20), although these differences were not significant. **Conclusions:** This equity intervention improved CT pts' FCs over time. Our findings highlight the substantial FCs of cancer CT pts, and underscore the need for interventions to address these concerns to improve access to CT participation for all pts with cancer.

6567 Poster Session (Board #393), Sat, 1:15 PM-4:45 PM

Impact of hospital safety-net burden on oncology patterns of care and outcomes. *First Author: Reith Sarkar, University of California, San Diego School of Medicine, La Jolla, CA*

Background: Safety-net hospitals serve a vital role in treating underserved populations. These hospitals often receive less funding, which could lead to different patterns of care for patients treated at these facilities. The purpose of this study was to determine the patterns of care and oncologic outcomes among a large cohort of cancer patients treated at safety-net hospitals. **Methods:** We identified 3,398,962 patients within the National Cancer Database with 10 common cancers including breast, prostate, lung, head and neck, colon, rectal, pancreas, cervix, bladder, and uterus diagnosed between 2004 and 2015. Safety-net burden was defined from the percentage of uninsured or Medicaid patients seen at each facility, and hospitals were then categorized as low (LBH), medium (MBH), or high burden (HBH) hospitals. We evaluated the impact of safety-net burden on patterns of care, as well as other outcomes including surgical margin status, and overall survival using multivariable linear, logistic, and Cox regression models. **Results:** Cancer patients seen at HBHs were more likely to be young, female, black, Hispanic, and reside in a low-income zip-code. HBHs were more likely to be academic, smaller institutions, and located in the South. After controlling for patient and tumor-related factors HBHs had differing patterns of treatment, and overall were less likely to operate (odds ratio [OR] 0.83; 95% confidence interval [CI] 0.82-0.84; $p < 0.0001$) and were more likely to provide radiation (OR 1.09; 95% CI 1.08-1.1; $p < 0.0001$) than LBHs. With respect to surgery, HBHs had higher rates of positive surgical margins (OR 1.08; 95% CI 1.06-1.1; $p < 0.0001$) than LBHs. HBHs had higher all-cause mortality when compared to LBHs (hazard ratio 1.09; 95% CI 1.08-1.10; $p < 0.0001$). **Conclusions:** Oncologic care at safety-net hospitals is associated with different patterns of care, as well as adverse clinical outcomes. Future research should focus on determining the etiology of this disparity, and work to devise strategies to improve outcomes among patients treated at safety-net hospitals.

6568 Poster Session (Board #394), Sat, 1:15 PM-4:45 PM

Overall survival based on oncologist density in the United States: Do we need to redefine underserved areas for oncologic care? *First Author: Kathan Mehta, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: ASCO has predicted shortage of 2,550 to 4,080 oncologists by 2020, disproportionately higher in underserved areas. The Conrad-30 program was established for international medical graduates, trained on J1 visas, to work in medically underserved areas (MUAs) and health professional shortage areas (HPSAs) to correct this disparity. Thirty spots per year are available for each state and primary care providers (PCP) are given priority. The designation of an area as MUA or HPSA is based on shortage of PCPs but not specialists. **Methods:** We evaluated the impact of oncologist density (OD) defined as number of oncologists per 100,000 (100K) population on overall survival and concordance with MUA or HPSA designation of areas by quartiles of OD. We studied the distribution of oncologists on visa in areas by quartiles of OD by merging SEER data with AMA physician's master file using Federal Information Processing Standards (FIPS) code of the area. **Results:** We identified 68,791 adult patients with newly diagnosed hematologic malignancies or metastatic solid cancers (excluding CNS cancers and patients with CNS mets) in 612 FIPS code areas captured by SEER in 2011. After controlling for confounders, compared to patients in areas with lowest quartile of OD (< 2.9 oncologists per 100K population), patients in areas with 2nd, 3rd and 4th quartile (2.9-6.5, 6.5-8.4, > 8.4 oncologists per 100K population respectively) of OD had better overall survival (HR 0.96, p = 0.001; HR 0.93, $p < 0.001$; HR 0.9, $p < 0.001$ respectively). There was no difference in proportion of MUA or HPSA designated areas among the four quartiles (79.6%, 71.9%, 64.5%, and 76.5% from 1st to 4th quartile, p = 0.1). There was no difference in proportion of oncologists working on visa among the 4 quartiles of OD (7.2%, 4.9%, 6.4%, and 6.4% from 1st to 4th quartile, p = 0.5). **Conclusions:** Patients in areas with higher OD have better overall survival. MUA or HPSA designation is not concordant with OD in different FIPS code areas. The Conrad-30 program is not promoting placement of oncologists on visa in areas with low OD. The Conrad-30 program should be amended to create designated spots for oncologists in each state proportionate to underserved population.

6569 Poster Session (Board #395), Sat, 1:15 PM-4:45 PM

Geographic distribution and survival outcomes for rural cancer patients treated in clinical trials. *First Author: Joseph M. Unger, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Studies show that cancer patients from rural areas have worse cancer outcomes than their urban counterparts. But studies relying on cancer population data are unable to account for differences in access to care. In contrast, clinical trial patients receive protocol-directed care by design, so large clinical trial databases are ideal for examining the impact of residency on outcomes. **Methods:** We compared the geographic distribution and survival outcomes for rural versus urban cancer clinical trial patients. We examined 36,995 patients from all 50 states enrolled in 44 phase III or II-III SWOG treatment trials from 1986-2012, comprising 17 different cancer-specific analysis cohorts. We examined overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS) for patients by rural/urban status to determine if residency – based on Rural-Urban Continuum Codes (RUCCs) – was associated with outcome. We used multivariate Cox regression to estimate the association of residency and survival outcomes, controlling for major disease-specific prognostic factors and demographic variables and stratifying by study. Different definitions of rurality were examined. The distribution of rural vs. urban patients by geographic region was described. **Results:** Overall, 19% of patients were from rural locations, the same as the rate of rural individuals in the U.S. Rural patients were older ($\geq$65 years, 31% vs. 27%, $p < .01$) and less likely to be African American (5% vs. 12%, $p < .01$), but were similar with respect to sex (40% each) and were well represented within major geographic regions. Clinical prognostic factors were very similar. In multivariable regression, rural patients with adjuvant-stage ER-/PR- breast cancer had worse OS (HR = 1.27, p = .008) and CSS (HR = 1.26, p = .02). No other statistically significant differences were found. Results were consistent regardless of the definition of rurality. **Conclusions:** Rural and urban patients with uniform access to cancer care through participation in a trial had similar outcomes. This finding suggests that improving access to uniform treatment strategies for cancer patients may help resolve the rural/urban disparity in cancer outcomes.

6570 Poster Session (Board #396), Sat, 1:15 PM-4:45 PM

Investigating hospice utilization for oncology patients using a claims database. *First Author: Margaret C. Horvath, UnitedHealthcare, Waltham, MA*

Background: Cancer is the second leading cause of death in the United States and also one of the most expensive diseases to treat. End of life care is often low in quality despite the availability of palliative care, advanced care planning, and hospice. Research studying Medicare beneficiaries has found most patients receive hospice, but with short length of stays (LOS). Limited studies exist on hospice use among non-elderly (18-64 year old) cancer patients with commercial insurance. **Methods:** Retrospective review of claims databases of Optum (Eden Prairie, MN) affiliated insurers identified patients, aged 18-64, who died of cancer between September 1, 2011 and August 31, 2016. Mortality information was sourced from the Social Security Administration Death Master File. Patients were identified as receiving 6 months of continuous insurance enrollment (CE) and 12 months CE prior to death date. Patients were described by cancer diagnosis and hospice LOS at the end of life. This project was considered exempt by the IRB at the University of Minnesota. **Results:** Among 15,330 cancer patients who died during this study period, we identified 3,730 patients aged 18-64 at time of death with 6 months of CE and a subset of 3,263 patients with 12 months CE. Our study included 99.5% of the target population. In the 6 month CE cohort, 2,263 (60.67%) patients received hospice with a median hospice LOS of 13 days, and 38.93% of patients received hospice received $\leq$7 days. We observed variation in hospice use by cancer type ranging from 49.11% (prostate cancer) to 66.84% (pancreatic cancer) $p < 0.001$. Median LOS ranged from 8 days (liver cancer) to 16 days (colorectal cancer). Similar results were found for the 12 month CE cohort. **Conclusions:** In our database, a majority of the non-elderly oncology patients received some hospice. We observed that over a third of the patients that received hospice had short LOS ($\leq$7 days), representing an opportunity for quality improvement. More studies are needed to improve the quality of EOL care for non-Medicare oncology patients in the U.S.

6571 Poster Session (Board #397), Sat, 1:15 PM-4:45 PM

Hospital utilization and disposition among patients with malignant bowel obstruction: A population-based comparison of surgical to medical management. *First Author: Sarah Bateni, University of California Davis Medical Center, Sacramento, CA*

Background: Malignant bowel obstruction (MBO) is often a terminal event in end-stage cancer patients. The decision to intervene surgically is complex, given the risk of harm in patients with a limited lifespan and the limited population-based research investigating clinically relevant outcomes with surgical versus medical MBO treatment. Therefore, we sought to compare hospital utilization and disposition among MBO patients treated with surgical versus medical management. **Methods:** We performed a retrospective analysis of hospitalized patients with MBO from 2006-2010 at all California licensed hospitals from the Office of Statewide Health Planning and Development dataset. Hospital-free days (HFD) at 30, 90, and 180 days were calculated accounting for all hospitalizations, emergency department visits, and skilled nursing facility lengths of stay. Adjusted-regression and competing risks models were used to compare HFDs, disposition, complications, in-hospital death, and survival for surgically versus medically treated MBO patients using inverse probability to treatment weighting with propensity scores. **Results:** We identified 4,576 MBO patients treated medically (74.8%) or surgically (25.2%). Surgical patients had higher rates of complications (44.0% vs. 21.3%) and in-hospital death (9.4% vs. 3.8%) with lower rates of disposition to home (75.4% vs. 88.6%) compared to medical patients ($p < 0.0001$ all). Surgical patients had fewer 30- and 90-day HFDs compared to medical patients ($p < 0.05$). However, at 180-days, there were no differences in HFDs between treatment groups. Additionally, there were no differences in overall survival for surgical and medical patients (median 6.5 vs. 6.4 months, $p > 0.05$). **Conclusions:** In this population-based analysis, medically managed MBO patients fared better with respect to less hospital utilization at 30 and 90 days, fewer in-hospital deaths, and more frequent returns to home. These data underscore the impact of surgical management on MBO patients at the end-of-life.

6572 Poster Session (Board #398), Sat, 1:15 PM-4:45 PM

Effect of blinding on completion rate of patient-reported outcome measures in FDA cancer trial submissions, 2007-2017. *First Author: Jessica Roydhouse, US Food and Drug Administration, Silver Spring, MD*

Background: Patient-reported outcomes (PROs) are commonly included in clinical trial data submitted for FDA review. Open-label designs are frequent in cancer trials. Between-arm differences in PRO missingness have the potential to affect results. We aimed to compare PRO completion rates between study arms pre- and on-treatment in randomized open-label and double-blind cancer trials. **Methods:** Descriptive analysis of RCTs supporting cancer indications submitted to FDA for regulatory review. We identified trials for malignant disease from 2007 – 2017 using internal FDA databases. Applicant study reports were reviewed to assess PRO use and reporting of completion rates. Completion rates were collected per PRO and compared between arms. Results were summarized at the trial and instrument level using descriptive statistics. **Results:** Ninety-six of 169 trials (57%) associated with malignant hematology and oncology indications from 2007 – 2017 contained PROs. Fifty-one of the 96 trials (53%) were randomized, controlled trials with useable information on PRO completion. Median completion rates at six months were close to 90%. At six months, 16% of PROs in the double-blind trials had between-arm completion differences of $>=$ 10%, and the median between-arm completion difference was 12%. Furthermore, 8% of PROs had a $>=$ 10% higher completion rate in the control arm of these double-blind trials. However, for open-label trials at 6 months, 20% of PROs had between-arm differences of $>=$ 10%, with a median between-arm completion difference of 25%. For these, completion was better in the experimental arm. **Conclusions:** PRO completion rates were generally high for those studies that reported them, even for open-label trials. However, between-arm differences in completion rates favoring the experimental arm were larger and more frequent in open-label trials. Imbalances in PRO completion rates between arms affect PRO interpretation. Procedures must be put in place to reduce missingness, and accurate reporting of completion rates upon trial conclusion is critical.

6573 Poster Session (Board #399), Sat, 1:15 PM-4:45 PM

Prevalence of quality of life(QoL) outcomes and association with survival in cancer clinical trials. *First Author: Bishal Gyawali, Program on Regulation, Therapeutics and Law, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA*

Background: QoL outcomes provide essential information for patients and physicians in oncology care, but these data are not always reported in pivotal trials of new therapies. We investigated the prevalence of quality of life outcomes in modern cancer drug trials and the relation, if any, between quality of life and surrogate endpoints. **Methods:** Retrospective cohort study of all phase III clinical trials of drugs for advanced or metastatic solid tumors published between 2010 and 2015. We investigated the inclusion and reporting of QoL endpoints in clinical trials of cancer drugs and the association between positive progression-free survival (PFS) and QoL outcomes. **Results:** Of the 352 Phase 3 trials included, 147 (42%) reported QoL outcomes. There were 162 (46%) that did not include a QoL endpoint and 43 (12%) that did not report pre-specified QoL endpoints, cumulatively enrolling a total of 125 962 patients. Factors significantly associated with lower rates of inclusion of QoL endpoints were cancer type (head and neck and other solid malignancies), primary endpoints of response rates or non-PFS surrogate endpoints, and smaller studies. Among the 147 trials that reported QoL outcomes, 99 (67%) reported no effect, 38 (26%) reported a positive effect, and 10 (7%) reported a negative effect of treatment on patients' global QoL. The correlation between PFS and positive QoL was low (r = 0.34; area under the curve [AUC]: 0.72). **Conclusions:** Despite the palliative intent of treatments in the advanced/metastatic setting, the availability of QoL data remains poor, primarily due to non-inclusion of QoL endpoints in large cancer clinical trials. Greater inclusion of pre-specified QoL measures and improved reporting of QoL outcomes are needed.

6574 Poster Session (Board #400), Sat, 1:15 PM-4:45 PM

Validity of using cancer registry data for comparative effectiveness research. *First Author: Zachary David Guss, University of California, San Diego School of Medicine, La Jolla, CA*

Background: Researchers often use cancer registry data to compare survival for different treatment options in clinical situations where higher level evidence does not exist. However, the retrospective non-randomized approach using cancer registry data for comparative effectiveness research raises important questions about study validity. The purpose of this project was to determine whether retrospective research with cancer registry data produces results concordant with randomized controlled trials (RCTs). **Methods:** Landmark RCTs involving surgery, systemic therapy or radiation were identified for nine common tumor sites including gastrointestinal, breast, lung, prostate, lymphoma, urinary, gynecologic, head and neck, and central nervous system. We identified experimental and control arms for each trial and recreated these arms using patients from the National Cancer Database (NCDB), matching eligibility criteria from the trial whenever possible. We used multivariable Cox regressions to determine hazard ratios for overall survival for each trial. The multivariable analyses controlled for potential confounders including clinical and tumor variables. We compared hazard ratios from the NCDB analyses with hazard ratios from randomized controlled trials. **Results:** Eighty-six RCTs were identified and included in this analysis. Overall survival hazard ratios for forty RCTs (45%) were found to be outside the 95% confidence interval reported for the RCTs. Fifty-one (59%) of the RCTs found no significant difference in overall survival between treatment arms, and among these trials 37 (73%) had significant findings showing superiority of one arm within NCDB. Thirty-five (41%) of the RCTs found a significant difference in overall survival between treatment arms, and among these trials 12 (34%) found no significant difference in survival within NCDB. The discordant results between RCTs and NCDB did not differ by disease site or treatment modality. **Conclusions:** Comparative effectiveness analyses using NCDB frequently produce results discordant from existing RCTs. These results suggest that comparative effectiveness research emanating from cancer registry should be interpreted with caution.

6576 Poster Session (Board #401), Sat, 1:15 PM-4:45 PM

Predicting acute care use following initiation of systemic therapy for solid tumors. *First Author: Robert C Grant, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Emergency department (ED) visits and hospitalizations are undesirable and costly. We developed and validated the PROACCT (Prediction Of Acute Care use during Cancer Treatment) score to predict at least one acute care visit during the first 30 days (AC30) after initiating systemic therapy for cancer. **Methods:** Using administrative data, we identified patients in Ontario with the 18 most common non-hematological cancers who initiated non-hormonal systemic treatment regimens between July 1, 2014 and June 30, 2015, randomly split into development and validation cohorts. We created a score to predict AC30 using multivariate logistic regression and backward covariate selection in the development cohort. Combinations of tumor sites and regimens were grouped into quintiles based on AC30. The score was assessed in the validation cohort. **Results:** AC30 occurred in 21% (3561/17144) of patients. Eleven factors predicted AC30 in the development cohort and formed the score: tumor site and regimen (2^{nd} quintile: 2; 3^{rd}-4^{th}: 3; 5^{th}: 4), Aggregated Diagnosis Group comorbidity index (6-10: 1; 11+: 2), recent/concurrent radiation (1), female sex (1), recent ED visit (1), rural residence (1), local health integration network (0, 1 or 2), and Edmonton Symptom Assessment Scale anxiety (4+: 1), lack of appetite (4+: 1), nausea (4+: 1), and tiredness (4+: 1). Among the 196 tumor-regimen combinations, tumors with poor prognoses, such as pancreatic and lung, and platinum- and taxane-containing regimens, carried the highest risk for AC30. The score had c-statistics of 0.66 and 0.65 in the derivation and validation cohorts, respectively (both $P < 0.001$) (Table). **Conclusions:** PROACCT identifies factors that predict AC30 in patients with solid tumors starting systemic treatment and could be incorporated into electronic health records to select patients for preventative interventions.

AC30 by PROACCT score.

	AC30/N (%)	
Score	**Derivation (N = 11493)**	**Validation (N = 5651)**
< 3	18/431 (4)	15/216 (7)
3	37/584 (6)	28/324 (9)
4	111/1083 (10)	67/572 (12)
5	223/1596 (14)	122/741 (16)
6	357/1974 (18)	158/925 (17)
7	407/1949 (21)	186/947 (20)
8	358/1514 (25)	217/768 (28)
9	360/1159 (31)	174/542 (32)
10	269/677 (40)	115/333 (35)
> 10	220/526 (42)	119/283 (42)

6577 Poster Session (Board #402), Sat, 1:15 PM-4:45 PM

Racial, age, and sex disparities in chronic lymphocytic leukemia (CLL) patients treated with novel therapies. *First Author: Meghan Thompson, Hospital of the University of Pennsylvania, Philadelphia, PA*

Background: Differences in outcomes have been reported in CLL pts receiving chemo±immunotherapy with non-Caucasians and males having inferior outcomes. Less is known if such disparities exist for pts receiving targeted therapies. We investigated how demographics impact outcomes of CLL pts treated with targeted agents. **Methods:** We analyzed 3 multicenter, retrospective cohort studies of CLL pts treated with ibrutinib (ibr) (front-line (F/L) or relapsed/refractory (R/R) disease) or venetoclax (ven) (R/R disease). Baseline demographics, responses (ORR), discontinuations (DC), progression-free survival (PFS), and overall survival (OS) were stratified by age ($<$ 65 vs $\geq$65 yr), sex (male (M) vs female (F)) and race (Caucasian vs other). Cox regression was used for comparisons. **Results:** 1068 pts were included: F/L ibr (n = 391), R/R ibr (n = 536), R/R ven (n = 141). F/L ibr pts were 38% F, 59% age $\geq$65 and 8% non-Caucasian. R/R ibr pts were 37% age $\geq$65 (sex / race data unavailable). R/R ven pts were 34% F, 63% age $\geq$65 and 13% non-Caucasian. Del17p was similar within all cohorts. AEs were the most common discontinuation (DC) reason in all ibr groups, while CLL progression was most common in ven pts. A higher proportion of M discontinued ven vs F (34% vs 17%). Table 1 includes ORR, PFS, OS and DC stratified by age, sex and race. **Conclusions:** In the largest series of pts treated with novel agents, we did not find differences in outcomes when stratified by age, sex and race. These data suggest ibr and ven may in part overcome traditional disparities.

	AGE: < 65 vs ≥ 65 years			**Sex: M vs F**			**Race: Caucasian vs other**		
	Ibr (F/L)	**Ibr (R/R)**	**Ven (R/R)**	**Ibr (F/L)**	**Ibr (R/R)**	**Ven (R/R)**	**Ibr (F/L)**	**Ibr (R/R)**	**Ven (R/R)**
ORR	85% vs 79%	67% vs 69%	68% vs 74%	80% vs 84%	NA	68% vs 81%	83% vs 79%	NA	71% vs 81%
PFS (HR for ≥ 65 years, F and other race as events)	HR 1.1 (0.6-2.0), p = 0.7	HR 0.9 (0.6-1.2), p = 0.3	HR 0.6 (0.3-1.3), p = 0.2	HR 0.9 (0.5-1.6), p = 0.7	NA	HR 0.7 (0.3-1.7), p = 0.4	HR 1.9 (0.7-4.8), p = 0.2	NA	HR 0.3 (0.03-1.9), p = 0.2
OS	HR 2.2 (0.9-5.5), p = 0.1	HR 1.4 (0.9-2.1), p = 0.1	HR 0.9 (0.3-2.5), p = 0.8	HR 0.5 (0.2-1.3), p = 0.1	NA	HR 0.8 (0.3-2.6), p = 0.7	HR 1.4 (0.3-5.9), p = 0.7	NA	No deaths in Non-Caucasians
DC	22% vs 25%	44% vs 47%	28% vs 28%	24% vs 24%	NA	34% vs 17%	NA	NA	NA

6578 Poster Session (Board #403), Sat, 1:15 PM-4:45 PM

Real-world data (RWD) on tumor response (rwTR) in advanced non-small cell lung cancer (aNSCLC) patients receiving cancer immunotherapy and targeted therapies. *First Author: Michael Lu, Genentech, Inc., San Francisco, CA*

Background: Overall response rate (ORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) is an established early efficacy endpoint used in clinical trials. Comparison of real world tumor response (rwTR) and ORR can provide important insights for health professionals, regulators, and researchers. **Methods:** We retrospectively analyzed electronic health records (EHRs) of patients with metastatic or recurrent NSCLC treated with epidermal growth factor receptor (EGFR)-targeted therapy (afatinib or erlotinib) and a programmed cell death 1 (PD-1) inhibitor (nivolumab), as well as a subset of *BRAF* mutation (*BRAF*mut)–positive patients in the Flatiron (FIH) EHR and FIH-Foundation Medicine (FMI) Clinico-Genomics database (CGDB) from 2011 to 2017. Structured and unstructured data elements from FIH EHRs were processed via technology-enabled abstraction. RwTR was based on abstraction of clinician's assessment of radiographic evidence. **Results:** All patients with rwTR (CGDB, n=595; *BRAF*mut, n=30) were evaluated. Observed rwTR rates for the relevant patient populations are described in the Table. **Conclusions:** This analysis demonstrates the potential of leveraging routinely captured EHRs to provide RWD on treatment effectiveness in patients with NSCLC. These results show that rwTR for targeted and immunotherapies appear to correlate well with RECIST ORR rates in pivotal clinical studies matched by EGFR mutation status, treatment, and line of treatment. Future work includes expanding similar rwTR evaluation to more treatment contexts.

ORR by line of therapy.

	rwTR		
	***EGFR* mut**	***EGFR* wt**	**Reference clinical study/ population/ RECIST response**
Afatinib			
1L, n = 29	56% (14/25)	25% (1/4)	LUX-Lung 3/ *EGFR* mut/ 56%
2L, n = 23	30% (6/20)	NA	
Erlotinib			
1L, n = 106	69% (60/86)	35% (7/20)	EURTAC/ *EGFR* mut/ 65% ENSURE / *EGFR* mut/ 63%
2L, n = 34	53% (8/15)	15% (3/19)	BR21/ *EGFR* (any)/ 9%
Nivolumab	**All comers**		
1L, n = 63	33% (21/63)	-	Checkmate 026/ 1L/ 26%
2L, n = 131	28% (37/131)	-	Checkmate- 017/ 2L+ squamous/ 20% Checkmate- 057/ 2L+ nonsquamous/ 19%
3L, n = 55	15% (8/55)	-	Checkmate- 017/ 2L+ squamous/ 20% Checkmate- 057/ 2L+ nonsquamous/ 19%

6579 Poster Session (Board #404), Sat, 1:15 PM-4:45 PM

State breast density inform mandate laws and utilization of adjunctive screening tests and cancer detection following screening mammography. *First Author: Cary Philip Gross, Yale School of Medicine, New Haven, CT*

Background: In response to concerns about the limited sensitivity of mammography among women with dense breasts, 32 states have enacted laws to inform patients about these limitations and recommend adjunctive screening tests such as breast ultrasound. Inform mandate laws represent a novel approach to ensure awareness of technologies that have not yet been proven to affect health outcomes. We evaluated the effect of inform mandate laws on utilization of adjunctive screening, biopsy and diagnosis of incident breast cancer. **Methods:** Using blinded administrative claims data from anonymous insurers conducting business in the United States, we included women age 40-59 who underwent screening mammography in 2015. We classified beneficiaries according to receipt of screening mammography in a state with an inform mandate law. Receipt of screening or diagnostic ultrasound, breast biopsy, and incident breast cancer within nine months of screening mammogram was identified from claims. Logistic regression was used to evaluate the association between inform mandate laws and receipt of screening ultrasound, diagnostic ultrasound, biopsy, and cancer detection, while adjusting for age and type of health plan. Robust variance estimates accounted for clustering by state. **Results:** Our sample included 1,595,864 women who received a screening mammogram in 2015. Of these women, 58.2% were living in a state with an inform mandate law in place at the time of index mammogram. The adjunctive screening ultrasound rate was 3.1% among women in inform mandate states vs 1.4% in non-mandate states. After adjustment, residence in an inform mandate state was associated with significantly higher odds of adjunctive screening ultrasound (OR 2.22, 95% CI 1.14-4.34). In contrast, inform mandate status was not associated with receipt of diagnostic ultrasound, breast biopsy, or cancer detection. **Conclusions:** Women residing in states with breast density inform mandate laws are more likely to receive screening breast ultrasound. However, there was no significant relationship between inform mandate laws and utilization of other adjunctive tests or the likelihood of cancer detection.

6580 Poster Session (Board #405), Sat, 1:15 PM-4:45 PM

Toward understanding toxicity over time (ToxT) in myeloma cooperative group trials: Feasibility of a novel longitudinal adverse event analysis in ECOG-ACRIN E1A06. *First Author: Susanna J. Jacobus, Dana-Farber Cancer Institute, Boston, MA*

Background: Given the many chronically administered agents now used in cancer therapy, there is pressing need to elucidate safety and tolerability of therapy over time. Conventional methods of evaluating adverse events (AEs) focus on the incidence of high grade toxicity. The Toxicity over Time (ToxT) analytic approach captures the AE time profile with graphs and tabular displays plus quantifies the impact accounting for AE onset, duration and patterns of severity. ToxT has been applied to Alliance trials (Thanarajasingam et al, *Lancet Oncol 2016).* The goal of this study was to demonstrate feasibility of application of the ToxT statistical package to an ECOG-ACRIN trial. E1A06 was of interest given results of similar efficacy between treatment arms but significant differences in toxicity and quality of life as well as overall suboptimal treatment adherence. **Methods:** Newly diagnosed, transplant ineligible multiple myeloma pts were randomized to MPT (melphalan, prednisone, thalidomide) or mPR (lower dose melphalan, P, lenalidomide). Pts received 12 cycles of induction (I) followed by T or R maintenance until progression. Grade (G) 3+ non-hematologic (NH) and G4+ hematologic (H) AE data were collected every cycle. Treatment-related AEs of high incidence during I were selected for initial evaluation. Analyses with ToxT incorporate Kaplan-Meier and repeated measures methods. **Results:** 306 pts were enrolled. G3+ NH toxicity rates over I were 36% mPR vs. 51% MPT. Median time to 1st occurrence for pts experiencing G3+ AEs was similar (48 days mPR vs. 54 days MPT) and associated with ECOG PS score and stage at baseline. Each arm had 14 cases of fatigue, occurring more gradually on MPT (37d vs. 55d). G4 leukopenia incidence rates were 4% mPR vs. 13% MPT, with median onset 19d vs. 31d, respectively. Infection incidence rates were higher and onset earlier on MPT (8%, 79d vs. 14%, 46d). **Conclusions:** The feasibility of applying ToxT to an ECOG MM dataset was demonstrated. Longitudinal AE analysis has the potential to guide patient education on AEs and timing of symptom control interventions, ultimately improving tolerability of chronically administered cancer therapies.

6581 Poster Session (Board #406), Sat, 1:15 PM-4:45 PM

Assessing the difference in efficacy and effectiveness of cancer systemic treatment (tx): A comparison of clinical trial (CT) overall survival (OS) and toxicity data with population-based, real world (RW) OS data. *First Author: Cameron Phillips, University of Toronto, Toronto, ON, Canada*

Background: Often, when counseling patients on therapy, we utilize CT survival and toxicity data to help inform decision-making. While it is commonly believed CT data, derived from highly selected patients (pts), overestimates OS and underestimates toxicity compared with unselected patients in the RW, less is known about how often this occurs and the magnitude of this difference. We aim to quantify systematically the magnitude of OS and toxicity differences between CTs and population-based RW involving contemporary cancer systemic txs. **Methods:** All pts receiving IV cancer drugs with palliative intent indications that were first funded in Jan 2008 – Mar 2017 under Cancer Care Ontario's New Drug Funding Program (NDFP) were identified. A literature search was performed to identify landmark CTs with established OS efficacy data (e.g. median OS, 1-year OS rate or Kaplan-Meier OS curves) for each drug indication. Serious adverse event (SAE) rates were collected. Drug indications were included if the public funding criteria matched the CTs' eligibility criteria. RW OS and hospitalization (H) rates during treatment were ascertained by linking NDFP data to other population-based databases with end of follow-up at May 31, 2017. **Results:** 32 indications from 21 drugs (9 chemotherapy, 10 targeted therapies, 2 immunotherapy) involving 8,344 CT pts and 29,424 RW pts were included. 29 indications (91%) showed worse OS in the RW when compared to CTs with a median median OS difference of 4.4 months (IQR: 3.2-10.0) and a median 1-year OS difference of 12% (IQR: 8%-21%). Drugs used in the last-line setting had worse OS difference at 1-year (22% vs. 11%). The median difference between RW H and CT SAEs was 12% (IQR: 6%-21%). **Conclusions:** In most cases, substantially worse OS and greater toxicity were observed in the RW compared to CTs. This study has established a catalogue of population-based OS and H for pts receiving contemporary cancer systemic txs, and provides more relevant information for health-care providers when counseling pts on survival expectations prior to the initiation of systemic txs in the real world.

6582 Poster Session (Board #407), Sat, 1:15 PM-4:45 PM

Enrollment in high-deductible health plans and access to care, out-of-pocket spending, and hospital emergency department use among cancer survivors. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: Little is known about the associations between enrollment in high-deductible health plans (HDHP) and access to care, spending, and health care utilization among working age cancer survivors. **Methods:** The 2010 to 2015 National Health Interview Survey was used to identify privately insured working age (18-64 years) cancer survivors (HDHP n = 1170; low-deductible health plan [LDHP] n = 2084) and those without a cancer history (HDHP n = 23,548; LDHP n = 50,251). We used multivariable logistic regression to examine associations between HDHP status, cancer history and three measures: reduced access to care for financial reasons, high out-of-pocket (OOP) spending, and hospital emergency department (ED) use. Predictive margins were generated to compare cancer survivors to those without a cancer history, stratified by HDHP status. Odds ratios (OR) were generated to compare HDHP to LDHP cancer survivors as well as the impact of health saving accounts (HSA) among HDHP enrollees. Analyses were also stratified by family income level (low, middle, or high). **Results:** Among low income HDHP enrollees, cancer survivors were more likely to report reduced access to care (24.8% vs 17.8%), high OOP spending (47.8% vs 34.5%), and ED use (30.1% vs 16.2%) than those without a cancer history (all $p < .05$). Compared to LDHP cancer survivors, HDHP cancer survivors were more likely to report reduced access to care (low income: OR = 2.18; high income: OR = 2.15), high OOP spending (low income: OR = 4.75; middle income: OR = 2.35; high income: OR = 2.05), and ED use (middle income: OR = 1.58, all $p < .05$). Among HDHP enrollees, HSA was associated with lower rates of reduced access to care (OR = .85) and ED use (OR = .88) and higher rate of high OOP spending (OR = 1.34, all $p < .05$), compared to HDHP enrollees without HSA. **Conclusions:** HDHP increases the risks of reduced access to care, high OOP spending, and ED use for cancer survivors, and the patterns vary by family income level. Future studies based on longitudinal data to investigate causal relationship is warranted, especially among low income working age cancer survivors enrolled in HDHPs.

6583 Poster Session (Board #408), Sat, 1:15 PM-4:45 PM

Work status after treatment for breast cancer: A controlled, prospective, longitudinal study of an ethnically diverse cohort. *First Author: Victoria Susana Blinder, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer-associated job loss is associated with financial strain, debt, and bankruptcy. The identification of workers at highest risk is critical to the development of interventions. **Methods:** We surveyed employed women aged 18-64 with stage I-III breast cancer who spoke Chinese, English, Korean, or Spanish. Baseline surveys were during adjuvant tx; follow-up surveys were 4 months post-tx. Our primary outcome was post-tx work status (working full- or part-time vs. any other work status). We used healthy peers to control for disparities in non-cancer unemployment and multivariable analyses to identify predictors of work status in pts. **Results:** Our sample (n = 440) was 23% black, 18% Chinese, 8% Korean, 30% Latina, and 21% non-Latina white (NLW). 31% had household income < 200% of the Federal Poverty Level (FPL), 26% were under-/uninsured, 33% worked in service/manufacturing, 84% had chemotx. Overall, 72% were working post-tx. The proportion of working pts vs. controls was 0.78 for blacks, 0.71 for Chinese, 0.73 for Korean, 0.77 for Latinas, and 0.96 for NLW. Among pts, independent predictors of *not* working were older age, Chinese ethnicity, low income, service/manufacturing job, lack of employer accommodations, and stage III cancer (Table 1). **Conclusions:** Breast cancer exerts a disparate negative impact on employment in minority women, which persists after controlling for disparities in background unemployment. Chinese pts were observed to have triple the odds of job loss (vs. whites). Interventions are needed to promote job retention in minority and low-income women, particularly those who lack work accommodations or are in high-risk jobs.

Odds of not working 4 months post-treatment.

	OR	95% CI	
Age*	1.07	1.04	1.11
Race/ethnicity			
Black†	2.41	0.95	6.08
Chinese†	3.04	1.16	8.00
Korean†	3.40	0.97	11.8
Latina†	2.31	0.93	5.74
Job type			
Service/manufacturing†	2.62	1.35	5.09
Sales/administrative†	1.35	0.63	2.92
Household income < 200% FPL	3.12	1.65	5.88
Employer was accommodating	0.33	0.20	0.57
Cancer stage			
II†	1.47	0.82	2.61
III†	2.65	1.21	5.81

*OR for 1-yr increase in age
†Reference values: white race, manager/professional, stage I
Not significant: employer size, self-employed

6584 Poster Session (Board #409), Sat, 1:15 PM-4:45 PM

Trends in chronic opioid therapy among cancer survivors. *First Author: Talya Salz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer survivors may be at increased risk of opioid use disorders, due to opioid exposure during therapy, prevalent pain after therapy, and heightened risk of addiction among those with tobacco- and alcohol-related cancers. We hypothesized that chronic opioid therapy (COT) receipt among survivors would exceed receipt among people without cancer. **Methods:** Adults ≥65 years in SEER-Medicare data diagnosed with lung (N = 16,192), colorectal (15,429), or breast (23,474) cancer between 2008 and 2013 were followed through 2014 or death. Survivors were matched 1:1 at diagnosis (index date) on age, sex, and race with cancer-free controls. We defined COT receipt as the presence of claims for ≥90 consecutive days of opioid prescriptions. We described proportion of survivors and controls receiving COT each calendar year. For each year after index date, we used logistic regression to compare COT receipt between survivors and controls. **Results:** Among controls, there was a secular trend of increased COT receipt from 3% in 2008 to 6% in 2013. Similarly, for survivors in the first follow-up year, COT receipt increased from 5% in 2008 to 10% in 2013. For each follow-up year, COT receipt among lung and colorectal survivors (but not breast cancer survivors) exceeded that of controls. However, the odds ratios comparing COT receipt between survivors and controls diminished over time since the index date (Table). **Conclusions:** A secular trend of increased COT receipt over calendar years was seen in survivors and controls, but the increase was blunted among survivors. Proportion of COT receipt among survivors approached that of controls as survivors lived longer after diagnosis. Although the opioid epidemic appears to include survivors, the common use of opioids during therapy does not appear to lead to later increased rates of opioid use beyond that of the general population. Differences between cancer populations merit further investigation.
Odds ratios for COT receipt (reference = controls)

Follow-up years after index date	1	2	3	4	5	6
Lung	3.03*	2.84*	2.01*	1.78*	1.88*	2.80*
Colorectal	1.39*	1.35*	1.23*	1.22*	1.13	1.13
Breast	1.03	1.05	1.06	0.99	0.89	0.85

* $p < .05$

6585 Poster Session (Board #410), Sat, 1:15 PM-4:45 PM

Prediction of venous thromboembolism (VTE) in multiple myeloma (MM): Myeloma clot score (MCS). *First Author: Kristen Marie Sanfilippo, Barnes and Jewish Hospital/Washington University, St Louis, MO*

Background: Guidelines support pharmacologic thromboprophylaxis in MM patients identified as "high-risk" for VTE. Tools for VTE risk assessment in MM are contradictory and have not been validated. Such risk stratification would allow for use of thromboprophylaxis in MM patients at high-risk of VTE while avoiding anticoagulant exposure in patients at low risk. We aimed to develop and validate a risk prediction model for VTE in MM. **Methods:** We identified patients starting chemotherapy for MM within the Veterans Administration between 9/1999 and 12/2013. Using a split-sample method, we randomly created derivation (2/3) and validation cohorts (1/3). Variables associated with an increased risk of VTE within 6-months of chemotherapy start (univariate $p \leq 0.05$) and those with a $p \leq 0.10$ and an effect consistent with prior literature were offered into a backward stepwise model. Variables were removed until remaining variables predicted VTE ($p < 0.05$ OR $p \leq 0.30$ **plus** consistency with prior literature). A Myeloma Clot Score (MCS) was developed based on the parameter estimates. **Results:** The derivation cohort included 3036 patients of who 371 developed VTE within 6-months of starting chemotherapy. The MCS (Table 1) had a c-statistic of 0.68 in the derivation cohort and similar in the validation cohort. Incidence of VTE over the 6-month study period by score is in Table 1. In the validation cohort, the Hosmer-Lemeshow test was nonsignificant, showing adequate calibration. **Conclusions:** We developed and validated a risk model for predicting VTE in patients with MM starting chemotherapy. This MCS could be used to select patients who are likely to benefit from thromboprophylaxis.

Multivariate model and incidence of VTE by MCS score.

				Incidence of VTE by MCS Score		
Multivariate Risk Model Covariate	Hazard Ratio	*p* value	MCS Points	Score Range	Derivation Cohort	Validation Cohort
VTE before MM	2.77	<0.001	4	≤1	3.7%	4.4%
Low-Dose Dexamethasone	2.12	<0.001	3	2-5	10.9%	11.2%
High-Dose Dexamethasone	2.61	<0.001	4			
Thalidomide	1.68	<0.001	2	6-8	23%	25%
Central Venous Catheter	1.49	0.07	2	≥9	44%	58.8%
Erythropoietin	1.38	0.01	1			
BMI ³ 25	1.32	0.02	1			
Diagnosis Year	1.05	<0.001	1*			
Asian Race	0.45	0.26	-3			
Warfarin	0.21	<0.001	-6			

*Patients diagnosed 1999-2007

6586 Poster Session (Board #411), Sat, 1:15 PM-4:45 PM

A novel approach to mine the Veterans Administration Informatics and Computing Infrastructure (VINCI) allows one to assess the efficacy of cancer therapies: Abiraterone and enzalutamide in Veterans with metastatic prostate cancer (PC). *First Author: Harshraj Leuva, James J Peters VAMC, Bronx, NY, US*

Background: Novel efficacy endpoints are needed that correlate with overall survival [OS] and can describe real world outcomes. **Methods:** We mined national VA data (VINCI) using a novel set of equations validated in $>$ 10,000 patients that estimate simultaneously occurring exponential rates of tumor growth [*g*] and regression [*d*] using data gathered while a patient receives cancer treatment. We have previously established that *g* is highly correlated with OS and can esti mate doubling time (dt). Importantly, since the equations include time as a variable, this approach is ideal for real world analyses where re-assessments depend on the practitioner and are highly variable. To validate *g* in a real-world cohort, we collected cases of PC, demographics, treatments and outcomes from VINCI and compared parameters by receipt of chemotherapies for PC. **Results:** 5,890 Veterans were treated with abiraterone [ABI], enzalutamide [ENZA] or both. Median age was 75 years including 2,596 Veterans $>$ 80 years, and 23% identified as African American [AA]. PSA values beyond the initial measurement were available in 88% of patients with little clinical difference between those with and those without serial PSA values. *g* and *d* could be estimated in 83-85%f Veterans with p-values for fits $<$ 0.1 in all and $<$ 0.001 in the majority. *g* values for Veterans receiving either ABI [$0.0038d^{-1}$; dt 182d] or ENZA [$0.0040d^{-1}$; dt 173d] in first line were indistinguishable (p = 0,27), suggesting comparable efficacy. Consistent with the clinical bias, in second line, ENZA [$0.0071d^{-1}$; dt 98d] appears superior to ABI [$0.0091d^{-1}$; dt 76d] ($p < 0.01$). However, preliminary analyses find *g* on 1st line ABI remains constant in the majority and ABI continuation may be beneficial. Importantly *g* was independent of age, treatment location, and race, demonstrating comparable benefit in AA and non-AA Veterans. **Conclusions:** This is the largest real world assessment of ABI and ENZA efficacy in PC with a high percentage of AAs. The results underscore the value of determining *g* as an excellent measure of efficacy and argue for its use in outcomes research.

6587 Poster Session (Board #412), Sat, 1:15 PM-4:45 PM

Cancer patient-reported knowledge and preferences for liquid biopsies and blood biomarkers at a comprehensive cancer centre. *First Author: Min Joon Lee, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Novel blood-based biomarkers, including cell-free DNA and plasma signatures, are becoming a reality in precision oncology. Yet, little is known about cancer patients' perspectives on blood biomarkers in clinical practice. **Methods:** A 54-item self-administered questionnaire and four interviewer-administered trade-off scenarios were administered to cancer patients across all sites at Princess Margaret Cancer Centre. **Results:** Of 632 eligible patients, 66% (n = 417) completed the survey; 54% female; median age 61 (range 18-101) years. Patients had a median accuracy score of 18% (range 0-81%) on their knowledge of the role of biomarkers on their own cancer. Disease site was significantly associated with knowledge (P = 0.029); patients with breast, genitourinary, and thoracic cancers performed better than patients of other sites. Females (P = 0.012) and those with higher education (P = 0.019) and income (P = 0.0016) also scored better. Scores were not associated with the stage at diagnosis, time since diagnosis, age or ethnicity. Using chart review, 91% had been evaluated in at least one setting with either tissue, blood, or clinical biomarkers; however, only 20% of them were aware of this. In the scenario-based preference testing, if given a choice, 90% (n = 372) preferred a liquid (blood) over a tissue biopsy; however, these patients only accepted a median waiting period of one additional week (IQR: 0-3 weeks) and a 5% decrease (IQR 0-10%) in sensitivity of identifying the right treatment before switching their preference to the tissue biopsy. The majority (n = 216; 58%) were not interested in switching even with no potential complications from tissue biopsy. People with higher education were more likely to switch based on the level of risk ($P < 0.001$). **Conclusions:** Although patients had limited understanding of their cancer-specific blood-based biomarkers, 90% preferred blood over tissue biomarkers, but with little tolerance to waiting longer for results or decreased test sensitivity. Developing blood biomarkers and performing liquid biopsies are therefore desirable to patients, but only if they had similar or improved test characteristics over their tissue counterparts.

6588 Poster Session (Board #413), Sat, 1:15 PM-4:45 PM

Safety and tolerability of cancer drugs studied in phase 3 randomized controlled trials (RCTs) over the last decade. *First Author: Domen Ribnikar, Institute of Oncology, Ljubljana, Slovenia*

Background: Data suggest that newly approved cancer drugs have worse safety and tolerability profiles than older drugs used as control groups in trials. However, less is known about the toxicity profile of cancer drugs studied in unselected phase 3 clinical trials including those not resulting in regulatory approval. **Methods:** We searched clinicaltrials.gov to identify phase 3 RCTs evaluating experimental drugs in patients with metastatic breast, colorectal, lung and prostate cancer. We included all RCTs completed between 1 January 2005 and 31 October 2016. Odds ratios (OR) and 95% CI were computed for the following safety and tolerability end points: toxic death, treatment discontinuation without progression and commonly reported grade 3-4 adverse events (AEs). Data were then pooled in a meta-analysis using RevMan 5.3 software. **Results:** The analysis included 143 RCTs comprising 88,603 patients. 75% of the trials evaluated targeted therapies (including endocrine and immunotherapy). Compared to control groups, experimental drugs were associated with higher odds of toxic death (OR, 1.14; 95% CI, 1.03-1.27), treatment discontinuation without progression (OR, 1.64; 95% CI, 1.56-1.71) and grade 3-4 AEs (see Table). **Conclusions:** New cancer drugs studied in phase 3 RCTs are associated with worse safety and tolerability profiles compared to standard therapies when reported by investigators and have increased treatment-related mortality. Cancer patients considering enrollment on phase 3 trials should be aware of these risks.

Toxicity	OR	95% CI	p	% of trials with significantly higher odds in the experimental arm	% of trials with significantly lower odds in the experimental arm
Toxic death	1.14	1.03-1.27	0.02	5	0
Treatment discontinuation	1.64	1.56-1.71	< 0.001	46	7
Anemia	1.15	0.96-1.38	0.13	14	11
Neutropenia	1.09	0.86-1.39	0.47	28	25
Thrombocytopenia	2.04	1.46-2.85	< 0.001	16	2
Diarrhea	1.97	1.59-2.42	< 0.001	33	5
Vomiting	1.19	1.01-1.41	0.04	8	3
Stomatitis	2.44	1.69-3.51	< 0.001	25	4
Hypertension	2.63	1.93-3.60	< 0.001	42	4
Cardiac	1.46	1.19-1.78	< 0.001	9	0
Fatigue/asthenia	1.30	1.16-1.46	< 0.001	24	5
Skin	3.58	2.53-5.07	< 0.001	43	8
Dyspnea	1.04	0.91-1.19	0.52	6	2
Neuropathy	1.14	0.66-1.96	0.65	11	11

6589 Poster Session (Board #414), Sat, 1:15 PM-4:45 PM

Classifying lung cancer stage from health care claims with a clinical algorithm or a machine-learning approach. *First Author: Gabriel A. Brooks, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer stage is a critical determinant of cancer outcomes, however stage is not available in claims-based data sources used for evaluating real-world outcomes. We compare two new methods for classifying lung cancer stage from claims data. **Methods:** We used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare data to identify patients with lung cancer diagnosis in 2011-'12 who received chemotherapy within 6 months of diagnosis. We developed two approaches for using claims records to classify stage group (AJCC stage 1-3 vs. stage 4), using SEER stage as the gold standard. The first method was a clinical algorithm that assigned stage group based on treatment received (inclusive of surgery, radiation, and chemotherapy). The second method employed an ensemble of machine learning algorithms and analyzed an expanded set of claims-derived variables that considered treatments received, inpatient and outpatient visits, diagnosis codes, and demographic variables. We then used the Least Absolute Shrinkage and Selection Operator to select parsimonious variable sets of $\leq$ 10, 15, 20, 30, 40, and 50 variables. Classification methods were evaluated and compared on the basis of sensitivity, specificity, and accuracy, in reference to the stage 1-3 group. **Results:** The study sample included 14,743 patients with a mean age of 72.1 years. 54.6% were male. The best performing machine-learning classifier was the random forests algorithm. Sensitivity, specificity, and accuracy for the clinical algorithm were 53% (95% CI = 52-54%), 89% (88-90%), and 71% (71-72%), vs. 91% (90-92%), 89% (88-90%), and 90% (90-91%) for the random forests with 15 variables. Key variables for the random forest algorithm included secondary malignancy codes, treatments received (including type of surgery, number of radiation fractions, and specific chemotherapies), presence of COPD, and geographic region. **Conclusions:** Compared with a clinically derived algorithm, a machine-learning classifier demonstrated substantially improved sensitivity and accuracy. Improved accuracy of claims-based stage classification can support clinically relevant, real-world analyses of cancer care quality and outcomes.

6590 Poster Session (Board #415), Sat, 1:15 PM-4:45 PM

Development of a dashboard for end-of-life care at an academic hospital. *First Author: Kerin B. Adelson, Yale University, New Haven, CT*

Background: Accurate, reproducible, transparent and continuous healthcare utilization measures derived from structured EHR data may facilitate higher value cancer care at the end of life in both community and academic settings. Prior manually abstracted data from Smilow Cancer Hospital at Yale-New Haven showed high rates of chemotherapy and hospital utilization within 30 days of death. However, these data were not actionable due to the challenges with manual collection, physician attribution and date of death. **Methods:** The Yale Smilow Cancer Hospital and Flatiron Health used a commercially-available obituary source to supplement EHR data for a cohort of patients who received care at Smilow and died in 2016 - 2017. We developed an algorithm to attribute each patient to the correct oncologist based on visit frequency. We then used structured EHR data to measure rates of utilization for the following measures within 30 days of death: inpatient admission, ICU, chemotherapy and immunotherapy. Automated reports with internal benchmarks were generated to summarize resource utilization by individual physician, disease team, and practice site with patient level detail. Prior to wide scale launch across our enterprise, we provided oncologists in our community based practices feedback on use of chemotherapy in the last 30 days of life. **Results:** We found high rates of utilization at the end of life at both academic and community sites, and were able to identify outliers at the site of care, disease team and physician level. In the group that received quarterly feedback on chemotherapy in the last 30 days of life we saw a 23% improvement (see table). **Conclusions:** Performance dashboards with patient-level granularity identify performance outliers and opportunities for care improvement interventions. The reusable date of death, physician attribution and dashboard infrastructure allows measurement over time and rapid development of new measures. Efforts are underway to apply patient risk stratification to interpretation of practice variation, in addition to benchmarking against a national patient sample.

Chemotherapy in final 30 days.

Timeframe	Measure Score	N
2017 Q1	30.3% (22.3, 39.5)	109
2017 Q2	24.6% (18.2, 32.5)	138
2017 Q3	23.3% (16.2, 32.3)	103

6591 Poster Session (Board #416), Sat, 1:15 PM-4:45 PM

Adherence to oral anticancer medications after implementation of an ambulatory adherence program at a large urban academic hospital. *First Author: Marjorie Adams Curry, Georgia Cancer Center for Excellence at Grady Health System, Atlanta, GA*

Background: Oral anticancer medications (OAMs) offer convenient administration, reducing the burden of cancer treatment, but create new challenges including adherence to treatment and toxicity management. Using the Quality Oncology Practice Initiative, we identified a baseline 30% OAM adherence in the cancer center at Grady Health System, the largest public hospital in Atlanta, Georgia. To improve patient adherence, we conducted a quality improvement initiative in our ambulatory hematology and medical oncology clinics. **Methods:** The aim of this initiative was to increase OAM patient adherence by 30 percentage points. Through cause and effect analysis, significant barriers to adherence were identified including a lack of reminders and increased toxicities. This led to the development of two strategies: low cost adherence aids and a pharmacist-led OAM adherence program. Patients initiating new OAM regimens were consulted by a pharmacist for education and assistance with drug procurement. Patient education consisted of one-on-one education, drug information handouts, a treatment calendar, and a pillbox filled by the pharmacist. Patients were scheduled for mid-cycle adherence and toxicity assessments with the pharmacist. The adherence endpoint was satisfied if the patient had the drug available $\geq$80% to $<$ 120% of the days evaluated for four treatment cycles. To define the impact of this QI initiative, we collected prescription refill data prior to and after the intervention using prescription fill data and specialty pharmacy records. **Results:** Data was collected from 50 patients prior and 52 patients after implementation of the QI initiative. Five hundred and ninety-one interventions were documented including drug acquisition support, pillbox preparation, treatment calendar creation, supportive care adjustments and toxicity management. The program increased adherence from 30% to 85% in 2 years. Furthermore, the variability in adherence among patients was reduced (CI -3.24 – 156.7 *vs.* 52 – 140). **Conclusions:** A pharmacist-led adherence program combined with low cost adherence aids exceeded the goal for the adherence initiative at Grady Health System.

6592 Poster Session (Board #417), Sat, 1:15 PM-4:45 PM

The impact of the ASCO Choosing Wisely campaign for breast and prostate cancer on physician behavior. *First Author: Danielle Lee Rodin, Harvard T.H. Chan School of Public Health, Boston, MA*

Background: In April 2012, ASCO published its Choosing Wisely (CW) list of low-value services not supported by clinical evidence. The effectiveness of this campaign in changing physician behavior in oncology remains unknown. **Methods:** Retrospective analysis of breast and prostate cancer patients diagnosed from 2010-2013 and contained in the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Quarterly rates of imaging tests (positron emission tomography, computed tomography, bone scans) for staging in low-risk prostate cancer (T1-2a, Gleason $<$ 7, PSA $<$ 10 ng/mL) and for staging and post-treatment surveillance in early-stage breast cancer (AJCC I and II, N0, no neoadjuvant chemotherapy) was determined. Change in the proportion of patients receiving low-value tests before and after publication of the CW recommendations was evaluated using interrupted time series analysis. Tests were attributed to the specialty of the referring provider associated with the claim. **Results:** The cohorts consisted of 14,596 prostate, 43,591 breast staging, and 32,548 breast surveillance patients. Use of staging tests for prostate cancer was declining pre-CW (-0.52% per quarter) and experienced a small, but significant increase in the rate of decline post-CW to -0.79% per quarter, P = 0.0013; average utilization was 26.5% of patients pre-CW and 20.7% post. Use of surveillance imaging for breast cancer was stable pre-CW at 25.2%; it decreased post-publication by -0.61 percentage points per quarter (P $<$ 0.001) to 21.3% post. No significant change in use of breast cancer staging was observed (-0.05% per quarter, P = 0.37), with an average rate of 10%. Low-value test orders by specialty presented in Table 1. **Conclusions:** Following CW, there was a modest change in some physician behaviors toward recommendations. Further multidisciplinary efforts coupled with incentives may be needed to educate providers on judicious use of imaging.

Distribution of low-value tests by specialty.

	Surgeons	Radiation Oncologists	Medical Oncologists	Primary Care Providers	Other/ Unknown
Prostate staging	63.9%	4.3%	1.6%	16.9%	13.2%
Breast staging	44.7%	0.6%	17.8%	24.6%	12.4%
Breast surveillance	8.3%	5.0%	25.0%	40.6%	21.1%

6593 Poster Session (Board #418), Sat, 1:15 PM-4:45 PM

Use of hypofractionated radiotherapy for early stage breast cancer after implementation of evidence-based clinical guidelines. *First Author: Santosh Gautam, HealthCore, Inc., Wilmington, DE*

Background: Evidence-based guidelines have endorsed use of hypofractionated whole breast irradiation (WBI), a shorter course regimen delivered over 3-4 weeks instead of conventional WBI over 5-6 weeks, for certain early stage breast cancer patients. In 2016, health insurer Anthem updated its clinical guidelines making hypofractionated WBI the standard for eligible members in its fully-insured plans. This change did not apply to self-insured groups allowing these members to serve as an internal control. The objective of the study was to evaluate the impact of this guideline change on adoption of hypofractionated WBI. **Methods:** We used Anthem claims data to identify women with incident breast cancer diagnosis followed by lumpectomy and subsequent WBI during 2015-2016. We further retained patients guideline-endorsed for hypofractionated WBI, i.e. those aged 50 or older, without prior chemotherapy or lymph node involvement. We defined hypofractionated WBI as 11-24 fractions (3-5 weeks of WBI) and conventional WBI as 25-40 (5-8 weeks of WBI). We compared pre-and post-intervention (year 2015 vs 2016) hypofractionated WBI rates between members in fully insured plans (intervention group) and members in other plans (comparison group) using a regression-adjusted difference-in-difference (DID) analysis controlling for age and comorbid conditions. **Results:** Compared to patients in comparison group (N = 2,333), those in intervention group (N = 728) were older (mean age 63.1 vs 61.4; p $<$ .001) and had more comorbid conditions (mean Deyo-Charlson index 0.74 vs 0.60; p = 0.002). The rate of hypofractionated WBI increased from 53% in pre- to 68% post-intervention period for intervention group, an increase of 28%. In contrast, the rate changed from 58% to 63%, an increase of just 9%, in comparison group. The adjusted DID results suggested that change in guidelines increased the hypofractionated WBI adoption rate by 9% (p = 0.035). **Conclusions:** The changes in health plan guidelines resulted in higher rates of hypofractionated WBI adoption. Health plans could play an important role in accelerated adoption of evidence-based guidelines.

6594 Poster Session (Board #419), Sat, 1:15 PM-4:45 PM

***CYP2C19*-guided voriconazole prophylaxis in neutropenic AML patients.** *First Author: James Kevin Hicks, Moffitt Cancer Center, Tampa, FL*

Background: Acute myeloid leukemia (AML) patients who have prolonged neutropenia are at increased risk of morbidity and mortality due to invasive fungal infections. Voriconazole (VCZ), an effective antifungal prophylactic, is metabolized by the polymorphic CYP2C19 enzyme. Approximately 25% of individuals are genetically predicted to be CYP2C19 rapid metabolizers, thus at increased risk of breakthrough fungal infections due to low VCZ concentrations. We implemented a quality improvement pilot utilizing *CYP2C19* genotype to optimize prophylactic VCZ dosing. **Methods:** AML patients with prolonged neutropenia are eligible for *CYP2C19* genotyping (Luminex xTAG CYP2C19 Kit v3). Phenotypes are assigned per Clinical Pharmacogenetics Implementation Consortium guidelines. *CYP2C19*-guided recommendations for our quality improvement pilot are as follows: avoidance of VCZ in ultrarapid metabolizers, VCZ 300 mg twice daily (BID) for rapid metabolizers, and VCZ 200 mg BID for all other phenotypes. Therapeutic drug monitoring (TDM) is performed at the discretion of the medical team (goal trough concentration of 1-5.5 mcg/ml). **Results:** To date, 193 AML patients have undergone *CYP2C19* genotyping; 3 (1.6%) ultrarapid, 50 (25.9%) rapid, 78 (40.4%) normal, 55 (28.5%) intermediate, and 7 (3.6%) poor metabolizers were observed. 154 patients (79.8%) received VCZ for prophylaxis, 11 (5.7%) for treatment, and 28 (14.5%) did not receive VCZ. Of the 154 patients receiving prophylactic VCZ, 137 (89%) were dosed per *CYP2C19*-guided recommendations. Pre-intervention (VCZ 200 mg BID) and post-intervention (VCZ 300 mg BID) VCZ trough concentrations were compared. Only 36.4% (4/11) of CYP2C19 rapid metabolizers receiving VCZ 200 mg BID achieved the goal trough concentration, whereas 75% (21/28) of rapid metabolizers receiving VCZ 300 mg BID achieved the goal trough concentration. *CYP2C19*-guided VCZ dosing resulted in trough concentrations in the target range for 70.1% (47/67) of all patients. **Conclusions:** Implementation of *CYP2C19* genotyping to guide VCZ prophylactic dosing is feasible, with 70.1% of all patients having a VCZ goal trough concentration. Future analysis will determine if *CYP2C19*-guided VCZ dosing prevents breakthrough fungal infections.

6595 Poster Session (Board #420), Sat, 1:15 PM-4:45 PM

Does training oncologists to have goals of care discussions affect healthcare utilization among patients with advanced cancer? *First Author: Nina A. Bickell, Mount Sinai School of Medicine, New York, NY*

Background: Aggressive treatment near the end of life is a measure of poor quality care. Goals of Care (GoC) discussions may affect healthcare utilization among patients with advanced cancer. We coached oncologists to improve communication skills (CS) & report the effect of CS coaching on hospital, ER, hospice & ICU admission in the last month of life. **Methods:** We randomized solid tumor oncologists at 4 academic, community, municipal and rural hospitals to participate in a RCT of communication skills training & recruited their newly diagnosed advanced cancer patients with $<$ 2 year prognosis. Ten CSs were assessed via checklist review of audiotaped visits. Charts were abstracted, patients or their caregivers were surveyed at 6 months to assess utilization of: chemotherapy, ICU, hospitalizations, ER visits and hospice in the last 30d of life and over the 6 months enrolled in the study. A GoC discussion included discussion of prognosis, treatment preferences, and what's important to patients given their cancer diagnosis. We enrolled 22 of 25 eligible oncologists (88%). 263 patients were recruited & surveyed to assess whether a GoC discussion occurred. 250 (95%) had charts abstracted and were resurveyed at 6 months to assess utilization at other hospitals. **Results:** Patients' mean age was 63 yrs (20-89), 60% male, 53% white, 29% black & 19% Latino. 35 patients (13%) died within 6 months of baseline survey with no difference between patients of intervention (INT) or control (CNTL) oncologists. Compared to CNTLs, INT oncologists' skills improved with coaching (1.63 vs -0.09; p = .04). 43% INT and 46% CNTL patients reported a GoC discussion. The average rate of hospitalization/ pt = 0.32 (0-3) and ER visits = 0.44 (0-4) with no difference between INT & CNTL. Rates of aggressive treatment in the last 30d of life varied: chemotherapy = 21%; ICU stay = 7% with no difference between INT & CNTL patients. Hospice enrollment occurred 2 weeks prior to death; no difference in INT vs CNT (13.5d vs 14d). **Conclusions:** Despite improving oncologists' communication skills to conduct GoC discussions, there was no impact on rates of hospitalization, receipt of aggressive treatments or enrollment in hospice at the end of life. Clinical trial information: NCT02374255.

6596 Poster Session (Board #421), Sat, 1:15 PM-4:45 PM

Improving documentation of pain and constipation management within the cancer center of a large public healthcare network. *First Author: Giselle Dutcher, Department of Medicine, Emory University School of Medicine, Atlanta, GA*

Background: Cancer patients commonly suffer from pain and constipation, and a high number of patients have inadequate control of these symptoms. At the Cancer Center for Excellence at Grady Health System, a large public healthcare network in Atlanta, baseline QOPI measures for pain and constipation documentation were below benchmark levels. We conducted a quality improvement (QI) initiative to improve the management of pain and constipation. **Methods:** Given the low baseline rates of QOPI documentation for pain (58%) and constipation (60%) assessment, we aimed for a 20-percentage point increase in documentation of these measures. Cause and effect analysis identified causal factors. This led the team to develop a new note template that automatically integrates pain and constipation assessment data from the nursing note into the practitioner's documentation. We developed a new process in the electronic medical record (EPIC) to link appropriate orders with the pain and constipation plan. Mandatory use of the new note began in June 2017. We reviewed documentation pre- (12 months) and post- (4 months) intervention. **Results:** Integrating a nursing assessment into the note for the practitioner increased pain score documentation from 66% to 87% and pain management from 47.2% to 83.2%. Similarly, documentation of constipation assessment increased from 18.9% to 82.8% and constipation management increased from 11.78% to 75%. This QI intervention improved pain control by the 3rd visit from 47% to 57%. This strategy also reduced emergency department (ED) visits and hospitalizations from 21% to 9%. **Conclusions:** Using a standardized visit template and mandated assessment of constipation and pain lead to an increase greater than the 20% goal for documentation of these symptoms. This intervention resulted in improved pain and constipation control. This strategy suggests a reduction in ED visits.

6597 Poster Session (Board #422), Sat, 1:15 PM-4:45 PM

Does training oncologists to have goals of care discussions increase and improve the quality of GoC discussions with advanced cancer patients? *First Author: Nina A. Bickell, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Advanced cancer patients often have a poor understanding of the incurability of their cancers and this correlates to higher rates of aggressive treatment near end of life. Goals of Care (GoC) discussions may affect patients' decisions about aggressive treatment near end of life. We coached oncologists to improve communication skills and assessed its impact on prevalence and quality of GoC discussions. **Methods:** At an academic, community, municipal and rural hospital, we recruited & randomized solid tumor oncologists & their newly diagnosed advanced cancer patients with $<$ 2 year prognosis. Prior to and after completing 4 coaching sessions, a post-imaging visit was audiotaped and reviewed by VitalTalk trained specialists to assess oncologists' communication skills. Consented patients were surveyed after their 3 month post-imaging visit & GoC discussions defined as: cancer treatment preferences, what's important to you in life given your diagnosis and prognosis. **Results:** We enrolled 22/25 eligible oncologists (88%) & 265 patients. On average, doctors were 44 yrs old (32-66) & in practice 14.5yrs (5-40). There was no significant difference between intervention (INT) and control (CNTL) oncologists' prior communication skills training (58% v 56%; p = 0.80) & comfort having GoC discussions (58% v 56%; p = 0.80). On average, CNTL physicians had no change in the number of demonstrated skills (5.45 to 5.36/10); INT physicians increased from 6.6 to 8.3/10 skills (p = 0.04). Patients' mean age was 63 yrs (20-89), 60% male, 52% white, 30% black & 19% Latino. Overall, 61% of patients reported their treatment's goal was to cure their cancer; 40% reported cure to be likely. 49% had a complete GoC discussion (48% INT v 51%; p = 0.61). 65% of patients reported their oncologist talked about their GoC, "the very best" they could imagine (63% INT v 68% CNTL; p = 0.39). 51% did not report a GoC discussion with no difference between INT (52%) & CNTL (49%) patients (p = 0.61). **Conclusions:** Using a coaching model to teach oncologists' communication skills improved skills to carry out a GoC discussion but did not increase rates of GoC discussions among advanced cancer patients with $<$ 2 year life expectancy. Clinical trial information: NCT02374255.

6598 Poster Session (Board #423), Sat, 1:15 PM-4:45 PM

Use of QT interval prolonging drugs (QT drugs) and electrocardiogram (ECG) monitoring in patients (pts) receiving first-line anti-cancer systemic therapy (tx): A population-based analysis. *First Author: Rossanna C. Pezo, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, ON, Canada*

Background: QT interval prolongation, measured on ECG, is a known toxicity of many drugs used in oncology and can lead to serious arrhythmias. To our knowledge, there are no published studies investigating ECG use in pts on standard systemic tx involving QT drugs. **Methods:** All cancer pts ≥ 66 years diagnosed in 2005-2011 in the Ontario Cancer Registry were linked to population-based administrative databases to ascertain pt demographics, comorbidities, systemic tx and ECG use. The Ontario Drug Benefit Program database was used to identify prescription QT drug use (as per CredibleMeds.org classification). Univariable and multivariable analyses were used to examine factors associated with ECG use within 30 days of systemic tx initiation. **Results:** A total of 59,484 pts (median age 74; 48% women) were included. Common cancers were breast (23%), prostate (22%), lung (10%) and colon (9%). Prior diagnoses included hypertension (56%), diabetes (24%), coronary artery disease (CAD; 24%), and heart failure (HF; 9%). Among pts on at least 1 QT drug (n = 48,236; 81%), the majority (n = 41,727; 87%) received a prescription within 30 days of systemic tx initiation, commonly for anti-emetics (n = 18,232; 44%). Overall, only 27% pts on QT drugs had an ECG within 30 days of systemic tx initiation; ECG use was low even among pts with CAD (35%), HF (42%), pts on ≥3 concurrent QT drugs (37%) and pts on anti-emetic (30%) and *anti-cancer* (21%) QT drugs. On multivariable analysis, adjusting for age, sex, comorbidities, rural setting and cancer type, ECG use was associated with recent cancer diagnosis (2011 versus 2005; OR = 1.37, 95% CI 1.26-1.49), Charlson score ≥1 (OR = 1.22; 95% CI 1.15-1.29) and multiple QT drugs (OR = 1.15 per each additional QT drug, 95% CI 1.12-1.17). Use of anti-emetic (OR = 0.93; 95% CI 0.88-0.99) and *anti-cancer* QT drugs (OR = 0.74, 95%CI 0.70-0.79) were paradoxically associated with fewer ECG use. **Conclusions:** Our study highlights common use of QT drugs and under-use of ECG in cancer pts at risk of arrhythmia. Since ECG is an inexpensive, non-invasive and widely available test, it should be used routinely for monitoring the QT interval in such pts.

6599 Poster Session (Board #424), Sat, 1:15 PM-4:45 PM

Implementation of dietary education within a multidisciplinary team approach to improve treatment accuracy and efficiency in prostate cancer external beam radiation therapy. *First Author: Taylor L Evans, James J. Peters VAMC, Bronx, NY*

Background: Prostate cancer is the most common cancer in the Veterans Health Administration. Radiation is an important treatment option for prostate cancer patients. Imaging is done before each daily radiation treatment to ensure the radiation beam is aimed accurately. Imaging can be inaccurate due to excess gas or stool in the rectum, which alters the treatment field and leads to delays in the daily treatment schedule, increased radiation exposure due to re-imaging, repetitive staff treatment delivery interventions, and an unsatisfactory veteran experience. **Methods:** A quality improvement project utilizing A3.9 Box Process Improvement Methodology (problem solving template) was undertaken to address identified gastrointestinal concerns hindering daily treatment. A dietitian integrated services into the radiation oncology clinic by providing dietary education and counseling to avoid gas-producing foods and manage bowel regularity for prostate cancer patients. Daily images were reviewed for accuracy. For 3 months prior to intervention, we examined daily treatment images and documented any interruption in treatment delivery from gas or stool in the rectum as a nutrition-related defect. Initial data analysis revealed that 62 of 195 (31.79%) daily treatment deliveries experienced nutrition-related defects. **Results:** As a result of changing the radiation therapy process to include dietary education to patients, we experienced a 53% reduction rate in nutrition-related defects (from 31.79% to 14.87%). Calculated cost avoidance showed an annual savings of approximately $19,300 with implementation of a multidisciplinary approach. A total of 120 daily treatment visits and 90 patient treatment hours can be saved annually with this approach. **Conclusions:** This project improved overall clinic function by implementing a multidisciplinary approach to prostate cancer radiation oncology care, increased patient's satisfaction, reduced excess radiation exposure, and improved department efficiency.

6600 Poster Session (Board #425), Sat, 1:15 PM-4:45 PM

Prevalence of HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) among newly diagnosed cancer patients treated in academic and community oncology practices: SWOG S1204. *First Author: Scott David Ramsey, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Universal screening of newly diagnosed cancer patients for HIV, HBV and HCV viruses is not routine in oncology practice. Amid concerns about viral reactivation and adverse outcomes during antineoplastic therapy, experts disagree about whether testing should be routinely performed. In this study we estimated the prevalence of HIV, HBV, and HCV infection among persons with newly diagnosed cancer. **Methods:** This multicenter, prospective cohort study included 9 academic and 9 community SWOG oncology institutions. Eligible patients included those with any malignancy presenting to clinic within 120 days after cancer diagnosis. Patients either provided documentation of known viral status or were tested for HIV, HBV or HCV upon enrollment. **Results:** In total, 3,092 patients were registered. The median age of the cohort was 61 years old, most were female (60%), 18% were black, 18% were Hispanic and 3% were Asian. Screened patients had similar clinical and demographic characteristics to those registered. Infection rates adjusted for cancer type were 9.7% for HBV, 2.8% for HCV and 1.4% for HIV. At clinic presentation, observed viral status was previously diagnosed for 17% of HBV patients, 69% of HCV patients and 94% of HIV patients. Cancers that had the highest prevalence per infection (HBV, HCV) included liver (22%, 18%), lung cancer (13%, 5%), head and neck cancer (13%, 5%) and non-colorectal GI cancers (15%, 1%). HBV risk was highest in those who had sexual contact with HIV+ person(s) or were infected with HIV or HCV. HCV risk was highest in those who injected drugs or were tested because they had on-the-job blood exposure, injection drug use or transfusion before 1992. **Conclusions:** The overall prevalence of HBV and HCV in this population of cancer patients is substantially higher than the general population (3.9% and 1.3%, respectively). Much of the HBV and HCV infection detected in this study was previously undiagnosed, suggesting that screening may be desirable. The low rate of previously unknown HIV infection suggests routine testing is unnecessary except in cancers highly associated with HIV. Funding: NIH/NCI CA189974, CA180888, CA180819

6601 Poster Session (Board #426), Sat, 1:15 PM-4:45 PM

Identifying and interpreting actionable molecular alterations from next-generation sequencing results in the community: A Sarah Cannon molecular cancer conference. *First Author: Holli Hutcheson Dilks, Sarah Cannon Research Institute, Nashville, TN*

Background: Next-generation sequencing (NGS) data can often be difficult to interpret and act upon for treating medical oncologists. Sarah Cannon developed a Molecular Cancer Conference (MCC) in May 2017 at a community clinic in Chattanooga, TN with the goal of helping medical oncologists identify and interpret molecular alterations from NGS results obtained in routine clinical practice. Herein, we report the workflow and effectiveness of the MCC in identifying actionable results and guidance in care. **Methods:** Molecular profiles from one community medical oncology office were reviewed by a MCC committee over a six month pilot period. The committee – made up of medical oncologists and research staff at the site, and a human geneticist, cancer cell biologist, and clinical pharmacologist linked in remotely from Sarah Cannon Research Institute in Nashville, TN via web-conference. The MCC met every 2 weeks to review all tissue- and blood-based NGS results from the interim. Mutations were analyzed using public databases and published literature; and patient diagnosis and clinical trial molecular inclusion/exclusion criteria were used to guide therapy and clinical trial recommendations, as well as approved therapies. **Results:** From 175 reports, 3608 molecular alterations were detected (avg. = 20.6 mut/pt; including VUSs) by commercially available NGS labs. Clinical trials were discussed for 148 patients (85%), and 26 patients (15%) were enrolled on clinical trials. Uncommon alterations were identified including a *FGFR2-VCL* fusion in cholangiocarcinoma, *ERBB2* amplifications in NSCLC, and two unique *ERBB2* VUSs in a HNSCC. Each of these mutations was treated with a targeted therapy as part of a clinical trial protocol. **Conclusions:** Sarah Cannon's MCC was established to review and analyze patient molecular profile reports for community-based medical oncologists. Utilization of the MCC resulted in patients being screened for and enrolled on clinical trials. These findings highlight the feasibility and impact of having an expert committee review complex results and provide scientific advice to help guide care for patients in the community.

6602 Poster Session (Board #427), Sat, 1:15 PM-4:45 PM

A nationwide analysis of palliative care service utilization in hospitalized metastatic cancer patients. *First Author: Kaushal Parikh, New York Medical College, Valhalla, NY*

Background: ASCO guidelines recommend palliative care consultation (PC) to patients with advanced cancer to improve quality of life and overall survival. However, limited data are available on contemporary trends in PC utilization in hospitalized metastatic cancer patients. **Methods:** We used the 2005-2014 Unites States National Inpatient Sample to identify all hospitalizations in adult patients with a primary or secondary discharge diagnosis of lung, prostate, breast, or colorectal cancers, with documented metastasis. Multivariable logistic regression models accounting for the complex survey design were used to analyze associations of PC with various cancer related complications, comorbidities, and patient and hospital demographics. **Results:** Of the 3,040,740 cases included in the study, 289,600 (9.5%) had PC. Median ages of patients with prostate, lung, colorectal, and breast cancers were 76, 67, 65, and 61 years, respectively. There was a 550% increase in PC utilization between 2005 and 2014 (2.7% to 17.5%; $P < 0.001$). While the utilization rate was highest with metastatic lung cancer (3% in 2005 to 20.2% in 2014; $P < 0.001$), increase in utilization was highest for colon cancer (577%; 2.2% in 2005 to 14.9% in 2014; $P < 0.001$). Overall, cancer related pain (adjusted Odds ratio (aOR) 2.35, 95% confidence interval (CI) 2.26-2.45; $P < 0.05$) and failure to thrive (aOR 2.19, 95% CI 2.09-2.29; $P < 0.05$) were strongly associated with PC referrals. Age $>$ 65 years (aOR 1.56, 95% CI 1.46-1.67; $P < 0.05$), respiratory failure (aOR 2.10,95% CI 2.03-2.16; $P < 0.05$), and sepsis (aOR 1.12, 95% CI 1.078-1.16; $P < 0.05$) were also independently associated with PC. PC was more likely to be utilized in teaching hospitals (aOR 1.25, 95% CI 1.16-1.34; $P < 0.05$), large-sized hospitals (aOR 1.25, 95% CI 1.13-1.37; $P < 0.05$), and west coast hospitals (aOR 1.31, 95% CI 1.17-1.47; $P < 0.05$). **Conclusions:** Despite a significant rise between 2005 and 2014, palliative care services are still underutilized for hospitalized advanced cancer patients in the United States. Cancer related pain and failure to thrive were strongly associated with PC utilization. Regional and hospital based variations exist in PC utilization in patients with metastatic tumors.

6603 Poster Session (Board #428), Sat, 1:15 PM-4:45 PM

TelePsychiatry for cancer patients undergoing active treatment. *First Author: Christian Otto, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Numerous studies have demonstrated the effectiveness of telepsychiatry in non-cancer related disease; however, there are limited reports of telepsychiatry for cancer patients under active treatment. The MSK Counseling Center initiated a telepsychiatry program for patients residing near MSK regional care sites with limited counseling services. **Methods:** Patients were identified who lived within the catchment area of two MSK regional sites in Westchester County and Suffolk County, NY. Patients were invited to participate who had previously been seen in-person who were scheduled for psychotherapy follow-up or medication management. Data on telepsychiatry visits performed by 5 psychiatrists was collected over a 2-year period beginning in January 2016. Telepsychiatry sessions took place between the patient at the MSK regional site and the psychiatrist at the Manhattan Counseling Center. Sessions were supported by Cisco Jabber Movi videoconferencing software and high definition videoconferencing equipment. Patients were asked to fill out a technology acceptability questionnaire post-visit. **Results:** Thirty-eight patients (14 males; 56.3 $\pm$ 10.8 years) with 19 cancer diagnoses, and 26 psychiatric diagnoses (1.8$\pm$ 0.9/patient) completed 159/187 telepsychiatry visits (cancellation rate 15.0%). Each patient had an average of 4.2$\pm$5.8 visits. Anxiety disorder-unspecified, adjustment disorder with mixed anxiety and depressed mood, and major depressive disorder were the three most common diagnoses. Fifty percent (N = 19) of patients completed the questionnaire. Most respondents (96.0%) highly agreed or agreed that telepsychiatry visits made it easier for them to obtain care, and that the quality of care was the same as in-person. The majority of patients who completed the questionnaire underscored the benefits of avoiding lengthy travel to Manhattan for appointments, the ease of scheduling, decreased appointment wait time, and the similarity to in-person visits. **Conclusions:** Telepsychiatry has high acceptability among cancer patients and offers a means of providing care to established patients who are stable, while decreasing the stress encountered from frequent travel, missed work, and associated caregiver requirements.

6604 Poster Session (Board #429), Sat, 1:15 PM-4:45 PM

Utilization of telemedicine at two high-volume cancer care organizations. *First Author: Rob Williams, Ontario Telemedicine Network, Toronto, ON, Canada*

Background: The Ontario Telemedicine Network (OTN) in Support of Cancer Care Ontario (CCO), and Memorial Sloan Kettering (MSK) are leveraging telemedicine and digital health care to improve patient/provider satisfaction, care coordination, and clinical outcomes, while decreasing costs. **Methods:** Data on patient telemedicine services and provider activity was reviewed, in addition to implementation challenges and lessons learned. New virtual services were outlined regarding their ability to enhance patient accessibility and clinical effectiveness. **Results:** OTN has enabled 268 CCO sites across the 14 Ontario Regional cancer centers which have generated 20,138 cancer telemedicine sessions in 2016/17. Prostate, lung, breast, and colorectal cancers had the highest telemedicine utilization. Telemedicine sessions were employed by 20% (N = 40) of provincial radiation oncologists, and 20% (N = 34) of medical oncologists. In 2015, telemedicine supported the delivery of oral and intravenous chemotherapy in 1,269 cases and facilitated 368 palliative care visits. Telemedicine saved patients: 6.4 million km of driving, 64K hours of travel time, and over $4.7 million in travel and accommodation costs. MSK sees 19K new actively treated patients annually, 76% access the patient portal to view appointment notifications, complete patient assessments, review lab results, retrieve learning materials, send and receive secure messages from providers, and review billing. Patient assessments include PRO-CTCAE daily symptom surveys, with symptom alerts, to track recovery in post-surgical patients. TeleGenetics at MSK has delivered 3416 virtual visits to patients and family members at four regional locations, telepsychiatry has supported 160 sessions to 3 regional sites; and an inpatient fall prevention program using video monitoring of a patient's movements has decreased falls 42% in GI and 34% in neurology cancer inpatients while decreasing patient attendant costs $393K. **Conclusions:** Utilization of telemedicine and digital care platforms among cancer patients and providers is steadily increasing due to convenience, significant cost savings, high satisfaction rates, increased care coordination, and improved clinical outcomes.

6605 Poster Session (Board #430), Sat, 1:15 PM-4:45 PM

The effect of supervised, individualized exercise on cost savings during cancer treatment. *First Author: Karen Y Wonders, Maple Tree Cancer Alliance, Dayton, OH*

Background: Research indicates that endurance exercise training is helpful in attenuating the deleterious effects of cancer treatments. However, nationally less than 5% of patients are ever referred to a cancer exercise program. Cost is a barrier to these programs, as they often are not reimbursable under most insurance plans. Therefore, the purpose of this investigation was to determine if exercise training during cancer treatment helped to minimize side effects and reduce health care costs. **Methods:** This was a retrospective, two-group study which ascertained the protective effect of an exercise-training program during cancer treatment. Medical records were reviewed to determine outcome data for length of hospital stays, hospital readmits, ER visits, treatment compliance, fatigue, and anxiety/depression related to oncology conditions. Patients were excluded if they had pre-existing conditions prior to treatment. Individuals in the exercise group (EX, n = 672) completed 12 weeks of prescribed, individualized exercise. Individuals in the sedentary group (SED, n = 728) did not participate in an exercise program during treatment. **Results:** Patients in the EX group had significantly lower reports of fatigue, pain, cardiac problems, depression, and anxiety than their SED group counterparts ($p < 0.05$). The EX group tolerated their treatment significantly better than the SED group ($p < 0.05$). Most notable, the EX group had a significantly lower number of ER visits, 30-day readmits, and length of stay ($p < 0.05$). **Conclusions:** These data point to a protective effect of individualized exercise that translated to improved patient outcomes and cost savings for the payer, provider, and patients, alike.

6606 Poster Session (Board #431), Sat, 1:15 PM-4:45 PM

A proportional comparison of cancer burden and patient advocacy organization (PAO) funding by histology demonstrates many underfunded histologies. *First Author: Suneel Deepak Kamath, Northwestern University Feinberg School of Medicine, Division of Hematology/Oncology, Chicago, IL*

Background: PAOs in oncology are vital in funding research for rare cancers, young investigators and innovative projects, but some histologies may be underfunded relative to their burden. This study examined the alignment of cancer burden by histology with PAO funding for each histology to raise awareness of areas of unmet need. **Methods:** The GuideStar database was used to find all cancer PAOs with > $5 million (M) in annual revenue (AR) using NTEE codes and 165 cancer-related search terms. Care delivery PAOs were excluded. PAOs were classified by the histology they support. AR was obtained from IRS Form 990s for each PAO. Total annual revenue (TAR) per histology was calculated by adding ARs for each PAO in that histology. Cancer burden based on annual incidence, deaths and person-years of life lost (PYLL) was obtained from SEER data. Comparison of TAR with incidence, deaths and PYLL of each histology was done using descriptive statistics. **Results:** 125 PAOs with TAR of $6.4 billion were included. 64 (51%) were histology agnostic. Cancers with the most PAOs were pediatric (14, 11%), breast (13, 10%), leukemia (4, 3%) and lung (4, 3%). There were no PAOs with AR > $5 M for esophageal, gastric, kidney or bladder cancers. Histology-agnostic PAOs had $5 billion (78%) of TAR. Cancers with largest TARs were breast ($460M, 7%), pediatric ($207M, 3%), leukemia ($201M, 3%) and lymphoma ($145M, 2%). The ratios of TAR by histology vs. incidence, deaths and PYLL are shown in Table 1. PAOs in pediatric cancer, breast cancer, leukemia and lymphoma had the highest ratios in all 3 metrics. Colon, liver and uterine cancer PAOs had the lowest ratios. **Conclusions:** Cancer PAOs generate substantial AR that complements government research funding. Cancer PAOs overall can be better funded, especially PAOs in GI, GU and gynecologic cancers to drive research and awareness.

	Breast	Colon	Uterine	Leukemia	Liver	Lymphoma	Lung	Melanoma	Ovary	Pancreas	Pediatric	Prostate
TAR (millions $)	460	18	5	201	6	145	92	14	23	58	207	76
TAR/Incidence ($)	1804	133	87	3241	115	1802	412	160	1012	1087	13,586	472
TAR/Deaths ($)	11,207	359	490	8219	185	6840	588	1433	1614	1354	115,901	2847
TAR/PYLL ($)	595	23	33	547	15	476	39	87	91	100	2255	278

6607 Poster Session (Board #432), Sat, 1:15 PM-4:45 PM

Duration of physician-industry relationships and prescribing changes in oncology. *First Author: Aaron Philip Mitchell, The University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Physicians who accept payments from a pharmaceutical company are more likely to prescribe that company's cancer drug[s]. Whether long-term physician-industry relationships are more likely than intermittent relationships to result in practice changes is unknown. **Methods:** Open Payments data, containing industry-physician financial transactions, was linked to Medicare Part D prescription drug claims for 2013-2015. We identified physicians who treated each of 4 cancer types which had multiple orally-administered treatment options: renal cell (axitinib, everolimus, pazopanib, sorafenib, sunitinib), lung (erlotinib, afatinib), CML (dasatinib, nilotinib), and prostate (abiraterone, enzalutamide). We used modified Poisson regression to test if the number of years (either 1, 2, or 3) in which a physician received payments was associated with increased prescribing of the paying company's cancer drug in 2015. We also tested whether physicians at NCI-designated cancer centers were more likely to receive industry payments. **Results:** The physician cohort sizes were: RCC, 674; lung, 966; CML, 367; prostate, 1,483. Controlling for physician characteristics including practice size, prescribing volume, and total dollar amount received, physicians who received payments in all 3 years (vs. 1 year) were more likely to use the paying company's drug within RCC (RR:1.69, 95%CI 1.32-2.17) and lung cancer (RR: 1.42, 95%CI 1.15-1.77), but not CML (RR:1.13, 95%CI 0.94-1.35) or prostate cancer (RR: 0.93, 95%CI 0.85-1.01). Results were similar comparing physicians who received payments in 3 years vs. 2 years: RCC RR:1.53, 95%CI:1.21–1.94; lung RR: 1.12, 95%CI:0.93–1.35; CML RR:1.13, 95%CI 0.94–1.35; prostate RR: 0.93, 95%CI:0.85–1.01. Physicians at NCI institutions were less likely to have received any industry payments during the study period (RR:0.70, 95% CI:0.61-0.80). **Conclusions:** Longer-term industry relationships may be associated with greater changes in drug prescribing than time-limited ones. Conflict-of-interest policies and disclosures may be more informative if specifying duration of industry relationships. This study was limited by a short time range, and lack of payment records prior to 2013.

6608 Poster Session (Board #433), Sat, 1:15 PM-4:45 PM

What role does the patient perspective play in determining access to innovative therapies? *First Author: Clare Frances Jones, PRMA Consulting Ltd, Fleet, United Kingdom*

Background: The 21st Century Cures Act 2016 (21st CCA) requires the FDA to do more to incorporate patient perspectives into their decision-making on products, particularly patients' experience of disease and effects related to treatment. This experience may be captured using patient-reported outcome measures (PROMs). We sought to understand how patient-relevant outcomes beyond survival were considered in evaluations of oncology drugs by regulators, oncology societies, and payers (health technology assessment [HTA] agencies), and how this might change in future. **Methods:** We reviewed EMA summaries of product characteristics and FDA package inserts of products approved in 2017 plus documents from completed or ongoing assessments by national HTA agencies in England, France, and Germany for reference to PROMs, quality of life, or symptoms of disease. PubMed and Google were searched for published ASCO value framework or ESMO MCBS v1.1 scores. Clinicaltrials.gov was searched to identify PROMs included in Phase 2 or 3 industry-sponsored trials initiated between 2013-2017. **Results:** None of the 16 FDA labels included any mention of PROMs or patient-reported symptom measures (other than AEs). Of 13 products in Europe, 7 reported PROMs or symptom measures. Few HTAs have been completed; documentation for 7 products (NICE 4; TC 1; IQWiG 4; G-BA 2) referred to measures of interest. No systematic scoring of newly approved products using ASCO was identified; ESMO MCBS v1.1 scores are available within updated treatment guidelines. Of 70 industry-sponsored Phase 2 or 3 trials, 68 reported including a PROM, the most commonly used were EORTC-QLQ-C30 (24% of trials) and associated disease-specific modules. Other pan-tumor PROMs used in > 1 trial included EQ-5D (23%) and PROMIS (4%) or PRO-CTAE (4%) (and only since 2015). Results will be updated in May 2018 **Conclusions:** To date, the 21st CCA appears to have had no impact on FDA approvals. However, recent inclusion of PRO-CTCAE or PROMIS in trials may be related to 21st CCA. In Europe there is wider consideration of PROMs. The use of these instruments and other patient-relevant measures of benefit by stakeholders determining access to innovative therapies should be monitored and encouraged further.

6609 Poster Session (Board #434), Sat, 1:15 PM-4:45 PM

Cost-effectiveness analysis of brentuximab vedotin with chemotherapy in newly diagnosed stage III/IV Hodgkin lymphoma. *First Author: Scott F. Huntington, Yale University, New Haven, CT*

Background: In a recent randomized, open-label trial (ECHELON-1), brentuximab vedotin combined with doxorubicin, vinblastine, and dacarbazine (A+AVD) decreased the risk of progression in adults diagnosed with stage III/IV Hodgkin lymphoma (HL) compared to standard bleomycin-containing chemotherapy (ABVD). However, the cost-effectiveness of incorporating brentuximab vedotin into the first-line setting is unknown. **Methods:** We constructed a Markov decision-analytic model to measure the costs and clinical outcomes for A+AVD compared to ABVD as first-line therapy in a cohort of patients with stage III/IV HL. Progression-free survival and transition probabilities were estimated from ECHELON-1 by fitting parametric survival distributions. Centers for Medicare & Medicaid Drug Pricing Files from December 2017 were used for drug costs (106% of average sales price). Additional expenditures and clinical utilities were estimated from literature. Lifetime direct health care costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated for A+AVD compared with ABVD from a societal perspective within the United States. Our model was also used to estimate price reductions of brentuximab vedotin that would achieve more favorable cost-effectiveness under indication-specific pricing. **Results:** A+AVD was associated with an improvement of 0.48 QALYs compared to treatment with standard ABVD. However, incorporating brentuximab vedotin into first-line therapy led to significantly higher lifetime costs ($334,863 versus $193,780), causing the ICER for A+AVD compared with ABVD to be $292,266/QALY. If indication-specific pricing was implemented, price reductions of brentuximab vedotin by 40% to 60% in the first-line setting would produce ICERs of $100,000 to $150,000/QALY. **Conclusions:** Substituting brentuximab vedotin for bleomycin during first-line therapy for stage III/IV HL is unlikely to be cost-effective under current drug pricing. Should indication-specific pricing be implemented, discounting brentuximab vedotin in the first-line setting by 40% to 60% could reduce ICERs to widely acceptable values.

6610 Poster Session (Board #435), Sat, 1:15 PM-4:45 PM

Cost-effectiveness of chimeric antigen receptor T-cell therapy in pediatric relapsed/refractory acute lymphoblastic leukemia. *First Author: Reith Sarkar, University of California, San Diego School of Medicine, La Jolla, CA*

Background: Chimeric antigen receptor T-cell (CAR-T) therapy is a new class of cancer therapy with promising results, but comes at a high upfront cost. We sought to evaluate the cost-effectiveness of CAR-T therapy among pediatric patients with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL). **Methods:** We built a microsimulation model for pediatric patients with r/r ALL who received either CAR-T therapy or standard of care chemotherapy. Outcomes modeled included costs, quality of life (health utility), treatment complications, and survival, all of which were estimated from published literature. Long-term survival beyond the time-frame of clinical trial data was estimated using Social Security actuarial life-tables adjusted with standardized mortality ratios. Cost-effectiveness was measured with the incremental cost-effectiveness ratio (ICER), with ICERs under $100,000 per quality-adjusted life year (QALY) considered cost-effective. One-way and probabilistic sensitivity analyses were used to assess overall stability of the model. **Results:** Compared to standard of care chemotherapy CAR-T increased the total cost of treatment by $378,600 and increased effectiveness by 6.72 QALYs, resulting in an ICER of $56,300 per QALY. The model was sensitive to assumptions about long-term CAR-T survival, the cost of CAR-T, and duration of IVIG required in CAR-T responders. The base model assumed a 79% one-year survival with CAR-T therapy, though if the one-year survival decreased to 61% then the ICER of CAR-T increased above $100,000 per QALY. If the cost of CAR-T infusion increased from $475,000 to $781,000, or if the duration of IVIG infusions extend beyond 12 years then the ICER of CAR-T therapy increased above $100,000 per QALY. In the probabilistic sensitivity analysis CAR-T was cost-effective in $>$ 99% of iterations at a willingness to pay of $100,000 per QALY. **Conclusions:** Despite its high cost, CAR-T therapy has an acceptable cost-effectiveness profile for pediatric r/r ALL. Additional follow-up of this cohort is required to establish long-term outcomes and further inform questions about the cost-effectiveness of CAR-T therapy.

6611 Poster Session (Board #436), Sat, 1:15 PM-4:45 PM

Trajectories of medical care cost by service type for recurrent and de novo advanced cancer patients. *First Author: Matthew P. Banegas, Kaiser Permanente Center for Health Research, Portland, OR*

Background: Understanding cost trajectories for advanced cancer patients may identify drivers of high cost transitions and inform cost reduction efforts. Total medical care costs were measured by service type in year prior to and following diagnosis of de novo or recurrent advanced breast (BC), colorectal (CRC), or lung cancer (LC). **Methods:** Data on patients with de novo or recurrent BC ($n_{stage\ IV}$= 352; $n_{recurrent}$= 765), CRC ($n_{stage\ IV}$ = 1072 and $n_{recurrent}$= 542) and LC ($n_{stage\ IV}$= 4042 and $n_{recurrent}$= 339) from 2000-2012 from three integrated health plans were used. Average monthly and total costs of ambulatory, inpatient, medication, and other services were estimated for (1) *pre-index*: 12 months preceding de novo or recurrent advanced cancer diagnosis (index); and (2) *post-index*: index month and following 11 months. Separate generalized linear repeated measures regression models estimated costs, controlling for demographic and clinical characteristics, for each cancer. Recurrent patients were stratified based on time from initial diagnosis to recurrence (<1 yr versus ≥ 1 yr). **Results:** Adjusted total medical care costs increased significantly from pre- to post-index for all services among de novo and recurrence ≥ 1 yr patients (Table). Among patients with a CRC and LC recurrence $<$ 1 yr, inpatient costs were significantly higher in pre- than post-index. **Conclusions:** Substantial variations in cost trajectories for advanced cancer patients were observed by cancer site and type of advanced disease. These estimates from a capitated system offer novel insight, as new payment models shift away from fee-for-service to bundled/episode-of-care payments.

		Stage IV		Recurrent < 1 yr		Recurrent ≥1 yr	
		Pre-Index	Post-Index	Pre-Index	Post-Index	Pre-Index	Post-Index
Cancer		Total Cost, in Thousands [2012$USD]					
Breast	Ambulatory	$1.6	$20.9	$16.5	$23.3	$8.1	$18.5
	Inpatient	$1.8	$19.0	$9.6	$13.4	$3.9	$15.2
	Medication	$1.5	$27.2	$12.2	$18.1	$6.6	$23.7
Colorectal	Ambulatory	$2.2	$16.5	$11.3	$15.5	$6.5	$13.9
	Inpatient	$2.1	$31.5	$34.4	$19.8	$7.2	$14.6
	Medication	$2.0	$16.8	$6.6	$19.9	$5.1	$17.1
Lung	Ambulatory	$3.5	$18.2	$18.2	$17.4	$9.2	$18.2
	Inpatient	$2.8	$19.0	$36.2	$17.3	$9.9	$14.0
	Medication	$4.1	$12.5	$5.5	$12.3	$6.4	$15.1

6612 Poster Session (Board #437), Sat, 1:15 PM-4:45 PM

The potential cost-effectiveness of first-line immunotherapy + chemotherapy for advanced non-squamous non-small cell lung cancer (NSCLC). *First Author: Joshua A. Roth, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: In May of 2017, the U.S. FDA granted accelerated approval for pembrolizumab + pemetrexed & carboplatin for previously untreated advanced non-squamous NSCLC—the only first-line indication for immunotherapy + chemotherapy ('IO+Chemo') in NSCLC. Preliminary value estimates are needed to inform decision making. Using data from the Phase II KEYNOTE-021 trial, we estimated the potential value of IO+Chemo from a U.S. payer perspective. **Methods:** We created a partitioned survival decision model to assess the cost-effectiveness of IO+Chemo vs. pemetrexed & carboplatin ('Chemo') in Stage IIIB/IV non-squamous NSCLC. One year overall (OS) and progression-free survival came from KEYNOTE-021 and were extrapolated with parametric curves. The base case used a Weibull curve for long-term OS (6% 5 year OS), and scenarios used Log-Logistic (21% 5 year OS) and Gompertz ($<$ 1% 5 year OS) curves to model more and less durable responses. First- and second-line therapy resource use and Grade 3/4 adverse event rates were derived from KEYNOTE-021. We applied 2017 Average Sales Price for drugs and 2017 CMS reimbursement for procedures. Utilities were derived from the literature. We estimated life years (LY), quality-adjusted life years (QALYs), and costs over a lifetime horizon. Outcomes were discounted at 3% per year. **Results:** In the base case, IO+Chemo and Chemo resulted in 2.23 and 1.43 LYs, 1.20 and 0.77 QALYs, and $328,640 and $147,418 cost, respectively. The IO+Chemo costs per LY and QALY gained were $227,149 and $422,313, respectively. The cost per QALY varied greatly in OS scenarios (See Table), showing the strong influence of durable responses on value. **Conclusions:** In the first cost-effectiveness analysis of frontline IO+chemo in advanced non-squamous NSCLC, we found that pembrolizumab-based therapy is unlikely to be cost-effective (ie $<$ $150,000 per QALY) regardless of long-term OS assumptions. Future studies should reassess IO+chemo value with Phase III KEYNOTE-189 data.

IO+Chemo: OS Curve Fit	IO+Chemo: QALYs Gained	IO+Chemo: Additional Cost	Cost Per QALY
Log Logistic	0.88	$189,830	$214,899
Weibull (Base Case)	0.43	$181,222	$422,313
Gompertz	0.09	$170,445	$1,891,845

6613 Poster Session (Board #438), Sat, 1:15 PM-4:45 PM

The financial impact of hypofractionated radiation for prostate cancer. *First Author: Assaf Moore, Tel Aviv University, Tel Aviv, Israel*

Background: Until recently, dose intensified radiotherapy with 1.8-2 Gy fractions was the standard radiation method for prostate cancer. Multiple studies have demonstrated similar efficacy and tolerability with moderate hypofractionation (2.5-3 Gy per fraction). In recent years there has been an increasing focus placed on understanding the cost and value of cancer care. The objective of this study was to assess the societal economic impact of treating localized prostate cancer in the United States (US) with moderate hypofractionation vs standard fractionation. **Methods:** We calculated the national annual target population of patients treated with definitive external beam radiotherapy using the Surveillance, Epidemiology, and End Results (SEER) database. Treatment costs for various fractionation schemes were based on billing codes and 2018 pricing by the Centers for Medicare and Medicaid Services (CMS). **Results:** We estimate that 28,500 patients with localized prostate cancer are treated with radiotherapy annually in the US. The cost of standard fractionation in 45 or 39 fractions is US$ 26,782 and 23,625 per patient, respectively. With moderate hypofractionation in 28 or 20 fractions, the cost is US$ 17,793 and 13,402 per patient, respectively. The use of moderate hypofractionation would lead to 24.7-50% annual savings of $US 166,147,848 – 381,128,820 in the United States. **Conclusions:** Moderate hypofractionation may have the potential to save approximately US$ 0.16-0.38 billion annually in the United States, likely without impacting survival or tolerability. Depending on insurance provider, this option may lead to lower personal financial toxicity. It would be reasonable for public and private payers to consider providing reimbursement only for moderate hypofractionation.

6614 Poster Session (Board #439), Sat, 1:15 PM-4:45 PM

A value framework analysis of the Canadian Cancer Trials Group. *First Author: Joseph Del Paggio, Department of Medicine, University of Toronto, Toronto, ON, Canada*

Background: To identify new therapies that offer substantial benefits to patients, investigators and research funding bodies may wish to consider value framework thresholds in the design of clinical trials. To our knowledge, existing value frameworks have not been applied to the research output of a cooperative cancer trials group. Herein, we apply the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) to the published output of the Canadian Cancer Trials Group (CCTG). **Methods:** Statistical design, study characteristics, and results of all published phase III trials of the CCTG were abstracted. Studies that showed a statistical significance in favor of the experimental therapy were graded using ESMO-MCBS v1.1. To identify the proportion of all trials that were designed to detect a difference which would be considered meaningful, we also applied the ESMO-MCBS to the statistical power calculations. We defined "substantial benefit" as trials that met a grade of A, B, 5, or 4 for the ESMO-MCBS. **Results:** During 1979-2017, CCTG published 477 trials. 132 trials were phase III and formed the study cohort; 49% of these trials were statistically "positive". The most common disease sites were breast (18%), hematologic (17%), and lung (15%). Forty-six percent of trials were conducted in the palliative setting. Experimental therapies included cytotoxic (36%), molecular (20%), and hormonal (10%) agents. Median sample size was 490. In 40% of trials the primary endpoint was overall survival; a survival surrogate was used in 33% of trials. Among the 58 "positive" trials for which the ESMO-MCBS could be applied, 28 (48%) met thresholds for substantial benefit. The ESMO-MCBS could be applied to the power calculation for 79 trials; 70% of these trials were designed to detect an effect size that could meet ESMO-MCBS thresholds for substantial benefit. RCT authors were more likely to strongly endorse the experimental therapy among those trials meeting ESMO-MCBS thresholds (74% vs 40%, $p = 0.010$). **Conclusions:** The majority of CCTG phase III trials are designed to detect clinically meaningful differences in patient outcome. However, only one quarter of all trials ultimately yield results that meet ESMO-MCBS thresholds for substantial benefit.

6615 Poster Session (Board #440), Sat, 1:15 PM-4:45 PM

Network metanalysis and cost-effectiveness of abiraterone, docetaxel or placebo plus androgen deprivation therapy (ADT) for hormone-sensitive advanced prostate cancer. *First Author: Pedro Nazareth Aguiar, Faculdade de Medicina do ABC, Santo Andre, Brazil*

Background: Prostate cancer is the leading neoplasm among men worldwide. The objective of this study is to evaluate the cost-effectiveness of the addition of chemotherapy or abiraterone to ADT after a network meta-analysis and an indirect comparison between chemotherapy and abiraterone. **Methods:** We made a literature review and included studies that evaluated the addition of docetaxel or abiraterone to ADT versus ADT alone for patients with castration-sensitive metastatic prostate cancer. Studies' outcomes were modeled on a logarithmic scale using the Bayesian hierarchical model for indirect comparisons between interventions. Then, we developed an analytical model to determine the cost-effectiveness of the addition of docetaxel or abiraterone versus ADT alone. Direct and indirect costs were included in the model considering Brazilian costs. **Results:** Four clinical trials were included in the network meta-analysis. Evidence suggests that the addition of abiraterone to ADT is the best therapeutic option in terms of OS ($>$ 95% probability; HR 0,81; 95% CrI 0,66 – 1,00) and FFS ($>$ 99% probability; HR 0,50; 95% CrI 0,40 – 0,62) compared to ADT plus docetaxel. Abiraterone plus ADT had fewer cases of febrile neutropenia than docetaxel plus ADT (1% versus 15%). Compared to ADT alone, the addition of chemotherapy generated 0.492 QALY and the addition of abiraterone generated 0.999 QALY. Abiraterone led to a QALY gain of 0.506 compared to docetaxel. In Brazil, the incremental costs per QALY were $40,500, $100,251 and $173,145, respectively. At current costs, docetaxel plus ADT is more cost-effective than abiraterone plus ADT. The factors that had the greatest influence on cost-effectiveness were the overall survival and failure-free survival confidence intervals. Price discounts on abiraterone purchasing was the factor that led to the greatest impact on the incremental cost (ranging from $100,000 to $40,000). **Conclusions:** We conclude that the addition of chemotherapy to ADT is more cost-effective than the addition of abiraterone to ADT. However, discounts on abiraterone cost might improve cost-effectiveness.

6616 Poster Session (Board #441), Sat, 1:15 PM-4:45 PM

Utilization of imaging during staging and surveillance of localized colon cancer in a large insured population. *First Author: Urshila Durani, Mayo Clinic, Rochester, MN*

Background: It is unknown if staging and surveillance imaging in Stage I/II colon cancer are under- or over-utilized. On one hand, the Choosing Wisely campaign advocates against positron-emission tomography (PET) imaging and overzealous use of CT surveillance. Meanwhile, the NCCN recommends CT chest/abdomen/pelvis (CT C/A/P) at staging for Stage I/II colon cancer. For Stage II only, NCCN recommends surveillance CT C/A/P every 6-12 months for up to 5 years. Herein, we measure both underutilization and overutilization of staging and surveillance imaging in Stage I/II colon cancer. **Methods:** Insurance claims data from 2008-2016 were queried using OptumLabs (Cambridge, MA) for Stage I/II adult colon cancer patients who underwent surgery alone. Utilization of PET and CT C/A/P imaging was evaluated both during initial staging (N = 6,291) and surveillance for patients with at least 1 year of follow up (N = 5,466). Over-utilization was defined as (1) any usage of PET during staging or surveillance or (2) $>$ 2 CT A/P or PET scans per year during surveillance. **Results:** Overall, 31% of Stage I/II colon cancer patients did not receive a staging CT A/P and 95% did not receive a CT chest on diagnosis. However, rates of staging CT A/P increased from 62% (2008) to 75% (2016) and rates of CT chest rose from 2.3% (2008) to 7.1% (2016). Use of PET imaging also increased slightly from 5.2% (2008) to 6.5% (2016) despite guidelines recommending against its use. On surveillance, 30% of patients with at least 1 year of follow up received a CT A/P or PET within the first year of surveillance. This dropped to 18% in year 2, 9% in year 3, 6% in year 4, and 3% in year 5 of follow up. Of patients who had surveillance CT A/P or PET, the proportion receiving $>$ 2 scans within the first year (representing overutilization) declined from 32% (2008) to 10% (2016), $p = 0.01$. **Conclusions:** A large proportion of Stage I/II colon cancer patients do not receive appropriate staging CTs at diagnosis; however, the utilization of PET imaging at staging remains appropriately low. Furthermore, the vast majority of patients undergoing surveillance do not even receive 3 years of imaging follow-up. Among those who do receive surveillance imaging, overutilization has declined over time.

6617 Poster Session (Board #442), Sat, 1:15 PM-4:45 PM

Immunotherapy (IO) versus non-IO for oncology drugs: Comparing survival benefits (SB) using restricted *mean* survival time. *First Author: Amanda Putri Rahmadian, Sunnybrook Research Institute, Toronto, ON, Canada*

Background: Current measures of *absolute* SB (*median* survival time/rate at fixed times on Kaplan-Meier (KM) curves) and *relative* SB (hazard ratios) are limited in properly capturing SB for IO trials. Restricted *mean* survival time (RMST) captures entire area under KM curves, directly measuring SB. This study aimed to quantify the magnitude of SB in recent oncology drugs using RMST difference and RMST ratio (*absolute* and *relative* SB, respectively), and compare those of IO and non-IO. **Methods:** All Food and Drug Administration approved oncology drugs from 01/2011-11/2017 and randomized control trials (RCTs) used for approval were identified. RCTs with overall survival (OS) or progression-free survival (PFS) as primary endpoints and published KM curves were included. Curves were extracted using established methods (Guyot et al., 2012) with DigitizeIt. RMST differences, ratios, and confidence intervals (CI) were calculated and meta-analyzed using random-effects models to estimate overall absolute and relative SB of contemporary oncology drugs, and to compare those of IO and non-IO. Meta-regression was used to adjust for confounders (crossover, time horizon, year approved, trial phase, companion diagnostics, and approval type). **Results:** 94 RCTs with 51 639 patients were included (13 IO and 81 non-IO). Overall RMST differences (*absolute* SB) were 1.55 mos for OS (95% CI 1.32-1.77) and 2.99 mos for PFS (95% CI 2.65-3.33). Overall RMST ratios (*relative* SB) were 1.11 for OS (95% CI 1.09-1.13) and 1.42 for PFS (95% CI 1.36-1.48). IO PFS RMST difference was less than non-IO (1.56 mos vs. 3.23 mos, $p <$ 0.00001), while RMST ratios were similar (1.33 vs. 1.43, $p = 0.16$). Contrastingly, IO OS RMST difference was larger than non-IO by 0.6 mos (2.02 mos vs. 1.43 mos, $p = 0.02$). OS RMST ratios were slightly larger for IO than non-IO (1.18 vs. 1.09, $p = 0.0006$). Meta-regression showed the adjusted SB for OS was 0.83 mos greater for IO vs. non-IO, $p = 0.01$. **Conclusions:** Overall, absolute SB of recent oncology drugs are modest. Unlike popular belief, observed SB of IO drugs are not dramatically superior to non-IO drugs. RMST differences and ratios of oncology drugs in clinical trials should be routinely reported to fully measure SB.

6618 Poster Session (Board #443), Sat, 1:15 PM-4:45 PM

Trends of hospitalizations with invasive fungal infections in patients with acute leukemia and hematopoietic stem cell from 2005-2014 in the United States. *First Author: Sukriti Kamboj, Guthrie/ Robert Packer Hospital, Sayre, PA*

Background: Invasive fungal infections (IFI) are a cause of morbidity, mortality and increased health costs in patients with Acute Leukemia (AL) and hematopoietic stem cell transplant (HSCT). With this study, we aim to examine trends of IFI related hospitalizations in patients with AL and HSCT in the United States. **Methods:** We utilized Nationwide Inpatient Sample (NIS) data from 2005- 2014 and identified patients with AL (acute lymphoblastic leukemia and acute myelogenous leukemia) and HSCT hospitalization using ICD 9 CM codes. Patients with missing information on age, gender and mortality were excluded. Patients with age < 18 years were excluded as well. IFI (candidemia, aspergillosis, zygomycosis) were identified by using appropriate ICD 9 codes in secondary diagnosis field. P-values for trends were generated using Cochran Armitage test. **Results:** A total of 666,567 hospitalizations with HM were identified. Out of which 15,316 (2.31%) had IFIs. A majority were males (57.8%), Caucasian (58%) and belong to age group 50-64 (36.8%). Overall Incidence of fungemia was 2.3% and remained stable over 11 years (2.16% in 2005 to 2.2 % in 20114, relative increase = 7.25%, p trend-0.0064). Overall In-hospital mortality was 21.84% (unchanged over 11 years with a relative decrease of 8.1 % with p trend - 0.131. After stratifying for specific IFIs, in-hospital mortality for candidemia (35.0%), zygomycosis (26.51%) and aspergillosis (18.48%). None of which have changed over 11 years. In multivariate analysis, old age (age > = 65 years), female gender was associated with higher mortality and elective admissions were associated with lower mortality. **Conclusions:** Despite much advances in fungemia treatment and prophylaxis, incidence and outcomes of IFI have not changed over last decade. Future studies to identify limiting factors are needed to provide crucial information to prevent fungemia and improve outcomes.

6619 Poster Session (Board #444), Sat, 1:15 PM-4:45 PM

Gastrointestinal (GI) cancer (CA) drugs approved by the US Food and Drug Administration (FDA): Clinical value and cost considerations. *First Author: Di Maria Jiang, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: The mounting cost of CA drugs has presented significant financial toxicity to all stakeholders over recent years. We aimed to assess the clinical value and cost of GI CA drugs approved by the FDA. **Methods:** Approved GI CA drugs between 2006 and 2017 listed on fda.gov and their updated supporting data were identified. Clinical benefit was quantified by ASCO Value Framework v2 2016 (range < 180) and ESMO Magnitude of Clinical Benefit Scale (MCBS) v1.1 2017 (range 1-5). Higher scores indicate larger net benefit. Substantial benefit was defined as grade 4/5 by ESMO. For EGFR inhibitor outcomes, only patients with wild-type KRAS were assessed. Preliminary data presented on fda.gov were used if trial data is unpublished. Toxicity was omitted if unavailable. The Micromedex REDBOOK was used to estimate the total drug cost for each new agent, based on 2018 average wholesale prices for median treatment durations (or progression-free survival if unavailable). **Results:** Five monoclonal antibodies (Mab), 5 targeted therapies (TT), 1 recombinant fusion protein, 3 cytotoxic (CT) and 2 immunotherapy (IO) agents received approval for metastatic GI CA. Median ASCO scores/drug cost in USD per patient were 36/ $65,310 (Mab), 38/$153,402 (TT), 55/$30,329 (CT) and 21/$78,864 (IO). Selected scores and drug costs are presented (Table). Only cetuximab for refractory colorectal CA (CRC) met the ESMO benefit threshold. *pNET: pancreatic neuroendocrine tumor; HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma; MSI-H: microsatellite instability-high* **Conclusions:** Although beneficial, most FDA-approved GI CA drugs met neither the ESMO definition of substantial improvement in benefit nor have a high ASCO value score, and incur considerable costs.

CA	Treatment Line	Approved Drug	ASCO value score	ESMO MCBS	Total Drug cost (USD) per patient
CRC	≥3	Cetuximab	72	5	44,132
		Panitumumab	2	1	23,939
pNET	≥1	Everolimus	1	2	153,402
		Sunitinib	38	3	200,610
HCC	1	Sorafenib	46	2	110,050
	2	Regorafenib	35	3	56,252
PDAC	1	Abraxane	62	1	38,171
	2	Nal-irinotecan	55	2	26,182
MSI-H	≥2	Nivolumab	44	3	98,208
	≥3	Pembrolizumab	28	2	216,952

6620 Poster Session (Board #445), Sat, 1:15 PM-4:45 PM

Can oral chemotherapy parity laws reduce patients' out-of-pocket (OOP) costs? *First Author: Andrea Phillips Sitlinger, Duke University Medical Center, Durham, NC*

Background: Insurance plans vary coverage for infusional (IV) vs oral drugs, leading some to suggest that patients on oral drugs pay more OOP than those on IV drugs. 43 states have passed laws requiring insurers to cover oral drugs equivalently to IV drugs. Yet, there is little evidence that these "parity laws" are effective. Our aim was to estimate impact of parity laws on OOP expenses for oral vs IV drugs. **Methods:** We sought to determine how quickly patients on oral vs IV drugs reach their plan's annual OOP maximum (max) as a surrogate for OOP expense. We used 2017 data from Healthcare.gov public use files to generate cost-sharing profiles for all 3,092 unique Marketplace plans. Chronic lymphocytic leukemia (CLL) and metastatic prostate cancer (mPC) were chosen as two representative malignancies since both have accepted, first-line, IV and oral treatment options. We created guideline-concordant, first-line treatment regimens for simulated patients with CLL (oral ibrutinib vs IV bendamustine/ rituximab) or mPC (oral abiraterone vs IV docetaxel). Drug, professional, facility, imaging, and lab claims were simulated to calculate OOP costs. The mean number of days to reach the OOP maximum for each Marketplace plan and treatment regimen were recorded. We assessed variation according to insurance coverage levels ("metal tier": Catastrophic, Bronze, Silver, Gold, Platinum). **Results:** For CLL patients, 95% of plans reached OOP max in approximately one month of treatment for both oral and IV drugs (oral: mean 36 days; IV: mean 29 days). 99% of mPC patients reached their OOP max for oral treatment in a mean 15 days, but only 57% of plans reached OOP max for IV mPC treatment. Metal tier impacts time to reach OOP max (table). **Conclusions:** Parity laws do not lower patient costs when both IV and oral treatment options are expensive. In these cases, patients reach the OOP max rapidly. The small subset of patients most likely to benefit from parity laws are those on oral therapy for a disease where the comparable IV drug is inexpensive (eg, generic docetaxel for mPC).

	Days to Reach OOP Maximum			
	CLL		mPC	
Metal tier	IV	Oral	IV	Oral
Catastrophic	1	1	190	1
Bronze	2	8	211	1
Silver	28	36	327	29
Gold	29	36	327	29
Platinum	113	36	285	29

TPS6621 Poster Session (Board #446a), Sat, 1:15 PM-4:45 PM

A randomized, controlled trial to assess a multi-level intervention to improve adherence to oral cancer medications. *First Author: Rashmika Potdar, Einstein Medical Center Philadelphia, Newtown Square, PA*

Background: Cancer treatment with oral cancer medication is complex. Cancer patients require substantial skills to adhere to- and achieve the goals of therapy. Medication adherence among cancer patients is increasingly important, as treatment with oral medications is increasingly prevalent. The rates of adherence to oral therapy vary widely by population, cancer type, and level of education. To date, however, there is no clear evidence on the effect of improvements in health literacy on patients' adherence to oral cancer medications. We hypothesize that compared to usual care, the addition of a multilevel intervention will result in greater adherence to oral cancer medications. **Methods:** In a single-center, patients are randomized 1:1 to receive usual care, including clinical care plus education by a registered nurse (Arm 1), or the addition of a multilevel intervention (Arm 2). The multilevel intervention includes a brief web-based educational video on cancer and oral cancer drugs, periodic reinforcement of educational messages with videos, brief phone calls 24 hours and 2 weeks after each encounter, and offer of facilitative services, if needed. Health literacy is recorded at baseline, using REALM R. Adult cancer patients on any oral cancer medication are eligible to participate in the study. Exclusion criteria include ECOG ≥3, concurrent chemo-radiation, hormonal therapy, nonadherence (defined as history of missing 2 or more Oncology clinic appointments), pregnancy, residence in a nursing home, dementia, or lacking decisional capacity. The primary outcome of interest is medication adherence, indicated by the proportion of expected refills completed for oral cancer medications during the follow up period. Secondary outcomes include adherence to follow up visits, adherence to other prescribed medications, healthcare utilization, and other healthcare outcomes. With a one-sided alpha = 0.05, the target sample size of 110 patients, would yield 90% power to test the primary hypothesis. To date, we have randomized 19 participants, and enrollment proceeds as planned. Clinical trial information: NCT03245411.

TPS6622 Poster Session (Board #446b), Sat, 1:15 PM-4:45 PM

Ambulatory cancer care electronic symptom self-reporting (ACCESS) for surgical patients: A randomized controlled trial. *First Author: Cara Stabile, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: An increasing proportion of cancer surgeries are ambulatory ($\leq$ 1 day in hospital) procedures. Providing patients and their caregivers with ongoing, real-time support after discharge is imperative to delivering high-quality postoperative care in this new health care environment. Despite abundant evidence that patient self-reporting of symptoms improves quality of care, **Reference:** 1. Kotronoulas G, Kearney N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. *Journal of Clinical Oncology.* 2014;32(14):1480-1501. the most effective way to monitor and manage such data remains unknown. **Methods:** This is a two-armed, prospective randomized controlled trial evaluating two approaches to the management of patient-reported data: (1) Team Monitoring—symptom monitoring by the clinical team, with nursing outreach if symptoms exceed normal limits; and (2) Enhanced Feedback—real-time feedback to patients about expected symptom severity, with patient-activated care as needed. It is hypothesized that Enhanced Feedback about expected symptom severity would be more effective than Team Monitoring in improving patient-centered outcomes and the patient/caregiver experience. Breast, prostate, gynecologic, and head and neck cancer patients undergoing ambulatory cancer surgery (n = 1,700) will complete an electronic survey about their symptoms for up to 30 days after surgery. Information provided to patients in the Enhanced Feedback group is procedure-specific and based on continuously updated survey data from previous patients. Qualitative interviews will also be performed. Accrual began in August 2017. Primary outcomes will evaluate unplanned emergency department visits within 30 days. Secondary outcomes will assess the patient/caregiver experience (i.e., patient engagement, patient anxiety, and caregiver burden). Findings will be relevant in designing future coordinated care models targeting improved health care quality and patient experience. Clinical trial information: NCT03178045.

7000 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Ivosidenib (IVO; AG-120) in mutant IDH1 relapsed/refractory acute myeloid leukemia (R/R AML): Results of a phase 1 study. *First Author: Daniel Aaron Pollyea, University of Colorado School of Medicine, Aurora, CO*

Background: IVO is an oral, targeted inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1) that is being evaluated in a phase 1 dose escalation and expansion study of mIDH1 advanced hematologic malignancies (NCT02074839). Here we report updated efficacy and safety data from all patients with R/R AML receiving IVO 500 mg once daily (QD). **Methods:** The primary efficacy endpoint was the CR+CRh rate (complete remission [CR] according to modified IWG 2003 criteria plus CR with partial hematologic recovery [CRh]). CRh was defined as absolute neutrophil count $> 0.5 \times 10^9$/L *and* platelet count $> 50 \times 10^9$/L. The overall response rate (ORR) comprised CR, CR with incomplete hematologic or platelet recovery, partial response, and morphologic leukemia-free state. The data cutoff date for this analysis was Nov 10, 2017. **Results:** A total of 258 patients were treated with IVO. Among 179 R/R AML patients who received IVO 500 mg QD, 17 (9.5%) remained on treatment at data cutoff. In R/R AML patients, the CR+CRh rate was 31.8% (95% CI: 25.1%, 39.2%), including CR in 24.0% (95% CI: 18.0%, 31.0%). Median duration of CR+CRh was 8.2 months (95% CI: 5.6, 12.0), and median duration of CR was 10.1 months (95% CI: 6.5, 22.2). The ORR was 41.9% (95% CI: 34.6%, 49.5%). Treatment was well tolerated; the most common adverse events (AEs) of any grade, irrespective of causality and occurring in ≥25% of 179 R/R AML patients were diarrhea (33.5%), leukocytosis (31.3%), nausea (31.3%), febrile neutropenia (29.1%), fatigue (28.5%), and electrocardiogram QT prolonged (25.7%). The majority of these AEs were grades 1–2 and unrelated to treatment. IDH differentiation syndrome (IDH-DS) was reported in 19 of 179 (10.6%) patients, including grade ≥3 IDH-DS in 9 (5.0%); study drug was held owing to IDH-DS in 6 patients (3.4%), and no instances of IDH-DS led to dose reduction, permanent treatment discontinuation, or death. Updated mutation clearance results will be provided. **Conclusions:** In a high-risk, molecularly defined R/R AML patient population, IVO induced durable remissions and was well tolerated. Studies in previously untreated AML populations are ongoing. Clinical trial information: NCT02074839.

7001 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Association of early intervention in transfusion independent (TI) patients (Pts) with lower-risk myelodysplastic syndromes (MDS) treated with attenuated doses of hypomethylating agents (HMAs) with high response rates and long duration of response. *First Author: Mahesh Swaminathan, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: HMAs are the standard of care for most pts with higher risk MDS. However, the role of the therapy is not well defined in lower risk MDS. Data from our center has indicated that attenuated dose schedules of HMA are safe and active in pts with low risk MDS (Jabbour et al. Blood 2018) but the safety and activity of these therapies is not known in TI pts with low risk MDS. To study this, we performed an analysis of a cohort pts with TI low risk or int-1 risk MDS by IPSS. **Methods:** Eighty-seven pts with low-risk or int-1 risk MDS treated with HMAs from 2012 to 2017 were analyzed. Pts had been treated in prospective trials of attenuated HMA at a single institution. Therapy could consist of decitabine 20 mg/m2 IV QD x 3 days every 28 days or azacitidine 75 mg/m2 daily x 3 days every 28 days or azacitidine at the same dose and schedule for 5 days. All pts were TI at baseline. **Results:** The median age was 70 (25-85); 64 pts (74%) were males; 57 pts (66%) were int-1 risk and 30 (34%) were low risk by IPSS. By the MDACC Lower Risk Prognostic Model: 51 pts (59%) were intermediate risk, 23 (26%) high risk and 13 (15%) low-risk. Cytogenetics were good in 59 (68%), intermediate in 22 (25%) and poor in 6 pts (7%). The median time to treatment was 4.13 months and the median number of prior treatments was 0 (0-1). The median total courses of treatment was 14 (1-41). TET2, ASXL1 and RUNX1 mutations occurred in 30%, 9% and 8%, respectively. Of the 87 pts, 80 were evaluable. No deaths were observed during the first 8 weeks of therapy and no severe hematological toxicity. The overall response rate (ORR) was 74% [CR – 40 (50%), mCR with and without HI – 5 (6%), 3 (4%), respectively, HIP – 10 (13%) and HIN – 1 (1%)]. The median OS was not reached and the median event-free survival (EFS) was 35.4 months. Two pts (3%) had progressive disease; 19 (24%) had no response; 6 (8%) progressed to acute myeloid leukemia. Five pts (6%) became transfusion dependent at the time of response evaluation. **Conclusions:** Early intervention with attenuated doses of HMAs in TI pts with lower risk MDS is safe and active and could potentially alter the natural history of MDS.

7002 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Bosutinib vs imatinib for newly diagnosed chronic myeloid leukemia in the BFORE trial: 24-month follow-up. *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Bosutinib is a dual Src/Abl tyrosine kinase inhibitor approved for the treatment of newly diagnosed chronic phase (CP) chronic myeloid leukemia (CML) and CML resistant/intolerant to prior therapy. Here we compare efficacy of first-line bosutinib and imatinib after ≥24 mo (median: 27 mo) of follow-up. **Methods:** In the ongoing, open-label, phase 3 BFORE trial (NCT02130557), 536 patients were randomized 1:1 to bosutinib (n = 268) or imatinib (n = 268 [3 untreated]). **Results:** Higher molecular and complete cytogenetic response (MR and CCyR) rates were observed for bosutinib vs imatinib at 12 mo; these differences continued after ≥24 mo (**Table**). The between-arm difference in major MR (MMR) rate was retained at 24 mo; however, differences in rates of deeper MRs (MR^4 and $MR^{4.5}$) were smaller. Times to MR and CCyR were shorter for bosutinib vs imatinib, consistent with 12-mo data. There were 6 transformations to accelerated/blast phase with bosutinib and 7 with imatinib. 71% vs 66% remained on bosutinib vs imatinib treatment. **Conclusions:** At 24 mo, a higher MMR rate was maintained with bosutinib vs imatinib. The results support the use of bosutinib as first-line therapy for CP CML. Clinical trial information: NCT02130557.

	Intent-to-treat (ITT) Population		
	Bosutinib n = 268	Imatinib n = 268	P*
Cumulative, any time on-treatment, %			
MMR	68.7	59.3	.024
MR^4	39.9	31.3	.040
MR4.5	25.7	19.0	.063
CCyR†	82.5	76.8	.113
MMR by 24 mo, %	67.2	57.5	.020
MMR, %			
At 12 mo	46.6	36.2	.013
At 24 mo	61.2	50.7	.015
MR^4, %			
At 12 mo	20.5	11.6	.005
At 24 mo	32.8	25.7	.073
$MR^{4.5}$, %			
At 12 mo	7.5	3.0	.020
At 24 mo	13.1	10.8	.428
Time to response (based on cumulative incidence), hazard ratio (HR)‡			
MMR	1.37		.004
CCyR†	1.34		.005
MR^4	1.39		.025
$MR^{4.5}$	1.42		.054
Overall survival (OS),§ %			–
At 12 mo	99.6	98.1	
At 24 mo	99.2	97.0	

* 2-sided *P* values not adjusted for multiple comparisons; *P* value for OS not provided until 5-y analysis
† Modified ITT population (bosutinib n = 246; imatinib n = 241); Philadelphia chromosome-positive patients with e13a2/e14a2 transcripts
‡ Bosutinib vs imatinib; HR > 1 indicates shorter time to response for bosutinib
§ 3 and 9 deaths in the bosutinib and imatinib arm, respectively, due to adverse event related (0 vs 1) or unrelated (2 vs 2) to study drug, disease progression (1 vs 3), and other causes (0 vs 3)

7003 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Long-term treatment-free remission (TFR) in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) after stopping second-line (2L) nilotinib: ENESTop 144-wk results. *First Author: François-Xavier Mahon, Cancer Center of Bordeaux, Institut Bergonié, INSERM U1218, University of Bordeaux, Bordeaux, France*

Background: TFR is a new treatment goal in CML. In the ENESTop study (NCT01698905) in pts with CML-CP who sustained a deep molecular response with 2L nilotinib, 57.9% and 53.2% remained in TFR 48 wk (primary endpoint) and 96 wk after stopping treatment, respectively. We report an analysis of longer-term durability of TFR in ENESTop. **Methods:** Pts treated with ≥ 2 y of nilotinib following > 4 wk of imatinib (≥ 3 y total) and achieving $MR^{4.5}$ (*BCR-ABL1* ≤ 0.0032% on the International Scale [$BCR\text{-}ABL1^{IS}$] by quantitative real-time PCR) on nilotinib were eligible. Following a 1-y consolidation phase, pts with no confirmed loss of $MR^{4.5}$ could attempt TFR; nilotinib was restarted upon loss of major molecular response (MMR; $BCR\text{-}ABL1^{IS} \leq 0.1\%$) or confirmed loss of MR^4 ($BCR\text{-}ABL1^{IS} \leq 0.01\%$). The data cutoff for this analysis was Oct 18, 2017, when all pts had completed ≥ 144 wk of TFR, restarted nilotinib, or discontinued the study. **Results:** Of 126 pts entering TFR, 61 remained in TFR at data cutoff, 58 restarted nilotinib (loss of MMR, n = 34; confirmed loss of MR^4, n = 24), and 7 discontinued the study in this phase. The TFR rate at 144 wk was 48.4% (95% CI, 39.4%-57.5%). Of 67 pts in TFR at 96 wk, 6 were no longer in TFR at 144 wk due to confirmed loss of MR^4 (n = 3; at 108, 120, and 144 wk), death (n = 2), or study discontinuation (n = 1; pt/guardian decision). Of 34 pts restarting nilotinib due to loss of MMR, 33 (97.1%) and 31 (91.2%) regained MMR and $MR^{4.5}$, respectively; of 24 pts restarting due to confirmed loss of MR^4, 23 (95.8%) regained $MR^{4.5}$. Stable $MR^{4.5}$ for 48 wk was achieved by 42 of 54 pts who regained $MR^{4.5}$ (77.8%). No disease progression or deaths due to CML were reported; 144-wk treatment-free survival rate was 52.0% (95% CI, 42.9%-60.4%). Of 68 pts who remained in TFR for > 96 wk, 10.3%, 51.5%, 19.1%, and 11.8% experienced any-grade musculoskeletal pain–related adverse events in the consolidation phase and first, second, and third 48 wk of TFR, respectively. **Conclusions:** These results demonstrate the long-term durability of TFR following 2L nilotinib and show that most pts restarting nilotinib regained stable $MR^{4.5}$. Pts should be routinely monitored for late loss of response. Clinical trial information: NCT01698905.

7004 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Moxetumomab pasudotox in heavily pretreated patients with relapsed/refractory hairy cell leukemia: Results of a pivotal international study. *First Author: Robert J. Kreitman, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: A pivotal multicenter, single-arm study evaluated moxetumomab pasudotox, a first-in-class recombinant immunotoxin, in patients (pts) with relapsed/refractory hairy cell leukemia (HCL). **Methods:** Eligible pts (≥2 prior systemic therapies, including ≥1 purine nucleoside analog) received moxetumomab pasudotox 40 μg/kg intravenously on days 1, 3, and 5 of 28-d cycles, up to 6 cycles. Disease response and immunohistochemistry (IHC) minimal residual disease (MRD) status were determined by blinded independent central review. Primary end point was durable complete response (CR), defined as CR with hematologic remission (blood count normalization, HR) for > 180 d. **Results:** Eighty pts (63 male; median age 60 y) received moxetumomab pasudotox. Median number of prior systemic therapies was 3 (2–11); 39 pts (49%) had > 3 prior lines of therapy and 60 (75%) had prior rituximab. At 16.7 months median follow-up, objective response (OR) rate was 75% (60/80), HR rate 80% (64/80), CR rate 41% (33/80), and durable CR rate 30% (24/80). Of 33 pts achieving CR, 27 (82%) had IHC MRD negative status. Median time to HR was 1 mo. Median duration of OR and median PFS were not reached. Most frequent treatment-related adverse events (AEs) were nausea (28%), peripheral edema (26%), headache (21%), and pyrexia (20%); 8% had infections and 3% had neutropenia deemed treatment related. Three deaths occurred; none were treatment related. Treatment-related AEs leading to discontinuation were hemolytic uremic syndrome (HUS; 4 [5%]), capillary leak syndrome (CLS; 2 [3%]), and increased blood creatinine (2 [3%]). Seven pts (9%) had CLS (grade 2: n = 5; grade 4: n = 2), 7 (9%) had HUS (grade 2: n = 2; grade 3: n = 3; grade 4: n = 2), and 4 (5%) had both. CLS and HUS were manageable and reversible (no plasma exchange in HUS). Median immunoglobulin levels remained unchanged after treatment. Median CD4 cell counts were stable or improved after the first week of treatment. **Conclusions:** Moxetumomab pasudotox achieved a high rate of independently assessed durable CR, with the ability to eradicate MRD in heavily pretreated HCL patients, and showed a favorable safety profile without immuno/myelosuppression. Clinical trial information: 01829711.

7005 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Factors impacting disease-free survival in adult B cell B-ALL patients achieving MRD-negative CR after CD19 CAR-T cells. *First Author: Kevin Anthony Hay, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Autologous T cells engineered to express a CD19-targeting 4-1BB-costimulated CAR (CAR-T cells) have produced high complete remission (CR) rates in adult B-ALL patients (pts; NCT 01865617), but factors associated with durable remission have not been determined. **Methods:** Pts who received CD19 CAR-T cells at or below the maximum tolerated dose with ≥ 6 months (mos) follow-up were included. Factors impacting disease-free survival (DFS) and overall survival (OS) were determined. **Results:** 56 pts (median age 40 yrs, range 20-76) with a median follow-up of 27.4 mos were studied. 50 (89%) achieved morphologic CR and 45 (80%) achieved CR without minimal residual disease (MRD- CR) by flow cytometry. Pts who achieved MRD- CR had better median OS compared to those with morphologic disease after CAR-T cells (16.8 vs 2.7 mos, p = .0301). In pts achieving MRD- CR, univariate analyses showed longer DFS with lower LDH (p = .0007), no extramedullary disease (p = .005), lower marrow blasts (p = .013), cyclophosphamide/fludarabine (Cy/Flu) lymphodepletion (p = .004), higher CAR-T cell dose (p = .033); and higher in vivo AUC d0-28 of CD4+ (p = .074) and CD8+ (p = .039) CAR-T cell counts. In a stepwise multivariable model, Cy/Flu lymphodepletion (HR 4.3, p = .001), low LDH (HR 1.4 for each 100 U/L increment, p = 0.003), and absence of extramedullary disease (HR 0.34, p = .001) before CAR-T cell infusion were associated with more durable DFS. In pts with normal LDH and no extramedullary disease who received Cy/Flu before CAR-T cells, the probabilities of 2 year OS and DFS were 62% and 62%, respectively. 18 pts underwent allogeneic HSCT after achieving MRD- CR (median 2.3 mos after infusion). Those with ≥5% marrow blasts before CAR-T cells who underwent HSCT had longer DFS and OS compared to those who did not receive HSCT (median EFS 20.0 vs 4.0 mos, p = .0006; OS 26.9 vs 6.7 mos, p = .035). In contrast, those with < 5% blasts before CAR-T cells may not benefit from HSCT after achieving MRD- CR (p = .14). **Conclusions:** More durable DFS after achieving MRD- CR was found in pts with low LDH, no extramedullary disease, and Cy/Flu before CAR-T cells. Those with morphologic disease before CAR-T cells who achieve MRD- CR may benefit from allogeneic HSCT. Clinical trial information: NCT 01865617.

7006 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Outcomes of patients (pts) treated with prior blinatumomab (Blin) in ZUMA-3: A study of KTE-C19, an anti-CD19 chimeric antigen receptor (CAR) t cell therapy, in adult pts with relapsed/refractory acute lymphoblastic leukemia (R/R ALL). *First Author: Bijal D. Shah, Moffitt Cancer Center, Tampa, FL*

Background: KTE-C19 showed promising efficacy (71% complete response [CR] or CR with incomplete hematologic recovery [CRi]) and manageable safety for pts with R/R ALL in Phase 1 of ZUMA-3 (Shah ASH 2017; NCT02614066). Blin, a CD19/CD3 bispecific T cell engager, is FDA-approved for R/R ALL. The impact of prior blin on KTE-C19 efficacy is unknown. Here, we report responses to KTE-C19 in pts who received prior blin. **Methods:** Eligible pts were aged ≥ 18 y with R/R ALL (Ph+ allowed), ≥ 5% bone marrow blasts (documented CD19+), and ECOG 0-1. Pts received 2, 1, or 0.5 × 10^6 CAR T cells/kg after low-dose conditioning chemotherapy. Pts who received the 2 × 10^6 dose could not have prior blin. Outcomes assessed included efficacy, safety, product characteristics, and levels of CAR T cells and cytokines in blood. **Results:** As of July 31, 2017, 29 pts were evaluable for safety, 24 for efficacy. Six, 14, and 9 safety-evaluable pts received 2, 1, and 0.5 × 10^6 CAR T cells/kg, respectively. Pts with (n = 11) vs without (n = 18) prior blin had worse performance status (ECOG 0: 27% vs 44%) and were more likely to be R/R to ≥ 2^{nd}-line therapy (55% vs 28%). With ≥ 8 wk of follow-up, 63% vs 75% of pts with vs without prior blin had CR or CRi, respectively. Overall, 88% (21/24) had minimal residual disease-negative remission (7/8 with vs 14/16 without prior blin). Of pts with vs without prior blin, 27% vs 28% had Grade ≥ 3 cytokine release syndrome and 36% vs 61% had Grade ≥ 3 neurologic events. KTE-C19 was manufactured successfully in both groups, with similar product characteristics (eg, CD4/CD8 ratio, % transduction). Pts with vs without prior blin had similar proportions of naïve (43% vs 36%) and effector memory (19% vs 20%) T cells. Postinfusion CAR T expansion was observed regardless of prior blin; peak CAR T cell levels occurred between Days 7 and 14 for both groups. **Conclusions:** While potentially confounded by multiple factors, these data demonstrate that prior blin did not preclude manufacturing of efficacious products. KTE-C19 continues to show promising efficacy and manageable safety in pts with R/R CD19+ ALL independent of prior blin. Clinical trial information: NCT02614066.

7007 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Tumor gene signature associated with neurotoxicity in R/R B-ALL patients treated with JCAR015, a CD19-directed CAR T cell product. *First Author: N. Eric Olson, Juno Therapeutics, Seattle, WA*

Background: CD19-directed chimeric antigen receptor modified T (CAR T) cells produce therapeutic responses in adult R/R B-ALL. However, CAR T therapy is also associated with serious toxicities including cytokine release syndrome (CRS) and neurotoxicity (NT). NT mechanisms are emerging and thus far efforts have focused on patient factors and CAR T product attributes and performance post infusion. **Methods:** RNA-Seq analyses was performed on pre-apheresis bone marrow samples obtained from 31 JCAR015 treated patients (ROCKET trial; NCT02535364). **Results:** Gene expression analysis identified a gene set that is differentially expressed between severe (grades 4-5, n = 7) NT patients and low (grades 0-1, n = 10) NT patients. The NT associated genes clustered B-ALL samples in public datasets (TARGET and GSE79533) by molecular subtype, with genes highly expressed in low NT ROCKET patients also being highly expressed in Ph+ and Ph-like subtypes. Genes highly expressed in severe NT ROCKET patients were highly expressed in non Ph-like subtypes in the public datasets. Machine learning applied to all ROCKET patients classified 16 patients as having Ph-like gene expression and 15 patients having non Ph-like expression. No grade 4+ NT events occurred in Ph-like patients, and grades 3+ (p = 0.03) and 4+ NT (p = 0.0002) were significantly more frequent in the non Ph-like patients. Looking at 3 other B-ALL CD19 CAR T studies (FHCRC2639, NCT01865617; MSK 09-114, NCT01044069 and PLAT-02, NCT02028455), no grade 4+ NT events were observed in any Ph+ patients, suggesting that this finding may not be limited to the ROCKET trial. Pre CAR T infusion plasma levels of CCL17, a chemokine highly expressed by RNA-Seq in low NT ROCKET patients and in the Ph-like B-ALL datasets, were also significantly higher in the grade 0-1 versus grade 4-5 NT group (p < 0.05). **Conclusions:** This exploratory analysis suggests that B-ALL subtypes differ in risk for CD19 CAR T associated NT with Ph-like patients being at significantly lower risk than non Ph-like patients. Risk stratification by molecular subtype or gene expression signature could play an important role in identifying patients at elevated risk for severe NT.

7008 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Initial results of two phase I trials delivering mbIL-21 ex vivo expanded haploidentical NK cells after fludarabine/cytarabine for patients with relapsed/refractory myeloid leukemias. *First Author: Stefan O. Ciurea, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NK cells play an important role in the control of malignancies but are ablated by high-dose chemotherapy. Thus, rapid recovery of NK cell number and function correlates with improved disease control. Haploidentical NK cells delivered after lymphodepleting chemotherapy can induce remission in patients with relapsed and/or refractory AML. **Methods:** We hypothesized that anti-leukemic activity could be increased without toxicity by adoptive transfer of expanded NK cells after reinduction with fludarabine, cytarabine, and G-CSF (FLAG), or mini-FLAG (4 days) for patients with low performance score. Haploidentical NK cell donors were selected by KIR ligand and/or KIR gene content. NK cells were expanded on feeder cells and cryopreserved in multiple aliquots. Patients received 3 NK-cell infusions per week for two weeks, beginning 3-10 days after chemotherapy. Response was assessed at day 30 after treatment. Parallel Phase I studies were opened using the same regimen and NK cell manufacturing platform at two centers (US and Brazil). **Results:** 13 patients have been treated to date, age 12-70 years (median 61y), with AML/MDS/CMML (11/1/1), having received 2-8 prior lines of therapy (median 4). 12 patients received 10^6 NK cells/kg/infusion, one received 5x10^6. One patient had no response and received other investigational therapy prior to formal disease assessment. One patient with pre-existing liver toxicity developed worsening hepatic dysfunction and died prior to day 30. Two patients achieved marrow remission but had residual CNS disease. The remaining 9 patients (69%) achieved $<$ 5% blasts by morphology, with/without peripheral count recovery, for overall marrow remission rate of 85%. One patient progressively improved in MRD status by PCR over a 4-month period after treatment, suggesting ongoing immunologic anti-leukemic activity. Immune correlative studies will be presented at the meeting. **Conclusions:** Multiple infusions of cryopreserved expanded NK cells can be safely delivered after high-dose chemotherapy, with encouraging responses on this first dose level. Clinical trial information: NCT01787474.

7009 Clinical Science Symposium, Mon, 4:30 PM-6:00 PM

A phase 1 dose escalation study of the *IDH1*m inhibitor, FT-2102, in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). *First Author: Justin M. Watts, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *Isocitrate dehydrogenase 1* mutations (*IDH1*m) occur in 7-14% of AML patients (pts) and 3% of MDS pts. FT-2102 is a highly potent, selective small molecule inhibitor of *IDH1*m without anticipated CYP or QTc liabilities at the recommended phase 2 dose. **Methods:** A Phase 1/2 study was initiated to evaluate the safety, PK/PD, and clinical activity of FT-2102 alone or in combination with azacitidine (AZA) or cytarabine in *IDH1*m AML/MDS pts. Safety for all pts and efficacy for evaluable pts are reported. **Results:** At the data cutoff, 35 pts with a median of 2 prior regimens (range 1-9) had received FT-2102 in dose-escalation, including 22 single-agent (SA) and 13 AZA combination (CO) pts. Sixteen pts remain on treatment (SA, n = 10; CO, n = 6) with a median of 2 treatment cycles (range 1-16); 4 pts discontinued for transplant. FT-2102 has been well tolerated both as SA and in combination with AZA. Overall, regardless of causality, most treatment emergent AEs (TEAEs) were grade (gr) 1/2; most common ($>$ 20%) TEAEs were fatigue (34%), nausea (29%), and febrile neutropenia (23%). The most common ($>$ 15%) gr 3/4 TEAEs were febrile neutropenia (23%), anemia (20%), and pneumonia (17%). Five (14%) pts had gr 3 differentiation syndrome that was manageable and did not result in discontinuation. Steady-state exposure that exceeded the target IC90 of *IDH1*m was achieved at 150 mg BID, resulting in a reduction of 2-HG to normal levels in the majority of pts. Best response in all evaluable SA pts (n = 16) included: 2 (13%) complete remissions (CR), 4 (25%) complete remissions with incomplete hematologic recovery (CRi), and 5 (31%) clinical benefit (CB; stable disease lasting $\geq$8 weeks), including 2 with $>$ 50% reduction of marrow blasts (MB). Best response in evaluable CO pts (n = 11) included: 2 (18%) CR, 1 (9%) CRi, and 5 (45%) CB, including 2 with $>$ 50% reduction of MB. **Conclusions:** FT-2102 has shown favorable safety, PK/PD, and clinical activity in *IDH1*m AML/MDS with a single agent complete response rate (CR/CRi) of 38% and a complete response rate of 27% in combination with AZA. Current data support the continued evaluation of 150 mg BID in the expansion and Phase 2 stages of the study. Clinical trial information: NCT02719574.

7010 Clinical Science Symposium, Mon, 4:30 PM-6:00 PM

Durable response with venetoclax in combination with decitabine or azacitadine in elderly patients with acute myeloid leukemia (AML). *First Author: Courtney Denton Dinardo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Venetoclax (VEN), an oral BCL-2 inhibitor, has synergistic activity when combined with hypomethylating agents. This clinical study explores the optimal dose and efficacy of VEN in combination with decitabine (DEC) or azacitadine (AZA) in elderly AML. **Methods:** This is an open-label, phase 1b, dose escalation and expansion study (NCT02203773) on the safety and efficacy of VEN, with DEC or AZA, in elderly patients ($\geq$65 years) with untreated AML. VEN was coadministered daily with 20 mg/m^2 of DEC on days 1-5 or 75 mg/m^2 of AZA on days 1-7, each 28 day cycle. VEN was dosed at 400, 800, or 1200 mg in the escalation phase, and 400 or 800 mg in the expansion phase. Complete remission (CR), CR with incomplete blood count recovery (CRi), overall survival (OS) and adverse events (AEs) were evaluated. **Results:** Data cutoff was July 7, 2017. Of 145 patients, 56% were male; the median age was 74 years (range: 65–86). Overall, 60, 74, and 11 patients received VEN at 400, 800, and 1200 mg, respectively. Key grade $\geq$3 AEs were febrile neutropenia (43%), thrombocytopenia (23%) and neutropenia (16%); pneumonia and bacteremia (all grades) occurred in 18% and 8% of patients, respectively. At 400mg of VEN, the rate of CR+CRi was 73% (76% with AZA and 71% with DEC); efficacy data are in the table. Minimal residual disease (MRD) assessment in marrow aspirates was performed at disease assessment in a central lab using multicolor flow cytometry assay; overall, 37% (36/97) of patients with CR/CRi had MRD levels below the 10^{-3} cutoff. Median follow up was 15.1 months. **Conclusions:** Preliminary data suggest that 400 mg of VEN has the optimal benefit-risk profile in combination with DEC or AZA, which demonstrated a tolerable safety profile with deep responses and durable outcomes in elderly patients with AML. Clinical trial information: NCT02203773.

		CR/CRi	Duration of CR/CRi	
Patient subgroup	n	n (%)	median months	OS
All VEN doses	145	97 (67)	11.3	17.5
Intermediate cytogenetic risk	74	55 (74)	12.9	NR
Poor cytogenetic risk	71	42 (59)	6.7	9.6
Secondary AML	36	24 (67)	NR	NR
Age ≥75 years	62	40 (65)	9.2	11.0
VEN 400 mg				
+ AZA	29	22 (76)	NR	NR
+ DEC	31	22 (71)	12.5	15.2
VEN 800 mg				
+ AZA	37	21 (57)	11.7	14.2
+ DEC	37	27 (73)	9.2	17.5

OS, overall survival; NR, not yet reached (if applicable)

7012 Poster Discussion Session; Displayed in Poster Session (Board #72), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Relationship of minimal residual disease (MRD) in acute lymphocytic leukemia (ALL) and putative leukemia stem cells (LSCs). *First Author: Jonathan Michael Gerber, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: MRD has emerged as a significant prognostic factor in ALL, but even levels $<$ 0.1% still carry a risk of relapse. It is theorized that relapse is due to resistant LSCs, which survive after therapy. Consistent with this, MRD in acute myeloid leukemia patients was enriched for LSCs, which were CD34$^+$ CD38$^-$ with intermediate (int) levels of aldehyde dehydrogenase (ALDH) activity (CD34$^+$CD38$^-$ALDH^{int}) [Gerber, et al. *Blood*, 2012]. A similar CD34$^+$CD38$^-$ALDH^{int} putative LSC population was subsequently found in ALL [Gerber, et al. *ASH*, 2016]. We hypothesized that MRD in ALL would also be enriched for LSCs. **Methods:** Bone marrow specimens were collected on an IRB-approved protocol at diagnosis and/or post treatment from 32 patients with B cell ALL over a 3-year span. CD34$^+$ cells were isolated by magnetic bead/column selection, then analyzed by flow cytometry (FACS) for CD19, CD34, CD38, and ALDH. Student's *t*-test was used for statistical comparisons. **Results:** Twenty-four patients were followed post therapy, 5 of whom achieved complete remission with $<$ 0.1% detectable MRD by clinical flow cytometry and/or PCR. Whereas clinical FACS detected a mean of 0.0164 $\pm$ 0.0116% MRD in the 5 cases, the LSCs constituted 31.95 $\pm$ 13.51% of the CD34$^+$CD38$^-$ stem/progenitor cells, a nearly 2,000-fold increase ($p < 0.05$). In fact, in all cases with clinically detectable MRD by FACS and/or PCR, LSCs were reliably detected in the CD34$^+$CD38$^-$ stem/progenitor population, at levels as low as 1 in 10^6 mononuclear marrow cells. Furthermore, while the CD34$^+$CD38$^-$ALDH^{int} LSC population represented only 9.15 $\pm$ 4.07% of the total leukemic burden at diagnosis, it constituted 58.14 $\pm$ 18.63% in the MRD state ($p < 0.01$). Of note, CD19 was expressed on the CD34$^+$CD38$^-$ALDH^{int} population in all cases, both at diagnosis and in MRD. **Conclusions:** MRD was enriched for CD34$^+$CD38$^-$ALDH^{int} cells in ALL patients, implying that the putative LSCs are more resistant than the bulk leukemic cells to therapy. The LSCs expressed CD19, even in the MRD state, suggesting that therapies directed against CD19 could target LSCs and might prove curative. LSC detection may serve as a highly sensitive test for MRD. These findings merit validation in a larger cohort.

7013 Poster Discussion Session; Displayed in Poster Session (Board #73), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Impact of minimal residual disease (MRD) status in clinical outcomes of patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) treated with inotuzumab ozogamicin (InO) in the phase 3 INO-VATE trial. *First Author: Elias Jabbour, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MRD negativity is a key prognostic indicator of patient (pt) outcome in ALL and is predictive of improved survival and disease-free status. In the INO-VATE ALL trial (Kantarjian, NEJM 2016), pts with R/R ALL who received InO vs standard chemotherapy (SC) achieved greater remission (CR/CRi; 81% vs 29%) and MRD-negativity (78% vs 28%, in pts with CR/CRi) and had improved overall survival (OS): 7.7 vs 6.7 months. This analysis was conducted to assess prognostic value of MRD negativity by end of treatment (EOT) with InO. **Methods:** INO-VATE pts who received InO (n = 164) were included. Among pts with CR/CRi, MRD status (by multiparametric flow cytometry at a central lab) was defined as negative (MRD–) if $< 1 \times 10^{-4}$ blasts/nucleated cells (n = 81), or as positive (MRD+; n = 83), based on assessment by EOT. OS, progression-free survival (PFS), and predictors of MRD status (by multivariate logistic regression) are reported from final study data as of Jan 4, 2017. **Results:** MRD– status with CR/CRi was associated with significantly improved OS and PFS (Table) vs MRD+ status with CR/CRi: unstratified HR 0.512; 1-sided P= 0.0009 for OS and HR 0.423; P< 0.0001 for PFS. Exploratory multivariate analyses indicated that 2nd salvage compared to 1st salvage (OR 0.499, 2-sided P= 0.058) was associated with lower likelihood of having MRD– status, while $< 1x10^9$/L absolute circulating blast count at baseline (OR 3.231, P= 0.002) and longer duration of remission (OR 1.033, P= 0.005) were associated with increased likelihood of having MRD– status. Clinical trial information: NCT01564784. **Conclusions:** Among pts who received InO in the INO-VATE trial, having CR/Cri and MRD– status at EOT was associated with the greatest survival outcomes. However, pts who achieved an MRD+ CR/CRi had much greater survival than those who did not have CR/CRi. In R/R ALL, use of InO may optimize chances to attain the primary goal of complete remission and MRD– status.

	CR/CRi and MRD– (n = 76)	CR/CRi and MRD+* (n = 45)	No CR/CRi (n = 43)
Median OS, mos [95% CI]	14.1 [8.6–23.0]	7.2 [5.8–10.8]	2.6 [1.9–3.6]
Median PFS, mos [95% CI]	8.6 [6.2–11.4]	5.4 [3.9–6.2]	1.4 [1.0–1.9]

*includes 6 pts with no MRD assessment

7014 Poster Discussion Session; Displayed in Poster Session (Board #74), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Nivolumab (Nivo) maintenance (maint) in high-risk (HR) acute myeloid leukemia (AML) patients. *First Author: Tapan M. Kadia, The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, TX*

Background: Frontline AML induction produces 60-70% complete remission (CR) rates but relapse is a major source of failure. Beside stem cell transplant (SCT), few options exist for post-CR maint in HR pts. Prior maint studies of cytotoxics were unsuccessful. Post SCT immune surveillance via tumor-specific cytotoxic T-cells may be important in suppressing AML relapse. Immune checkpoint inhibitors may restore host immune surveillance in post-CR maint. **Methods:** This is a pilot phase II study of nivo maint in HR AML pts in CR, ineligible for SCT. Pts ≥ 18 yrs with a HR feature in 1st CR (CR1) or any pt in 2nd CR (CR2) who received induction & ≥ 1 consolidation cycle & were within 12 months (mos) of CR were eligible. Treatment was: nivo 3mg/kg IV Q2 weeks for 6 mos, then Q4 weeks until 12 mos on study, & then Q3 mos until relapse. All pts had baseline cytogenetic (CG) & molecular testing, & minimal residual disease (MRD) assessment by flow cytometry. Blood & marrow samples were collected for immune correlatives. CR duration (CRd) is compared to a similar historical cohort with median (med) of 8 mos. **Results:** 14 pts (med age 56 yrs): 11 pts were in CR, CRp (1), & CRi (2) at enrollment; 11 pts (79%) were in CR1, 2 pts (14%) in CR2, & 1 pt (7%) in CR4 was treated. Baseline mutations: TP53 (n = 3), DNMT3a (2), IDH2 (2), NPM1 (2), TET2 (3). HR features: 5 (36%) persistent MRD, 4 (29%) adverse CG, 1 (7%) adverse mutation alone, 1 t-AML (7%) & 3 pts (21%) in ≥ CR2. Pts received a med of 4 (1-17) cycles of therapy. At med F/U of 11 mos (1.4 – 26), med CRd was not reached. 6- & 12-mo rates of CRd were 79% & 71%, respectively. The 12- & 18-mo estimated OS were 86% & 67%, respectively. Therapy was well tolerated; 5 pts had grade 3/4 immune-related events. 1 pt had thyroiditis, treated with steroids & hormone replacement; 1 pt with transaminitis responded to dose interruption; 2 pts had pneumonitis treated with steroids & dose interruption. All 4 pts resumed rx after interruption. 1 pt had autoimmune hemolytic anemia & came off study. Most pts have detectable MRD while on therapy & in CR; 1 pt cleared MRD & 1 pt normalized CG. **Conclusions:** Maint nivo is safe & feasible in HR AML. The study continues to surpass expected rate of 6-mo CRd of HR pts. Correlatives profiling the immune repertoire are being analyzed. Clinical trial information: NCT02532231.

7015 Poster Discussion Session; Displayed in Poster Session (Board #75), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Profiling the immune checkpoint pathway in acute myeloid leukemia. *First Author: Paola Dama, University of Chicago, Chicago, IL*

Background: The immune checkpoint pathways in AML patients especially during the course of chemotherapy induction were seldom studied. This study was to characterize these pathways in AML patients treated on a prospective clinical trial to combine Selinexor with high-dose cytarabine (HiDAC) with mitoxantrone (Mito) (NCT02573363). **Methods:** Multiparameter flow-cytometry was utilized to monitor the changes in expression of immune checkpoint receptors using bone marrow and peripheral blood samples at diagnosis and following remission induction therapy in 26 patients with AML enrolled to the study. Expression of CD47, PD-L1, PD-L2 and Gal-9 was assessed on $CD34^+$ AML blasts and $CD34^-$ cell populations. In parallel, we evaluated expression of inhibitory (PD1, CTLA4, LAG3, TIM3) and stimulatory co-receptors (CD28, ICOS, CD137, OX40, CD40L, HLA-DR) on $CD4^+$ and $CD8^+$ T cell subsets. Flow cytometry data were analyzed with FlowJo-10 software. The Mann Whitney Test, Wilcoxon Rank test and Spearman's rank correlation analysis were applied. **Results:** The percentage of $CD34^-$ $Gal9^+$ cells was significantly higher in patients who experienced treatment failure (TF) after chemotherapy, comparing with those in complete remission (CR), with median of 36.9% (range: 1.7% -98.3%) versus a median of 3.8% (range: 0.18%-60.1%; $p < 0.05$). There was no difference of PD-L1 expression in these two patient groups. At the time of remission, we observed significant increase of expression of PD-L1 on BM CD34- cells, Tim3 on BM CD4+ and CD8+ T cells, as well as co-stimulatory checkpoint receptors: CD137 (4-1BB), HLA-DR on BM CD4+ cells, and OX40 on BM CD8+ T cells. In peripheral blood, the PD1 expression on CD4 cells was much higher at the time of remission comparing to that at the diagnosis. These data suggested an exhausted T cells status at the time of disease remission on the clinical trial treatment. **Conclusions:** Our small study demonstrated high level expression of Gal9 in CD34- cells in the BM at diagnosis in patients who failed induction chemotherapy. Increased expression of Tim 3 on CD4 and CD8 T cells in the BM and high PD-1 in peripheral CD4+ T cell at the disease remission suggested an exhausted immune status, which could be targeted with checkpoint inhibitors.

7016 Poster Discussion Session; Displayed in Poster Session (Board #76), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Treg infiltration and the expression of immune checkpoints associated with T cell exhaustion in AML. *First Author: Patrick Williams, University of Texas MD Anderson Cancer Center, Department of Cancer Medicine, Houston, TX*

Background: Better defining the immune checkpoint landscape of Acute Myeloid Leukemia will facilitate the rational selection of immune checkpoint targets and combination approaches for future clinical trials. **Methods:** Flow cytometry was performed on bone marrow aspirates (BMA) from 107 patients with AML treated at the MD Anderson Cancer Center. We evaluated the expression of inhibitory (PD1, CTLA4, LAG3, TIM3) and stimulatory receptors (GITR, OX40, 41BB, ICOS) on T cell subsets and the expression of their ligands (41BBL, B7-1, B7-2, ICOSL, PDL1, PDL2 and OX40L) on AML blasts. We correlated the expression of these markers with age, karyotype, a baseline next generation sequencing for 28 myeloid-associated genes including P53, DNA methylation proteins (DNMT3a, IDH1, IDH2, TET2) and FLT3, as well as prior treatment history. **Results:** When gating on $CD45^+$ cells, compared to healthy donors, patients with new and relapsed AML had an increased frequency for $CD3^+$ T cells (60.3% vs 78.0% vs 81.1%, P = 0.02), Tregs (1.7% vs 2.02 vs 3.02, P = 0.02), $PD1^+$ $CD8^+$ T cells (12.1% vs 27.3% vs 30.3%, P = 0.02) and $OX40^+$ $CD8^+$ T cells (0.62% vs 0.85% vs 2.26%, P = 0.03), $PD1^+$ $CD4^+$ T effector cells (13.2% vs 13.4% vs 25.5%, %, $P < 0.01$) and $OX40^+$ $CD4^+$ T effector cells (0.79% vs 4.81% vs 5.86%, P = 0.04). Compared to healthy donors, patients with new and relapsed AML had a higher incidence of exhausted $PD1^+$ $TIM3^+$ $CD8^+$ T cells (0.75% vs 1.36% vs 1.72%, P = 0.09), $PD1^+$ $TIM3^+$ $CD4^+$ T effector cells (0.75% vs 2.2% vs 2.8%, P = 0.16), $PD1^+$ $LAG3^+$ $CD8^+$ T cells (2.71% vs 4.69% vs 8.98%, $P < 0.01$) and $PD1^+$ $LAG3^+$ $CD4^+$ T effector cells (2.71% vs 14.3% vs 13.5%, P = 0.05), with bimodal distributions. The Treg to $CD8^+$ T cells correlated with increased frequencies of $PD1^+TIM3^+$ and $PD1^+LAG3^+$ $CD8^+$ T cells (P = 0.01). Blasts in BMAs from patients with TP53 mutated AML were more frequently positive for PD-L1 (6.95% vs 12.5%, P = 0.05). **Conclusions:** The increased Treg and exhausted T cell frequency in AML BMAs point to worsening exhaustion of the immune response. The dual contributions from Tregs and checkpoint ligand expression by blasts to immune suppression indicate that these pathways may play an important role in AML survival and therefore patients may benefit from checkpoint antibody therapy.

7017 Poster Discussion Session; Displayed in Poster Session (Board #77), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Post hoc exploratory analysis of two phase 2 trials of quizartinib monotherapy in patients (pts) with *FLT3*-ITD–mutated (mu) relapsed/refractory (R/R) AML with or without prior 1st-generation FLT3 tyrosine kinase inhibitors (TKI) treatment. *First Author: Mark J. Levis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: First-generation (1st gen) FLT3 TKIs such as sorafenib (SOR) / midostaurin (M) are increasingly used for treatment of *FLT3*-mu acute myeloid leukemia (AML). Quizartinib (Q) is a highly potent and selective FLT3 inhibitor with strong clinical antileukemic activity in pts with *FLT3*-ITD mu R/R AML. Analyzing the clinical activity of Q in pts with prior TKIs may provide early insights into an important clinical question about potential benefit of agents with varying kinase and safety profiles. **Methods:** This post hoc exploratory analysis was done in two phase 2 trials of Q monotherapy in *FLT3* mu R/R AML (Studies (A) NCT01565668, (B) NCT00989261) to assess Q activity in pts w/ prior FLT3 TKI therapy. Pts with *FLT3*-ITD allelic frequency ≥ 3% were considered *FLT3*-ITD positive for this analysis. 27 of 261 *FLT3*-ITD mu pts received prior SOR and/or M (24 SOR, 1 SOR and M, 2 M) in Study A (Q 90, 135, or 200 mg/d). 11 of 72 *FLT3*-ITD mu pts received prior TKIs (10 SOR, 1 SOR and M) in Study B (Q 30 or 60 mg/d). In both studies, Q was given for 28-day cycles until relapse, intolerance, or proceeding to HSCT. **Results:** In Study A, composite complete remission (CRc = CR+CRp+CRi) and overall response rates (ORR = CR+CRp+CRi+PR) with Q were 33% (9/27) and 67% (18/27), respectively, in prior-TKI-treated pts, compared with 53% (117/221) and 75% (165/221), respectively, in the TKI-naive pts. In Study B, CRc and ORR were 36% (4/11) and 45% (5/11), respectively, in prior-TKI-treated pts, compared with 48% (29/61) and 69% (42/61), respectively, in the TKI-naive pts. Median survival durations in Study A were 24.6 wk for prior-TKI-treated pts and 24.7 wk for TKI-naive; in Study B they were 20.9 wk and 23.7 wk, respectively. **Conclusions:** This analysis demonstrates meaningful clinical activity of Q in *FLT3*-ITD mu R/R AML pts with prior 1st gen FLT3 TKI exposure. Limitations are small sample size and post hoc analysis. Further studies, including mutational analyses, are warranted to further characterize the potential mechanism/s of response to Q in pts who have failed prior FLT3 TKI. Clinical trial information: NCT01565668; NCT00989261.

7018 Poster Discussion Session; Displayed in Poster Session (Board #78), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Erythropoietic cellular analyses in luspatercept-treated lower-risk myelodysplastic syndromes (MDS): Phase 2 PACE-MDS study. *First Author: Uwe Platzbecker, Universitatsklinikum Dresden, Dresden, Germany*

Background: Luspatercept (ACE-536) is a TGF-β family ligand trap promoting late-stage erythroid (E) differentiation and increases in hemoglobin. Endpoints of the ongoing, phase 2, open-label study in MDS include E response (IWG HI-E), RBC transfusion independence (RBC-TI, ≥8 weeks), and molecular/bone marrow (BM) morphological characteristics associated with response. **Methods:** MDS IPSS low or int-1 patients (pts) were treated every 3 weeks subcutaneously (up to 1.75 mg/kg) in the base/extension studies (NCT01749514/NCT02268383). BM and blood samples were analyzed prior to and at the end of 5 cycles of treatment (EOT) by central morphology and flow cytometry according to ELN guidelines to investigate E precursors, soluble transferrin receptor (sTfR), and reticulocytes (retics) in relation to response. **Results:** Data (as of 08Sept2017) were available for 49 pts (≥0.75 mg/kg) with evaluable flow and BM data. HI-E and RBC-TI responses were 61% (30/49 pts) and 55% (16/29 pts), respectively. At baseline, M/E ratio was lower and sTfR two-fold higher in R vs NR, mirrored by an increase in erythroid precursors. By EOT, retics were increased in R and remained unchanged in NR. **Conclusions:** These data suggest that expanded late-stage erythropoiesis at baseline is associated with a response to luspatercept. Responses were accompanied by further expansion of erythropoiesis (or activation of bone marrow) and increased release of reticulocytes, supporting luspatercept as an erythroid-maturation agent (EMA). Clinical trial information: NCT01749514, NCT02268383.

HI-E responder characteristics.	(n)	Baseline	EOT
M/E ratio	R (30)**	1.0 (0.3, 11.5)	0.9 (0.1, 3)
(BM morphology)	NR (19)	2.1 (0.6, 9)*	1.5 (0.2, 32.3)*
BM erythroid precursors (%, flow cytometry)	R (30)	9.5 (0.9, 43.6)	14.7 (3, 53.3)
	NR (19)	4.5 (1.2, 24.3)*	5.6 (0.6, 41)*
BM proerythroblasts (%, flow cytometry)	R (30)	8 (1, 22.2)	5.9 (0.6, 30.7)
	NR (19)	10.9 (1, 57.5)	11.2 (3.9, 32.3)*
sTfR (nmol/L)	R (29)**	68.4 (23.7, 181.1)	79.6 (10.6, 270)
	NR (19)**	35.6 (8.8, 249.7)*	44.7 (11.6, 279.9)* n = 17
Absolute retics (10^9/L)	R (26)**	35.9 (7, 154)	53.2 (9.9, 200) n = 25
	NR (15)	29.2 (21, 168)	38.6 (14, 183) n = 16

Median (min, max) *$p < 0.05$ R vs NR **$p < 0.05$ baseline vs EOT M = myeloid; NR = non responder; R = responder

7019 Poster Discussion Session; Displayed in Poster Session (Board #79), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

First-in-human study of ABBV-075 (mivebresib), a pan-inhibitor of bromodomain and extra terminal (BET) proteins, in patients (pts) with relapsed/refractory (RR) acute myeloid leukemia (AML): Preliminary data. *First Author: Gautam Borthakur, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pts with RR AML have a poor prognosis. BET proteins bind acetylated histone tails, leading to the upregulation of oncogenic target genes; their inhibition can block aberrant transcription in tumor models. ABBV-075 is a pan-BET inhibitor with antitumor activity in vitro and in xenograft models of AML. This 2-part first-in-human study assesses the safety and PK of ABBV-075 at various monotherapy or combination dosing schedules (NCT02391480). In part 1, the recommended phase 2 dose for ABBV-075 monotherapy in pts with solid tumors was identified. Here, we report preliminary data from part 2 in pts with RR AML. **Methods:** Adult pts with RR AML received daily ABBV-075 as monotherapy (ABBV075-mono) or combined with venetoclax (ABBV075-VEN). The dose-limiting toxicity (DLT) period was 28 d (ABBV075-mono) or 21 d (ABBV075-VEN). Thrombocytopenia was not considered a DLT. **Results:** As of 1 Jan 2018, 19 pts (median age: 65 y [range, 30–78]; 14 pts had ≥3 prior therapies) were enrolled: 12 pts in ABBV075-mono, 7 in ABBV075-VEN cohorts. Median time on treatment was 39 d (range, 3–213). There were no DLTs; 16 pts experienced AEs. AEs irrespective of causality in > 3 pts were: anemia (11), fatigue (11), dysgeusia (10), nausea (9), diarrhea (7), decreased appetite (7), febrile neutropenia (6), thrombocytopenia (6), and dry mouth, vomiting, contusion, decreased platelet count, decreased weight, hyponatremia, and hemoptysis (4 each). 15 pts had grade ≥3 AEs (anemia [11]); 13 pts had serious AEs (febrile neutropenia [4]). 10 pts died of causes unrelated to ABBV-075, 5/10 pts due to AML progression. In ABBV075-mono cohorts, bone marrow blast count was ≤50% of baseline in 4/11 evaluable pts. 1 pt (female; normal cytogenetics; *STAG2* mut) reached complete remission with incomplete hematologic recovery (thrombocytopenia) in cycle 5, still maintained at 8 m from treatment start. At cutoff date, the median overall survival for all pts was 3.2 m, and 4 pts were still in treatment without progression for 1, 6, 20, and 24 w. Enrollment is ongoing. **Conclusions:** ABBV-075 was well tolerated and showed antileukemic effects in pts with RR AML. Clinical trial information: NCT02391480.

7020 Poster Discussion Session; Displayed in Poster Session (Board #80), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Analysis of anti-leukemic activity, predictive biomarker candidates, immune activation and pharmakodynamics in R/R AML and MDS in response to treatment with bemcentinib (BGB324), a first-in class selective AXL inhibitor, in a phase II open-label, multi-centre study. *First Author: Bjorn T. Gjertsen, Centre for Cancer Biomarkers CCBIO, Department of Clinical Science, University of Bergen, Bergen, Norway*

Background: Bemcentinib (BGB324) is a first-in-class, oral selective inhibitor of the RTK AXL currently in ph II clinical development across several cancer types. AXL overexpression has been established as an independent negative prognostic factor in AML whereas AXL inhibition via bemcentinib has shown anti-leukemic activity and immune activation in pre-clinical models of AML and other cancers. **Methods:** N = 35 R/R AML or MDS (interm-2 and high-risk) pts received bemcentinib monotherapy in this two part 3+3 dose escalation and cohort expansion study. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in a selection of pts pre-dose and at C2D1. Gene expression analysis was carried out by qPCR using TaqMan. Phosphorylation of AXL and downstream targets PLCγ1, Erk/MapK and Akt was carried out by single cell flow and mass cytometry. Clonal evolution was analysed by exome sequencing and TruSight myeloid panel. The TCRb- and IGH-repertoire was investigated using Biomed TCRb-A/B and Biomed2 FR-2/3 primer pools and NGS on an Illumina MiSeq platform. **Results:** Treatment was generally well-tolerated with most AEs being mild or moderate in severity. 2 pts achieved complete responses with incomplete recovery of peripheral counts (CRi) and 5 achieved partial responses (PR). 8 pts reported disease stabilisation for more than 4 months. Levels of plasma soluble AXL and angiogenin and BM SLFN-11 expression correlated with pt benefit. Whole exome sequencing analysis showed conservation of clones which may limit the evolution of resistant blasts. Immune activation was observed by T- and B-cell receptor diversification. PhosphoFlow analysis of AXL and downstream signalling intermediates evidenced target inhibition. **Conclusions:** Bemcentinib is well tolerated in MDS and AML pts and exhibits anti-leukemic activity through multiple mechanisms including immune modulation. Pt benefit (CRi/PR/SD > 4 mths) is predictable by measurement of plasma markers soluble AXL and angiogenin. Clinical trial information: NCT02488408.

7021 Poster Discussion Session; Displayed in Poster Session (Board #81), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Is there a benefit of re-induction therapy in adult patients with AML with <20% blasts? *First Author: Kavya Kannamma Kannan, Wake Forest University School of Medicine, Winston-Salem, NC*

Background: Decision on re-induction (RI) therapy in adult patients with newly diagnosed acute myeloid leukemia (AML) who have received induction chemotherapy (ICT) when there are less than 20% blasts on day 14 nadir bone marrow biopsy (NBMB), is difficult due to the lack of efficacy data and the toxicity associated with RI. We sought to determine the utility of RI in this group of patients. **Methods:** We identified 270 adults with AML treated at Wake Forest Baptist Health with ICT between 2002-2009. We excluded 37 patients who did not have a NBMB. NBMB were classified as negative (< 5% blasts), suspicious (< 5% blasts with morphological suspicion for residual disease or 5-20% blasts) and positive (> 20% blasts) for residual disease. Complete remission (CR) was achieved if recovery BM had < 5% blasts along with platelet recovery to at least 100,000 cells/microliter and absolute neutrophil count of at least 1000 cells/microliter. A CRi was defined as having either platelet or neutrophil recovery but not both. Kaplan Meier estimation was used to calculate the median OS and survival estimates at 1, 2, and 3 years post induction. **Results:** Of the 233 patients, 106 (45.5%) had NBMB findings suspicious for residual disease (sRD). Of these patients, 66 (62.3%) underwent RI and 40 (37.7%) did not. Of those who received RI, 52 of 66 (78.8%) achieved a CR/CRi. In the patients who did not receive RI, 32 of 40 (80.0%) achieved a CR/CRi. There was no statistical difference in median OS with and without re-induction in patients with sRD overall and when sub classified into favorable, intermediate and poor cytogenetic categories. **Conclusions:** Our retrospective analysis raises questions of the utility of RI in adult patients with AML with less than 20% blasts on nadir marrow. This finding warrants prospective trials for further validation.

sRD(106)	RI (66)	No RI (40)
Demographics		
Age		
< 60	27 (40.9%)	20 (50.0%)
> or equal to 60	39 (59.1%)	20 (50.0%)
Gender		
Male (57.5%)	40 (60.6%)	21 (52.5%)
Female (42.5%)	26 (39.4%)	19 (47.5%)
Cytogenetic risk		
Favorable (16%)	11 (16.7%)	6 (15.0%)
Intermediate (71.7%)	46 (69.7%)	30 (75.0%)
Poor (12.3%)	9 (13.6%)	4 (10.0%)
Median OS in months (p-0.7484)	16.9	20.1
Favorable (p-0.4415)	NA*	NA*
Intermediate (p-0.5018)	16.9	20.1
Poor (p-0.4839)	6.4	5.2

7022 Poster Discussion Session; Displayed in Poster Session (Board #82), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Clonal evolution in acute myeloid leukemia (AML): Relapse after a long remission period. *First Author: Musa Yilmaz, Baylor College of Medicine, Houston, TX*

Background: Late relapse in AML occurring more than 5 years after achieving remission is uncommon and underlying biological events are poorly understood. We aim to determine the clonal events resulting in late relapse of AML. **Methods:** We identified patients (pts) with AML who received intensive induction chemotherapy between 1990 and 2010, achieved complete remission (CR), and remained in CR for at least 5 years. A total 349 pts were identified, and 15 (4%) relapsed beyond 5 years. Whole exome-sequencing was performed in diagnosis (dx) and 1st relapse bone marrow samples (available in 10 pts). **Results:** A total of 43 driver mutations were identified in 10 pts, of which 12 were primary tumor specific, 18 relapse-specific, and 13 were shared between primary and relapsed tumor (Table). Twenty-seven of 43 driver mutations (63%) were nonsynonymous SNV and 16 (37%) were indels. At relapse, 3 clonal evolution patterns were identified: pattern 1, the founding clone in the primary tumor gained additional mutations and evolved into the relapse clone and a subset of primary tumor mutations were not detected at relapse (UPN 1, 5, 6, and 7); pattern 2, the founding clone in the primary tumor gained additional mutations at relapse (UPN 9, 10, 12, and 14); pattern 3, relapsing clone harbored none of the primary tumor mutations, thus it represented a new clone (UPN 3 and 15). **Conclusions:** Relapse after a long remission in pts with AML is associated with persistence of the founding clone and acquisition of new relapse-specific mutations in the majority. Understanding the mechanisms of such quiescence may assist in increasing CR duration in pts with AML.

Driver mutations identified in 10 primary-relapse pairs.

UPN	Age at Dx	CR Duration (year)	Primary Specific	Shared	Relapse Specific
1	17	24	*NRAS*	*DNMT3A*	*ASXL1, RUNX1*
3*	34	12	*NF1, FANCM, ZRSR2*¥*	none	*XPO1*
5	44	8	*NF1*	*DNMT3A, TET2*	*TET2*†
6	38	8	*NRAS, MYO1A*	*IDH1, PRRG1*	*FLT3, GNAI2, RAD21, RNF128*
7	57	8	*CHD2*	*IDH2, SRSF2*	*AR, TRAPPC8, ASXL1, RUNX1*
9	75	7	none	*ASXL1*	*NF1*
10	37	6	*FLT3, RELN*	*DNM2*	none§
12	67	6	none	*IDH2, SRSF2*	*NPM1*
14	63	6	none	*IDH2, SRSF2*	*FLT3, TET2, GATA2*
15	60	6	*KRAS*	none	*IRF1*

*UPN: unified pt number, †Different TET2 mut., ¥ 2 different ZRSR2 mut., *allo-SCT in CR1, § at relapse karyotype showed newl del 7q and persistent del 5q*

7023 Poster Discussion Session; Displayed in Poster Session (Board #83), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 11:30 AM-12:45 PM

Impact of numerical variation, allele burden and mutation length on outcomes in acute myeloid leukemia with fms-like tyrosine kinase receptor-3 internal tandem duplication (FLT3-ITD) mutation. *First Author: Ahmad Ghorab, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: While high allelic burden is known to be associated with adverse outcomes in FLT3-ITD mutated AML, the impact of numerical variation and insert size on clinical outcome of AML patients (pts) is not well studied. **Methods:** Analysis included 330 newly diagnosed AML pts with FLT3-ITD mutation diagnosed between 3/1999 and 11/2015. Overall survival (OS) was calculated from the time of diagnosis to death/last follow up time (LFU). Relapse free survival (RFS) was calculated from response to relapse/LFU. **Results:** Table 1 summarizes patient characteristics, response and OS, RFS according to mutation number, size, allelic burden and stem cell transplantation (SCT). Because of the time frame, only 20% pts had frontline exposure to FLT3 inhibitors. **Conclusions:** Numerical variation and insert length had no significant impact on outcomes while lower allelic burden, FLT3 inhibitor therapy trended towards better RFS. SCT had a significant favorable impact on both OS and RFS.An expanded contemporary cohort analysis is ongoing.

Patient characteristics and outcomes:

Characteristics	Number; N (%), or Median [range]	Response	Number; N (%), or Median [range]
Age, years	60 [17-88]	**Treatment Regimen**	
Male	165 (50)	With FLT3 inhibitor	67 (20)
WBC (x10^6 /L)	12.2 [0.2-278.2]	Without FLT3 inhibitor	263 (80)
Hemoglobin (g/dL)	9 [4.1-13.1]	**Treatment Response**	
Platelets (x10^3/L)	43 [1-326]	Complete Remission (CR)	208 (63)
Bone marrow blasts (%)	70 [11-98]	CR without platelet recovery	24 (7)
Peripheral blast (%)	44 [0-99]	SCT	89 (27)
Diploid Cytogenetics	240 (73)		

FLT3-ITD Mutation	N	Median OS (months)	p-value	N	Median RFS (months)	p-value
Numerical Variation						
Single ITD	225	12	**0.18**	80	6.2	**0.88**
Multiple (≥ 2) ITD	105	17.3		41	6.1	
Allele Burden						
Low (< 50%)	271	13.6	**0.58**	103	6.6	**0.06**
High (≥50%)	57	9.6		18	4.9	
ITD Length (base pair; bp)						
Short (< 70 bp)	200	13.7	**0.25**	69	6.2	**0.46**
Long (≥70 bp)	72	17.4		28	5.7	
Treatment Regimen						
With FLT3 inhibitor	67	16.3	**0.14**	24	8.6	**0.06**
Without FLT3 inhibitor	263	12.4		99	6.1	
SCT						
Yes	89	Not Reached	**< 0.0001**	26	8	**0.01**
No	241	9.8		97	5.8	

7024 Poster Session (Board #84), Mon, 8:00 AM-11:30 AM

iCare 1: A prospective clinical trial to predict treatment response based on genomics-informed computational biology in patients with acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). *First Author: Leylah Drusbosky, University of Florida, Gainesville, FL*

Background: Cytotoxic agents (7+3, HiDAC) and hypomethylating agents (HMAs) fail in the majority of MDS and AML pts. The aim of this study is to determine the predictive values of a genomics-informed computational biology method (CBM) in pts who are treated with standard of care (SOC) therapy. **Methods:** AML or MDS pts were recruited to a prospective clinical trial to assess predictive values by comparing CBM predictions of treatment response to actual clinical response. Genomic profiling was done by cytogenetics, whole exome sequencing, and copy number variation analysis. All genomic data were entered into CBM, which creates disease-specific protein network maps using PubMed. Digital drug simulations were done by measuring drug effect on a cell growth score. Each pt-specific protein network map was screened for the extent to which each pt's therapy reduced simulated disease growth. Clinical outcomes were prospectively recorded. For AML, CR+PR was used to define response (IWG 2003). For MDS, CR+PR+HI was used to define response (IWG 2006). Western blots were performed on pathway proteins. 2x2 tables and Fisher's exact tests were used to compare CBM prediction values vs empiric drug administration. **Results:** 135 pts were recruited, and 101 have had all genetic tests performed. 50/101 pts received 61 treatments and were eligible for efficacy evaluation. 33/50 had AML, 15/50 had MDS. Western blot validation showed correct prediction of 4 activated networks (Akt2, Akt3, PIK3CA, Erk1/2), with 89% accuracy. 55 drug outcome predictions were correctly matched to their actual clinical outcomes, resulting in 90% prediction accuracy, 93% PPV, 92% NPV, 93% sensitivity, and 88% specificity. The accuracy of CBM was significantly greater than empiric drug administration (p = 1.664e-05). **Conclusions:** CBM that models multiple genomic abnormalities showed high predictive value of protein network perturbations and clinical outcomes after SOC treatments. This technology could be used to establish eligibility criteria for precision enrollment in drug development trials, and will be used in upcoming precision medicine trials. Clinical trial information: NCT02435550.

7025 Poster Session (Board #85), Mon, 8:00 AM-11:30 AM

Determining the sensitivity of primary acute myeloid leukemia (AML) samples with FLT3-ITD or FLT3-D835 mutations to FLT3 inhibitors using an ex vivo drug sensitivity screen. *First Author: Mara Rosenberg, Oregon Health & Science University, Portland, OR*

Background: AML has high molecular complexity and certain markers are predictors of overall survival. Mutations in FLT3-ITD, for example, lead to a poor prognosis with outcomes further worsened by co-occurring mutations in DNMT3A. Small molecule inhibitors have been developed to target a select number of these mutations such as Midostaurin on FLT3-ITD and FLT3-D835. However, the impact of the specific FLT3 mutation or the effect of co-occurring mutations in DNMT3A and NPM1 on drug sensitivity is not fully known. **Methods:** We identified 503 primary AML samples tested with an ex-vivo drug sensitivity screen that includes 130 small-molecule inhibitors and over 10 FLT3 inhibitors. Mononuclear cells were screened, metabolic viability assessed, and drug response summarized by area under the curve (AUC). **Results:** FLT3-ITD was the strongest indicator for response to FLT3 inhibitors (Table 1). Sensitivities were similar with DNMT3A and/or NPM1 co-mutations. Further, FLT3-D835 mutant samples showed no increased sensitivity to FLT3 inhibitors compared to non-FLT3 mutated samples. **Conclusions:** The similar ex-vivo drug sensitivity profiles inFLT3-ITD AML with or without DNMT3A and/or NPM1 mutations suggest co-treatment with FLT3 inhibitors will allow for improved overall survival in these cohorts. Additional clinical testing may further characterize the effect of FLT3-D835 mutations on targeted therapies and the impact of co-mutations. Some FLT3-ITD inhibitors showed increased potency compared to Midostaurin suggesting alternative treatment choices for select AML patients.

Mean AUC values (± confidence interval) for each drug by sample classification.

Classification	Quizartinib	KW-2449	Cabozantinib	Sorafenib	Sunitinib	Midostaurin
ITD+	37(±3)*	55(±5)	45(±4)*	52(±4)	55(±4)	56(±4)
ITD+ / DNMT3A+	36(±5)*	55(±6)	41(±7)*	48(±7)	54(±7)	60(±7)
ITD+ / NPM1+	35(±4)*	52(±6)	39(±5)*	48(±5)	53(±4)	53(±6)
D835+	46(±8)*	70(±8)	53(±11)	59(±8)	61(±8)	69(±9)
FLT3-	57(±2)*	77(±2)	67(±2)*	73(±2)	74(±2)	75(±2)

*Drug AUC differs from Midostaurin ($p < 0.001$). Sample classification differs from FLT3 Negative cohort ($p < 0.001$).

7026 Poster Session (Board #86), Mon, 8:00 AM-11:30 AM

Initial report of a phase I study of LY2510924 with idarubicin and cytarabine (IA) in relapsed/refractory (R/R) AML. *First Author: Prajwal Boddu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LY2510924 is a peptide antagonist of CXCR4, a key component of the CXCR4/SDF-1 signaling axis that is critical for homing of stem cells in the bone marrow and activation of downstream pathways involved in cell proliferation and survival. In a preclinical AML model, LY2510924 showed significant activity as a single agent and in combination with chemotherapy (*Cho et al. Blood* 2015). **Methods:** A phase I study was designed to determine the safety and toxicity profile of combination therapy of LY2510924 with IA in patients (pts) with R/R AML. Pts aged 18 to 70 years who failed prior therapy (≤ salvage 3) were eligible. LY2510924 is administered from days 1-7 followed by IA starting day 8. In responders, 4-6 consolidation cycles were administered. Two dose escalation levels (10 and 20 mg) were planned, according to a 3+3 design; up to 12 pts to be enrolled in phase I portion. **Results:** Eleven pts have been enrolled with a median age of 55 (range, 19-70) years. Of 10 pts tested, 2 (20%) had complex cytogenetics. Median prior therapies were 1 (1-3). Six pts were treated at dose level '0' (10 mg) and 5 at dose level '1' (20 mg); 3 of 5 treated at dose level '1' were evaluable for response. Most non-hematologic toxicities were grade 1-2 in severity. At dose level '0', 1 pt experienced dose limiting toxicity (DLT) (2 grade 3 DLTs: rash and hypo-cellular marrow). No major toxicities occurred at dose level '1'. At '0' dose level, 1 pt had a CR and 2 had CRi; at dose level '1', 1 achieved CR; the overall response rate was 44%. By flow cytometry, 4 of 9 had ≥ 50% decrease in CXCR4 mean fluorescence intensity. **Conclusions:** Combination of LY2510924 with IA is safe in R/R AML pts. Dose-escalation to 40 mg of LY2510924 is planned to achieve > 90% blockade of CXCR4 receptor occupancy, followed at the expansion phase of the study at recommended phase 2 dose level. Clinical trial information: NCT02652871.

7027 Poster Session (Board #87), Mon, 8:00 AM-11:30 AM

CX-01, an inhibitor of CXCL12/CXCR4 axis and of platelet factor 4 (PF4), with azacitidine (AZA) in patients with hypomethylating agent (HMA) refractory AML and MDS. *First Author: Eric Huselton, Washington University in St. Louis, St. Louis, MO*

Background: Outcomes are poor for older patients with AML and MDS who progress on HMAs. Blocking the CXCL12/CXCR4 axis may be therapeutic as this is essential for retention of malignant stem cells in the bone marrow (BM), where they may be protected from the genotoxic stresses of chemotherapy. CX-01 is a low molecular weight heparin derivative with minimal anticoagulant activity that disrupts the CXCL12/ CXCR4 axis, and neutralizes the activity of PF4, a negative regulator of megakaryopoiesis. We hypothesized that CX-01 would re-sensitize patients with HMA-refractory AML and MDS to AZA and mitigate thrombocytopenia. **Methods:** Patients with HMA-refractory INT-1 or greater MDS and AML received 7 day continuous infusion of CX-01 with 7 day AZA 75 mg/m^2 in 28 day cycles. The primary objective was to assess the overall response rate (ORR). **Results:** To date, 20 patients were treated and 12 are evaluable for response with a BM biopsy after C2. The median age was 74 years. 9 patients had secondary AML, 7 had MDS INT-1, 2 had MDS INT-2, and 2 had de novo AML. 10 patients had poor risk cytogenetics and/or p53 mutations. Baseline BM showed a median 16% blasts. Patients were heavily pretreated, receiving a median of 6 cycles of prior HMA cycles (range 4-20) with 10 patients receiving > 1 prior line of therapy. Patients received a median of 2 cycles of CX-01 with AZA (range 0-5). Of the 12 evaluable patients, there was 1 complete response (CR), 3 marrow CRs (with incomplete count recovery), 7 stable disease, and 1 progressive disease for an ORR of 33%. There was no significant difference in baseline characteristics of responders and the rest of the cohort. 3 of 4 responders had hematologic improvement, 2 with normalization of platelet counts. Median duration of response is 212+ days, with 2 patients disease-free at 192 and 233 days, and all four responding patients still alive. CX-01 was well tolerated, with all severe AEs thought unlikely to be related to CX-01. **Conclusions:** CX-01 and AZA appears to have an encouraging response rate in HMA-refractory AML/MDS. Treatment was feasible with no instances of study related severe AEs. This trial is ongoing to evaluate the ORR and OS of all patients treated. Clinical trial information: NCT02995655.

7028 Poster Session (Board #88), Mon, 8:00 AM-11:30 AM

Inotuzumab ozogamicin (InO) treatment in patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): Analysis from INO-VATE by bone marrow blast percentage (BMB%). *First Author: Anjali S. Advani, Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Background: InO is a calicheamicin-conjugated antibody targeting CD22 on ALL blast cells. Here we report outcomes in R/R ALL patients (pts) receiving InO or standard of care chemotherapy (SC) in the phase 3 INO-VATE trial according to baseline BMB%, an indicator of disease burden. **Methods:** Adults with CD22+ ALL due to receive salvage treatment were randomized 1:1 to InO (n = 164) or SC (n = 162). Dosing and methods were published previously (Kantarjian et al, NEJM 2016). BMB% was defined as low (< 50%), moderate (50–90%), and high (> 90%) at start of treatment. **Results:** At baseline, characteristics across all groups were balanced and median BMB% was 28%, 78%, and 95% in the low, moderate, and high disease burden subgroups. Complete remission rates were significantly higher in InO vs SC pts, with 74% vs 46%, 75% vs 48%, and 70% vs 17% achieving CR/CRi in low, moderate, and high BMB% subgroups. Significantly more pts in the InO arm achieved minimal residual disease negativity: 29/53 (55%), 52/79 (66%), and 16/30 (53%) for low, moderate, and high BMB% compared with 10/48 (21%), 11/83 (13%), and 2/30 (7%) for SC, respectively. InO-treated pts also had improved progression-free survival vs SC, with hazard ratios of 0.44 (97.5% CI, 0.26–0.74, 1-sided P= 0.0001) for low, 0.50 (97.5% CI, 0.34–0.75, P< 0.0001) for moderate, and 0.33 (97.5% CI, 0.16–0.69, P= 0.0002) for high BMB%. Overall survival (OS) was favored in the InO arm across groups (Table) with potentially the greatest difference seen in pts with high BMB% (HR = 0.60 [97.5% CI 0.32–1.129, 1-sided P= 0.03]). Clinical trial information: NCT01564784. **Conclusions:** InO treatment resulted in superior efficacy over SC across all BMB% subgroups out to 2 years follow-up, particularly in patients with the greatest disease burden by BMB%.

	OS Probability, Mos (95% CI)		
BMB%	**6**	**12**	**24**
Low			
InO (n = 53)	56.6 (42.3–68.7)	34.0 (21.7–46.6)	30.0 (18.3–42.5)
SC (n = 48)	59.5 (43.7–72.3)	38.8 (24.6–52.8)	2.4 (0.2–11.0)
Moderate			
InO (n = 79)	61.7 (50.0–71.4)	35.6 (25.1–46.2)	21.1 (12.8–30.8)
SC (n = 83)	51.3 (39.7–61.8)	34.0 (23.7–44.6)	15.0 (8.0–24.0)
High			
InO (n = 30)	53.3 (34.3–69.1)	26.7 (12.6–43.0)	13.3 (4.2–27.8)
SC (n = 30)	32.6 (16.4–49.8)	12.2 (3.2–27.8)	8.1 (1.4–22.6)

7029 Poster Session (Board #89), Mon, 8:00 AM-11:30 AM

Extensive safety profile of inotuzumab ozogamicin (InO) in relapsed/refractory acute lymphoblastic leukemia (ALL) patients enrolled in the phase 3 INO-VATE trial. *First Author: Ryan Daniel Cassaday, University of Washington School of Medicine and Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: In INO-VATE, patients (pts) treated with InO vs standard chemotherapy (SC) had significantly greater remission rates and longer overall survival (OS), with 23% reduced risk of death (Kantarjian et al, NEJM 2016). Here we report detailed safety outcomes from long-term follow-up. **Methods:** Study methods were previously published. Adults with CD22+ ALL in 1st or 2nd salvage were randomized 1:1 to InO (n = 164) or SC (n = 162). Data up to Jan 4, 2017 are reported. **Results:** Adverse event (AE) and serious AE rates were similar between arms even though more cycles of InO than SC were administered (Table). Grade (Gr) 3-4 AE rates were higher with SC, while more Gr 5 AEs occurred with InO vs SC (6% vs 2%); 5 cases (3%) were veno-occlusive disease (VOD). More pts taking InO discontinued due to AEs, most often from infections (10 [6%]) including pneumonia and sepsis, hepatobiliary disorders (7 [4%]), or blood/lymphatic disorders (BLD) including cytopenias (5 [3%]). For SC, discontinuations were most often from infections (6 [4%]) or BLD (3 [2%]). More hepatic AEs (any Gr) occurred with InO: 83 (51%) vs 52 (36%), including VOD (23 [14%] vs 3 [2%]). A lower percentage of death was seen with InO: 131 (80%) vs 126 (88%) for SC. Fewer InO pts died from ALL: 80 (49%) vs 100 (70%) for SC. Clinical trial information: NCT01564784. **Conclusions:** Safety data from the final report of INO-VATE are consistent with previous reports of data that also include greater efficacy (longer survival) seen with InO vs SC. Temporary discontinuation and dose reduction of InO were used to manage serious or severe AEs. Data suggest vigilant monitoring, treatment, and/or prevention for the most common events such as VOD and infections are needed to optimize outcomes.

	Treatment-emergent AEs (TEAEs)		Treatment-related TEAEs	
	InO (n = 164)	SC (n = 143)	InO (n = 164)	SC (n = 143)
Total AEs	2023	2112	764	980
Pts with AEs, n (%)	163 (99)	143 (100)	144 (88)	130 (91)
Serious AEs	85 (52)	72 (50)	52 (32)	42 (29)
Gr 3-4 AEs	147 (90)	138 (97)	114 (70)	114 (80)
Gr 5 AEs	26 (16)	16 (11)	9 (6)	3 (2)
Post AE, n (%):				
Discontinued	31 (19)	11 (8)	15 (9)	6 (4)
Dose reduced	5 (3)	3 (2)	4 (2)	1 (1)
Temporary discontinuation	72 (44)	17 (12)	51 (31)	12 (8)
Temporary discontinuation + dose reduced	3 (2)	1 (1)	3 (2)	0

7030 Poster Session (Board #90), Mon, 8:00 AM-11:30 AM

Outcomes with inotuzumab ozogamicin (InO) in patients with Philadelphia chromosome–positive (Ph+) relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). *First Author: Wendy Stock, Section of Hematology/Oncology, Department of Medicine, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: InO, a CD22-directed antibody-drug conjugate, is approved to treat adults with R/R ALL. Historically, patients (pts) with Ph+ ALL (~20–30%) have had poor prognoses compared with Ph− pts. **Methods:** Pts with R/R ALL received InO in a phase 1 dose-finding/phase 2 study (1010; DeAngelo et al, Blood Adv 2017) and a phase 3 trial (1022; Kantarjian et al, NEJM 2016) comparing InO vs standard chemotherapy (SC). We analyzed outcomes in Ph+ pts (Ph chromosome or BCR-ABL gene by FISH) treated with InO (InO-1010 or InO-1022) or SC based on final data from each study. **Results:** In 1010 and 1022, respectively, 16 and 22 Ph+ pts received InO; 27 Ph+ pts were randomized to SC in 1022 (22 received SC). Pts in 1010 were heavily pretreated. Among Ph+ pts in 1022, 19 (86%) InO pts and 26 (96%) SC pts had previous tyrosine kinase inhibitors (TKIs). Prior stem cell transplants (SCT) were 8 (50%) for InO-1010, 7 (32%) for InO-1022, and 9 (33%) for SC. Also, 15 (94%), 10 (45%), and 15 (56%) pts were treated in ≥2nd salvage for InO-1010, InO-1022, and SC, respectively. Efficacy outcomes are shown (Table). A total of 3 (19%) InO-1010 pts, 9 (41%) InO-1022 pts, and 5 (19%) SC pts proceeded to SCT after treatment. The most common non-hematologic grade 3-4 adverse events with InO in Ph+ pts were gastrointestinal disorders (31%) in 1010 and multi-organ laboratory abnormalities (41%) in 1022; 2 Ph+ pts in each InO study had veno-occlusive liver disease. Among SC pts, infections (55%) were the most common grade 3-4 nonhematologic events. Clinical trial information: NCT01363297. **Conclusions:** In Ph+ pts with R/R ALL who failed prior TKIs +/- SCT, InO-treated pts had higher rates of CR/CRi, MRD negativity, and subsequent SCT. However, overall outcomes in 1022 InO vs SC were still inferior to those reported in Ph– pts; thus additional treatment combinations should be explored.

Efficacy Endpoints	InO-1010 (n = 16)	InO-1022 (n = 22)	SC (1022) (n = 27)
Complete remission (CR/CRi), n (%)	9 (56)	16 (73)	15 (56)
Minimal residual disease (MRD) negativity, n (%)	10 (63)	14 (64)	5 (19)
Overall survival (mos), median (95% CI)	7.4 (4.3–11.3)	8.7 (3.6–14.1)	8.4 (5.0–14.3)
Progression-free survival (mos), median (95% CI)	4.4 (1.8–5.9)	3.9 (2.1–9.2)	3.1 (1.1–6.2)

7031 Poster Session (Board #91), Mon, 8:00 AM-11:30 AM

Phase 1 trial of pegzilarginase in patients (pts) with relapsed/refractory (R/R) AML or MDS refractory to hypomethylating agents (HMAs). *First Author: Geoffrey L. Uy, Washington University School of Medicine, St. Louis, MO*

Background: In vitro studies demonstrate that AML cells are arginine auxotrophs and are metabolically vulnerable to arginine depletion (PMID: 24018014 & 25896651). To test the clinical utility of arginine depletion in AML we performed a phase 1 trial of pegzilarginase, a pegylated, recombinant, cobalt-substituted, human arginase I in pts with R/R AML or MDS (NCT02732184). **Methods:** Pts with R/R AML or HMA-refractory MDS were enrolled in a phase 1 dose escalation study using a 3+3 design. The primary endpoint was MTD. Other endpoints included safety, PK, PD (arginine & ornithine), immunogenicity, preliminary clinical activity, and expression of ASS1, ASL, & OTC in blasts. **Results:** Twenty-one pts (19 AML, 2 MDS) were treated with weekly pegzilarginase 0.12 to 0.48 mg/kg. Low ASS1 expression was observed in the majority of pt samples by rtPCR. Eleven pts received at least 4 doses. One dose-limiting toxicity (DLT) of reversible G4 encephalopathy was observed at 0.48 mg/kg. Seven pts were then enrolled at 0.36 mg/kg. No DLTs were observed but 4 pts discontinued treatment before receiving 4 doses (3 - disease progression, 1 - withdrew consent). Related serious or ≥ Gr3 AEs in ≥2 pts were nausea and vomiting (3 pts each), and diarrhea and fatigue (2 pts each). Related AEs in ≥10% of pts included nausea (10 pts, 2 Gr 3), vomiting (9, 2 Gr 3), fatigue (7, 1 Gr 3), decreased appetite (6), diarrhea (3, 2 Gr 3), and dizziness (3, 1 Gr 3). The pegzilarginase $t_{1/2}$ was ~39 to 49 hr at ≥ 0.24 mg/kg and depleted arginine to ~10% of baseline for ≥48 hrs. One of 14 pts developed a low titer of anti-drug antibodies 4 weeks after start of treatment that was no longer detected at end of treatment (3 weeks after last dose). No clinical responses were observed. **Conclusions:** Pegzilarginase was well tolerated up to 0.36 mg/kg with a manageable safety profile. PK/PD data support weekly dosing, as confirmed by a rapid and sustained reduction in blood arginine. The observed results are consistent with a recent Ph 2 trial of arginine depletion in AML (PMID:28900115), suggesting depletion of arginine alone is insufficient for clinical activity in AML. Alternative approaches including combination therapy may be required. Clinical trial information: NCT02732184.

7032 Poster Session (Board #92), Mon, 8:00 AM-11:30 AM

A retrospective study of comorbidities and complications in elderly acute myeloid leukemia (AML) patients in the U.S. *First Author: Neil Dhopeshwarkar, Daiichi Sankyo, Basking Ridge, NJ*

Background: Treatment decisions are often influenced by comorbidity and functional capacity. Comorbidity burden in patients with AML has been shown to increase by age, but there is limited characterization of comorbidities and complications in elderly AML patients, who generally are underrepresented in clinical trials. We characterized elderly AML patients in terms of comorbidities and complications. **Methods:** Patients (≥ 65 years) with a primary diagnosis of AML (SEER ICD-O Recode 35021 and ICD-9 205.0x) were identified from the SEER-Medicare Linked Database (2000-2013) and were followed till end of 2014. AML patients were matched 1:1 to patients without cancer on age, sex, geographic region, and race. A subset of relapsed and/or refractory (R/R) AML patients was identified using a modified previously validated algorithm. Comorbidities were assessed using NCI index scores. Incidence rates were calculated for select complications. Cox Proportional Hazards models were used to assess risks of complications. **Results:** The median age in AML and matched non-cancer patients (3,911 matched pairs) was 77 years (65-101 years) with 54% being male. AML patients had more comorbidities (52.1 % vs. 48.3% with ≥1 comorbidity) and higher comorbidity scores (NCI scores: 0.97 vs. 0.84, $p < 0.01$) at baseline (up to 12 months prior diagnosis) compared to non-cancer controls. Among other complications, incidence rates (per 100 person years) of cardiovascular disease (CVD) (54.0 vs. 8.8, $p < 0.01$), type 2 diabetes (T2D) (25.4 vs. 4.8, $p < 0.01$), and stroke (17.0 vs. 5.7, $p < 0.01$) were higher among AML patients. After adjusting for age, sex, region, NCI score, and baseline myelodysplastic syndrome, AML patients had a significantly higher risk of CVD (HR 4.61, 95% CI 4.07-5.21), T2D (HR 3.85, 95% CI 3.35-4.42), and stroke (HR 2.60, 95% CI 2.32-2.92). Similar results were observed in the R/R AML group. **Conclusions:** Elderly AML patients had higher comorbidities and rates of complications compared to matched non-cancer patients. Clinical decisions should consider the presence of comorbidities and complications. Further research is needed to better understand the association between AML and chronic health outcomes.

7033 Poster Session (Board #93), Mon, 8:00 AM-11:30 AM

Hypomethylating agent (HMA) treatment as a bridge to allogeneic hematopoietic cell transplantation (HCT) for relapsed/refractory acute myeloid leukemia (RR-AML). *First Author: Michael Richard Grunwald, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Outcomes for patients (pts) with RR-AML are poor, with limited treatment options. Salvage HMA therapy has been explored for RR-AML but is often considered palliative. We examined response and survival in RR-AML pts treated with HMA therapy, including HCT rates and outcomes. **Methods:** All RR-AML pts initiated on HMAs at our institution between August 2013 and August 2017 were analyzed. Overall response rate (ORR) included complete remission (CR), CR with incomplete platelet recovery (CRp), CR with incomplete count recovery (CRi), and hematologic remission (defined by neutrophils $>$ 1000/μL, platelets $>$ 100k/μL, transfusion independence, and no peripheral blasts). We assessed the number of pts receiving HCT and their outcomes. Overall survival (OS) was estimated by Kaplan-Meier method. Log rank test was used for comparisons. **Results:** Fifty RR-AML pts received HMAs. Median age at HMA start was 58 years (range, 24-81); 54% of pts were male. NCCN risk categories at diagnosis were 14% favorable, 32% intermediate, and 54% unfavorable. FLT3-ITD mutations were present in 21% of pts, FLT3-TKD in 10%, and NPM1 in 31%. Most pts (72%) received azacitidine; 28% received decitabine. Concomitant with their HMA, 28% of pts received lenalidomide, and 16% (all FLT3-ITD) received sorafenib. Cytoreduction with hydroxyurea or cyclophosphamide was given to 20%. Among 37 evaluable pts, ORR was 57%. For the entire 50 pt cohort, ORR was 42%; median OS was 9.5 months. There was no correlation between survival and NCCN risk at diagnosis ($p = 0.98$) or at the start of HMA ($p = 0.85$). Most pts (84%) had received 1 prior line of therapy, while 16% had received 2 lines. Pts naïve to HMAs had OS superior to those with previous HMA exposure (median OS, 13.0 vs. 5.3 months; $p = 0.02$). Following HMA therapy, 14 pts (28%) underwent HCT. In this group with a median follow-up of 19.2 months, 1-year OS was 100%, and 2-year OS 78%. **Conclusions:** HMA therapy for RR-AML can yield response and survival rates comparable to other, more toxic therapies. Additionally, HMAs can be used to bridge RR-AML pts to HCT, with encouraging outcomes. These results warrant validation in a large prospective study.

7034 Poster Session (Board #94), Mon, 8:00 AM-11:30 AM

Treatment of relapsed/refractory (R/R) B-cell malignancies by chimeric antigen receptor T cells cultured from 50-100 mL peripheral blood in 7-10 days. *First Author: Lu Han, Department of Immunology, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China*

Background: Anti-CD19 chimeric antigen receptor (CAR) T cells for R/R B-cell malignancies has been remarkably effective in recent clinical trials. However, the training process is complex and long. We try to seek a method, which the preparation process is simple and short. **Methods:** We extracted 50-100 mL peripheral blood from patients (pts), and the CAR-T cells cultured 7-10 days to back to pts. All pts received a chemotherapy of cyclophosphamide and fludarabine followed by 1- 3x 10^6 CAR- T cells/kg, and were monitored for response. **Results:** CAR-T cells were capable of large numerical expansion in 7-10 days, up to about 5x10^8 magnitudes, and the culture success rate reached to 100%. We treated 29 pts with R/R B-cell malignancies (17 ALL and 12 B-cell lymphoma). Complete remissions (CRs) was achieved in 16 ALL pts (100%) 1 month after CAR-T cells infusion and CRs in 15 pts were MRD-negative, except 1 pt died in cytokine release syndrome (CRS). The CRs were 71.4% at 3 months and 56.0% at 6 months, respectively. 12 pts experienced CRS and severe CRS had 11.76% in ALL.Of 12 B-cell lymphoma, 4 achieved CR, 5 achieved PR, and 3 had progress disease (PD) when evaluated in 2 months. The CRs and overall response were 37.5% and 50.0% at 6 months, respectively. 2 pts were observed with CRS in lymphoma. **Conclusions:** Treatment of R/R B-cell malignancies with a high CRs by CAR-T cells, which cultured from 50-100 mL peripheral blood and achieved larger amount of amplification in short time. These results could be benefit for more high-risk pts. Clinical trial information: NCT02924753 NCT0310709.

7035 Poster Session (Board #95), Mon, 8:00 AM-11:30 AM

Quality of life and psychological distress in patients with acute myeloid leukemia (AML). *First Author: Julia Carp, Massachusetts General Hospital, Boston, MA*

Background: Older patients with AML face difficult treatment decisions as they can be treated either with multi-drug 'intensive' chemotherapy requiring a prolonged hospitalization, or 'non-intensive' chemotherapy. Although clinicians often perceive intensive chemotherapy as more burdensome, studies comparing older patients' quality of life (QOL) and psychological distress while receiving these treatments are lacking. **Methods:** We conducted a longitudinal study of older patients ($\geq$ 60 years) newly diagnosed with AML receiving intensive (i.e. 7+3: cytarabine/anthracycline combination) or non-intensive (i.e. hypomethylating agents) chemotherapy at two tertiary care hospitals. We assessed patient's QOL [Functional Assessment of Cancer Therapy-Leukemia], and psychological distress [Hospital Anxiety and Depression Scale [HADS]] at baseline and 2, 4, 8, 12, and 24 weeks after diagnosis. We compared the proportion of patients in each group reporting clinically significant depression or anxiety (HADS subscale cut off $\geq$ 7) and used mixed linear effects models to compare QOL and psychological distress longitudinally between groups. **Results:** We enrolled 75.2% (100/133) of eligible patients within 72 hours of initiating intensive (n = 50) or non-intensive (n = 50) chemotherapy. Baseline QOL, depression, or anxiety symptoms did not differ between the groups. At baseline, 33.33% (33/100) and 30% (30/100) of the overall cohort reported clinically significant depression and anxiety, respectively, with no differences between groups. At 4 weeks, 41.98% (34/81) of patients in the overall cohort reported clinically significant depression, with no differences between groups. In mixed linear effects models, there were no differences in QOL (β = -0.71, SE = 1.12, P = 0.527), depression (β = 0.24, SE = 0.20, P = 0.226), or anxiety (β = -0.16, SE = 0.19, P = 0.386) symptoms over all time points. **Conclusions:** Older patients with AML receiving intensive and non-intensive chemotherapy experience similar QOL and high rates of psychological distress. These findings underscore the need to develop supportive care interventions for older patients with AML, regardless of their initial treatment strategy.

7036 Poster Session (Board #96), Mon, 8:00 AM-11:30 AM

In acute myeloid leukemia patients CpG-methylation changes associate with resistance to induction chemotherapy. *First Author: Christian Dietger Niederwieser, Department of Internal Medicine IV, Hematology and Oncology, University Hospital Halle, Germany, Halle, Germany*

Background: Acute myeloid leukemia (AML) is a heterogeneous disease associated with epigenetic alterations targetable with demethylating agents. However, predictive response markers are missing. Here we analyzed the methylation changes of transcription factor (TF) binding motifs in resistant patients after treatment with or without azacytidine (Aza) followed by induction chemotherapy. **Methods:** Twenty refractory patients from the AML-AZA trial of the Study Alliance Leukemia receiving Aza followed by induction chemotherapy (n = 16/105) or chemotherapy alone (n = 4/109) were selected to perform genome wide DNA methylation analyzes using a 450K Illumina array (Illumina, San Diego, USA) before and on day 15 after therapy start. Methylation changes from day 0 to 15 corrected for %blasts were identified and motifs detected using HOMER software (Salk institute, San Diego, USA). Methylation variation was analyzed according to treatment with Aza and/or chemotherapy. **Results:** In the Aza/chemotherapy group, a total of 389 differentially methylated regions (DMRs), most of them single CpGs, were identified, 176 hyper- and 213 hypomethylated. In methylation clustering analyses, patients with a reduction/increase of blasts clustered separately together. Those with blast reduction were more likely female and *FLT3*-ITD mutated. The most highly represented *de novo* motifs (differential enrichment between 2 sets of sequences) were associated with 5 (hypermethylation) and 10 TFs (hypomethylation). The chemotherapy only group had 7181 DMRs, 5752 hyper- and 1429 hypomethylated. We found 24 and 12 TFs for the hyper- and hypomethylated loci in these patients, respectively. The *known* motifs (based on listing of motifs from previous data) in the Aza/chemotherapy group of the enriched TFs were analyzed [hyper-: 17 TFs (Jun-AP1 ($p = 1e-7$); hypomethylated: 4 TFs, GATA ($p = 1e-2$)]. For the chemotherapy group we found 90 TFs [EHF ($p = 1e-126$)] and 43 TFs [RUNX1 ($p = 1e-18$)] for hyper- and hypomethylated sites, respectively. **Conclusions:** DNA methylation of specific TF binding motifs may be associated with therapy resistance and could be used for response prediction of therapy with Aza and/or chemotherapy. Clinical trial information: NCT00915252.

7037 Poster Session (Board #97), Mon, 8:00 AM-11:30 AM

Factors influencing first-line therapy of acute myeloid leukemia (AML) patients (pts) in the Connect MDS/AML Disease Registry. *First Author: Christopher R. Cogle, University of Florida, Gainesville, FL*

Background: Historically, only about 40% of AML pts ≥ 65 y of age receive first-line therapy (1LTx) due to high adverse event and low 5-y survival rates. With the introduction of new agents to treat AML, we sought to identify current factors influencing 1LTx across clinical practice settings. **Methods:** The Connect® MDS/AML Registry (NCT01688011) is an ongoing US, prospective observational cohort study of pts with newly diagnosed AML (≥ 55 y) or MDS. Baseline demographics, median census income per capita (determined by ZIP code), disease characteristics, and genomic and treatment data were collected on AML pts enrolled from Dec 2013 to Oct 2017. Pts were categorized as receiving 1LTx (low- or high-intensity) or best supportive care (BSC) based on care provided ≤ 45 d after AML diagnosis (dx). Pts participating in clinical trials (n = 11) were excluded to focus on standard treatment practice. Uni- and multivariable logistic regression identified factors associated with 1LTx. **Results:** Data on 378 AML pts from 100 institutions (19 academic, 81 community/government) were analyzed. Median age was 70 y (range 55–92), 64% were male, and 83% were white. Most had private/Medicare insurance coverage (86%); average median income was USD 25,984. 77% of the cohort received 1LTx; 23% received BSC. 11% died ≤ 45 d after dx, of whom 90% had received 1LTx ($P < 0.05$). 77% had FISH or cytogenetic testing and 71% had molecular genetic testing, with 46% harboring ≥ 1 gene mutation. While age and comorbidities were predictors of 1LTx ($P < 0.1$) in univariable analyses, they were not independent predictors in multivariable analyses. In multivariable modeling, independent predictors of 1LTx were insurance coverage ($P < 0.01$), income ($P < 0.01$), and diagnostic genomic testing ($P < 0.05$). Probability of receiving 1LTx was lower in the Midwest ($P < 0.01$). **Conclusions:** In this preliminary analysis, 1LTx in AML pts was more strongly associated with diagnostic genomic testing and social determinants of health, such as income, insurance coverage, and geographic location. This highlights access and cost as potential barriers to AML pts receiving beneficial treatment. Clinical trial information: NCT01688011.

7038 Poster Session (Board #98), Mon, 8:00 AM-11:30 AM

Low-toxic myeloablative conditioning regimen in haploidentical hematopietic stem cell transplantation for elderly patients with acute myeloid leukemia. *First Author: Cynthia Aristei, Radiation Oncology Section, Department of Surgery and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia, Italy*

Background: Elderly candidates for hematopoietic stem cell transplantation (HSCT) cannot tolerate myeloablative conditioning regimens because of regimen-related toxicity and mortality rates. To lower them in elderly patients with acute myeloid leukemia (AML) who underwent 1-haplotype mismatched (haploidentical) HSCT, we designed a conditioning regimen with total marrow/total lymphoid irradiation (TMI/TLI) and low chemotherapy doses. The graft contained, as adoptive immunotherapy, a ratio of conventional T cells (Tcons) and T regulatory cells (Tregs) that induce a Graft versus Leukemia effect with a low incidence of Graft versus Host Disease (GvHD). **Methods:** July 2015-October 2017: 14 AML patients (median age 62 years, 6 in 1th and 7 in 2nd complete remission, 1 in partial remission) underwent haploidentical HSCT. Composite comorbidity/age scores were 1/2 in 7 patients and 3/4 in 8. TMI/TLI target volumes were skeletal bones, major lymph node chains and spleen. TMI/TLI was delivered from day -7 to day -4, in 2 daily fractions of 1.5 Gy (TMI) and 1.3 Gy (TLI) (total doses 13.5Gy and 11.7Gy respectively). Chemotherapy: tiothepa 2.5 mg/kg on days -10 and -9; fludarabine 30 mg/m^2 from days -10 to -6; cyclophosphamide 15 mg/kg on days -8 and -7. Haploidentical grafts consisted of 10x10^6/kg purified CD34+cells, 1x10^6/kg Tcons, 2 x10^6/kg freshly isolated Tregs. No post-transplant immunosuppression was given. **Results:** All patients sustained primary full-donor type engraftment and 11/14 are alive and relapse-free at a median follow-up of 18 months. Grade II-IV acute GvHD developed in 6 patients (43%) and chronic GvHD in none. Transplant-related causes of death were veno-occlusive disease (1), sepsis (1) and acute GvHD (1). Immune reconstitution was good, with peripheral blood T cells rapidly increasing. **Conclusions:** This innovative TMI/TLI-based conditioning with low dose chemotherapy and adoptive immunotherapy with Tcons and Tregs was efficacious as there have been no relapses to date. It was associated with low regimen-related toxicity and mortality. This exploratory analysis needs to be confirmed in a larger cohort of patients enrolled in a clinical trial.

7039 Poster Session (Board #99), Mon, 8:00 AM-11:30 AM

Characteristics and outcomes of acute myeloid leukemia (AML) with extramedullary disease (EMD). *First Author: Fevzi Firat Yalniz, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: EMD has been reported in 2.5-30% of AML patients (pts). The association with modern cytogenetic and molecular features and their prognostic value have not been fully explored. **Methods:** We reviewed medical records of all AML pts treated at MDACC from 8/12 to 1/2018. **Results:** Among 2388 pts, 88 (4%) had EMD; 30 were newly diagnosed. The sites involved were skin (n = 14), central nervous system (CNS) (n = 6), musculoskeletal (n = 4), nodal (n = 4) and intestinal (n = 2). 27/30 (90%) had concomitant marrow disease. Most relevant characteristics are in Table. Cytogenetics (CG) were not different between EMD and non-EMD pts (p = 0.1). Compared to non-EMD pts, pts with EMD had more *KIT* mutations (p = 0.003) but not *FLT3-ITD*, *NPM1*, *RAS* or *IDH*. The median overall survival (mOS) was shorter (6.1 vs 18.4 months; p = 0.004) in pts with EMD. On univariate analysis, the presence of any EMD (p = 0.02), skin involvement (p = 0.04) but not CNS (p = 0.9) was associated with shorter OS. There was no OS difference between *KIT*-mutated and wild-type EMD pts (p = 0.5). Of the 58 relapsed EMD (28 in 1st relapse and 30 in ≥2nd relapse), 13 had isolated EMD, 45 had concurrent marrow disease and 18 had prior SCT. The common sites involved were CNS (n = 32; 23 had isolated and 9 had ≥ 2 sites), skin (n = 11) and musculoskeletal (n = 6). Compared to non-EMD pts, there was no difference in CG and molecular characteristics. On univariate analysis, the mOS was not significantly different in pts with relapsed EMD compared to non-EMD pts (5.8 vs 5.9 months; p = 0.3), whether in first relapse (p = 0.3) or ≥2nd relapse (p = 0.5). **Conclusions:** AML with EMD carries a poor prognosis. The role of genetic and molecular markers warrants further investigation especially for treatment planning and clinical follow-up post remission.

	Non-EMD n = 2300	EMD at relapse n = 58	EMD upon AML diagnosis n = 30	p
Age	64 (17-95)	56 (20-78)	59 (23-81)	0.08
Male	1322 (57)	31 (53)	24 (80)	0.04
WBC x 10^9/L	4.1 (0.1-479)	5.8 (0.6-142)	12 (1.8-186)	< 0.001
IDH1	340 (16)	5 (12)	2 (8)	0.2
IDH2	300 (14)	5 (12)	4 (15)	0.5
RAS	254 (12)	6 (12)	6 (21)	0.1
KIT	339 (16)	7 (17)	10 (37)	0.01
FLT3ITD	542 (25)	9 (17)	5 (17)	0.3
NPM1	317 (15)	10 (20)	5 (18)	0.7
CG				0.1
Favorable	107 (5)	3 (5)	4 (14)	
Intermediate	1226 (63)	38 (69)	19 (65)	
Adverse	620 (32)	14 (26)	6 (21)	

7040 Poster Session (Board #100), Mon, 8:00 AM-11:30 AM

Outcomes by number of induction cycles with CPX-351 vs 7+3 chemotherapy in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia (sAML). *First Author: Tara L. Lin, University of Kansas Medical Center, Kansas City, KS*

Background: CPX-351, a liposomal encapsulation of cytarabine (C) and daunorubicin (D) at a synergistic ratio, is approved in the US for treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. In a phase 3 study, CPX-351 improved survival and remission rates vs 7+3 in patients (pts) aged 60-75 y with newly diagnosed high-risk/sAML. This exploratory analysis compared outcomes in 1 vs 2 induction phases. **Methods:** Pts were randomized 1:1 to receive 1-2 inductions of CPX-351 (100 units/m^2 [C 100 mg/m^2 + D 44 mg/m^2] on Days 1, 3, 5 [2nd induction: Days 1, 3]) or 7+3 (C 100 mg/m^2/d continuously for 7 d [2nd induction: 5 d] + D 60 mg/m^2 on Days 1-3 [2nd induction: Days 1-2]). Pts achieving complete remission (CR) or CR with incomplete platelet or neutrophil recovery (CRi) could receive up to 2 consolidations. **Results:** 304 pts were treated with CPX-351 (n = 153) or 7+3 (n = 151). A greater proportion of pts treated with CPX-351 achieved remission after 1 induction vs 7+3 (CR: 45% vs 28%; CR+CRi: 55% vs 34%; Table). Remission rates after 2 inductions were comparable between arms (CR: 21% vs 24%; CR+CRi: 31% vs 35%; Table). The frequency of grade 3-5 treatment-emergent adverse events (TEAEs) in pts with 1 induction was similar for CPX-351 (75/105 [71%]) vs 7+3 (74/100 [74%]). In pts with 2 inductions, fewer pts had grade 3-5 TEAEs with CPX-351 (38/48 [79%]) vs 7+3 (48/51 [94%]). Febrile neutropenia was the most common grade 3-5 TEAE with both CPX-351 and 7+3 (1 induction: 58% vs 57%; 2 inductions: 60% vs 80%). Serious TEAEs were similar with CPX-351 and 7+3 (1 induction: 33% vs 33%; 2 inductions: 29% vs 26%). **Conclusions:** Pts treated with CPX-351 were more likely to achieve remission after 1 induction vs 7+3; remission rates were similar after 2 inductions. Pts who received CPX-351 had a similar frequency of grade 3-5 TEAEs after 1 induction and fewer grade 3-5 TEAEs after 2 inductions vs 7+3 pts. Clinical trial information: NCT01696084.

	1 induction			2 inductions		
	CPX-351 (n = 105)	7+3 (n = 100)	Odds ratio (95% CI)	CPX-351 (n = 48)	7+3 (n = 51)	Odds ratio (95% CI)
CR, n (%)	47 (45)	28 (28)	2.08 (1.17, 3.73)	10 (21)	12 (24)	0.86 (0.33, 2.21)
CR+CRi, n (%)	58 (55)	34 (34)	2.40 (1.36, 4.21)	15 (31)	18 (35)	0.83 (0.36, 1.93)

7041 Poster Session (Board #101), Mon, 8:00 AM-11:30 AM

A phase 2 study of hyper-CVAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia (ALL): Updated results. *First Author: Abdul Hamid Bazarbachi, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In vitro studies showed that ofatumumab (O), a type I human antibody that targets a different CD20 epitope compared to rituximab, induces more potent antibody-dependent and complement mediated cell death. We hypothesized that substituting rituximab with ofatumumab, as part of Hyper-CVAD (HCVAD) regimen, may further improve outcomes in pts with Philadelphia chromosome (Ph) negative CD20+ ALL. **Methods:** Pts received 4 cycles (cy) of HCVAD [cy 1, 3, 5, 7 consisted of cyclophosphamide, doxorubicin, vincristine, and dexamethasone] alternating with 4 cy of methotrexate-cytarabine (MTX-ara-C, even cy 2, 4, 6, 8). Ofatumumab was infused on day 1 and 11 of cy 1 and 3; and day 1 and 8 of cy 2 and 4. For maintenance, pts received POMP, and late intensification with MTX/PEGylated asparaginase and O-HCVAD. Intrathecal MTX-Ara-C was used for CNS prophylaxis. Minimal residual disease (MRD) was assessed using multiparameter flow cytometry. **Results:** A total of 68 pts were enrolled (Table) and 65 were evaluable for response. Sixty-four pts (98%) achieved CR/CRp, 39/62 (63%) achieved negative MRD at time of CR, and 62/67 pts (93%) achieved negative MRD overall. Time to negative MRD was median 0.7 mo (range, 0.4-7.8). Pts received one to eight (median: 8) cy of intensive phase chemotherapy. The most common non-hematologic grade 3/4 toxicitiy was infection; occurred in 37 (56%) and 55 (81%) pts during induction and consolidation, respectively. At median 27 mo of follow-up (range 4-73), 51 pts (75%) are alive; 17 pts (25%) are receiving maintenance, 15 pts (22%) have relapsed, 14 pts (21%) have completed maintenance, and 12 pts (18%) have received ASCT in CR1. The 2-year CRD and OS were 79% and 81%, respectively. The 2-yr OS was 80% in both pts with $<$20% and $\geq$20% CD20 expression. **Conclusions:** O-HCAVD is highly effective and safe combination regimen in pts with CD20+ Ph-negative ALL. Clinical trial information: NCT01363128.

Clinical Characteristics (n=68)	N (%)/ Median [Range]
Age, years	41 [18-71]
ECOG PS > 1	7 (11)
CNS disease	2 (3)
CRFL2+	8/34 (24)
TP53+	10/42 (24)
CD20 expression	
> 20 %	42 (62)
10-20 %	7 (10)
1-10 %	19 (28)
Cytogenetics	
Diploid	24 (35)
Low hypodiploidy/near-triploidy	6 (9)
High hyperdiploidy	5 (7)
Complex	3 (5)
Misc.	30 (44)

7042 Poster Session (Board #102), Mon, 8:00 AM-11:30 AM

Mutant IDH (mIDH) inhibitors, ivosidenib or enasidenib, with azacitidine (AZA) in patients with acute myeloid leukemia (AML). *First Author: Courtney Denton Dinardo, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ivosidenib (IVO; AG-120) and enasidenib (ENA; AG-221) are oral inhibitors of mIDH1 and mIDH2 proteins. *In vitro*, mIDH inhibitor + AZA combinations enhance cell differentiation and apoptosis. We report results of an ongoing phase 1b/2 study of mIDH inhibitors + AZA in patients (pts) with newly diagnosed (ND) AML (NCT02677922). **Methods:** Adult pts with m*IDH* ND-AML ineligible for intensive treatment (Tx) receive continuous IVO (mIDH1) 500 mg or ENA (mIDH2) 100 or 200 mg QD, plus SC AZA 75 mg/m^2 x 7d, in repeated 28d cycles. Response is defined by IWG 2003 AML criteria. **Results:** At data cutoff (Sep 1, 2017) 17 pts had received IVO 500 mg (n = 11) or ENA 100 mg (3) or 200 mg (3) + AZA in the phase 1b portion of the study; 11 were ongoing. *IVO:* Median age was 76 yrs. Median number of Tx cycles was 3 (range 1-13).Three pts discontinued Tx, 2 due to progressive disease (PD).AEs in $\geq$4 pts (any grade) were nausea (n = 8), constipation (6), fatigue (5) and diarrhea (4). Grade 3-4 hematological AEs (Table) occurred at similar frequency to what has been reported for AZA alone. Serious AEs in $>$ 1 pt were pneumonia, febrile neutropenia (n = 2 each). Eight of 11 pts responded, including 4 complete remissions (CRs). *ENA:* Median age was 68 yrs. Median number of Tx cycles was 9 (1-13). Three pts discontinued Tx, 2 due to PD. Most common AEs (any grade) were nausea and hyperbilirubinemia (n = 4 each). Serious AEs in $>$ 1 pt were pyrexia, bilirubin increase, pneumonia (n = 2 each). Four of 6 pts responded, including 2 CRs. **Conclusions:** mIDH inhibitor + AZA regimens were generally well tolerated in pts with ND-AML. Most AEs were grade 1-2 GI events and ENA-related indirect bilirubin elevations due to off-target UGT1A1 inhibition. Response rates are encouraging. Phase 1b enrollment completed in late 2017; updated data for all 23 IVO and 6 ENA pts will be presented, as well as longitudinal changes in m*IDH* variant allele frequencies. Enrollment continues in the phase 2 portion of this study (ENA + AZA) and the phase 3 AGILE study of IVO + AZA (NCT03173248). Clinical trial information: NCT02677922.

Grade 3-4 hematological AEs.

	IVO 500 mg + AZA (n = 11)	ENA 100 mg + AZA (n = 3)	ENA 200 mg + AZA (n = 3)
	n		
Thrombocytopenia	1	0	1
Anemia	2	0	1
Febrile neutropenia	2	0	1
Neutropenia	1	0	2
Lymphocyte decrease	0	0	1
WBC decrease	0	0	1

7043 Poster Session (Board #103), Mon, 8:00 AM-11:30 AM

A randomized open label exploratory controlled trial of CLT-008 myeloid progenitor cells (MPC) to decrease infections during induction for AML. *First Author: Camille N. Abboud, Siteman Cancer Center, Washington University of St. Louis, St. Louis, MO*

Background: Induction chemotherapy for AML results in prolonged neutropenia and a high risk of infection. CLT-008 is a human off-the-shelf allogeneic MPC preparation manufactured by ex vivo culture expansion of CD34+ cells. Following infusion MPCs are expected to home to bone marrow (BM) and produce neutrophils. **Methods:** 163 subjects with de novo AML (age $\geq$55) and receiving HIDAC or 7+3 induction were randomized on Day 0 (first day of induction) to receive either CLT-008 (7.5x10^6 cells/Kg) on Day 9 + GCSF qd starting on Day 14 (treatment) or GCSF alone starting on Day 14 (control) qd until ANC recovery to 500/μL. Most endpoints were assessed from Day 9 to Day 28 and included days in a Febrile Episode (primary endpoint), microbiologically defined bacterial or fungal infections (MDI, adjudicated by a blinded independent committee), and days in hospital (to Day 42). The safety population (S-subjects) included those who received CLT-008 or GCSF. The evaluable population (E-subjects) included those who received CLT-008 or GCSF alone, were in study $\geq$ 28 days and did not receive additional chemotherapy before Day 28. **Results:** Baseline characteristics were balanced. The mean number of days in febrile episodes was 6.7 in treated and 7.1 in controls (NS) between the groups. In S-subjects, MDI was diagnosed in 14/70 treated vs 21/71 controls, a decrease of 32%. MDI with bacteremia was diagnosed in 7/70 treated vs 12/71 control subjects. MDI without bacteremia was diagnosed in 8/70 vs 11/71. In E-subjects, mean hospital stay was 3 days less in treated vs control. Remission rates and days to ANC recovery were similar in the two groups. All subjects assessed (n = 18) for chimerism had CLT-008 cells detected in peripheral blood on the day of infusion and 72% had CLT-008 detected in one or more of peripheral blood, BM or gingiva prior to ANC recovery. Infectious deaths occurred in no CLT-008 and 2 control subjects. GVHD was not observed. Antimicrobial use will be presented. **Conclusions:** Subjects receiving CLT-008 showed a decreased incidence of infections and days in hospital suggesting that myeloid progenitors may provide a new option to reduce infections in AML patients undergoing induction therapy. Clinical trial information: NCT02282215.

7044 Poster Session (Board #104), Mon, 8:00 AM-11:30 AM

Long-term survival of adults with B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) after treatment with blinatumomab and subsequent allogeneic hematopoietic stem cell transplantation (HSCT). *First Author: Max Topp, Medizinische Klinik und Poliklinik II, Würzburg, Bayern, Germany*

Background: In BCP-ALL, blinatumomab has demonstrated efficacy in two phase 2 trials: MT 103 -203 (Gökbuget et al, Blood 2017) in minimal residual disease (MRD) and MT 102 – 211 in relapsed/refractory (R/R) disease (Topp et al Lancet Oncology 2104). We describe the long-term outcomes after blinatumomab followed by HSCT. **Methods:** Survival after blinatumomab and HSCT in continuous complete remission (CCR) was evaluated. In the MRD trial, 116 patients between Nov 2010 and Feb 2014 were treated with blinatumomab; in the R/R trial, 189 patients between Jan 2012 and Oct 2013 were treated. Follow up in both trials continued through 2017. **Results:** Most patients with HSCT in CCR in the MRD trial were $>$35 yrs of age whereas those in the R/R trial were younger (Table). After follow up of at least 3 yrs in the MRD trial of patients $\leq$35 yrs, 16/26 (62%) were alive with HSCT vs 2/9 (22%) for non-HSCT; in patients $>$35 yrs, 19/48 (40%) and 13/27 (48%) were alive with HSCT and for non-HSCT, respectively. Median overall survival (OS) from HSCT was not reached in patients $\leq$35 yrs in either trial (Table). **Conclusions:** These results suggest that in transplant-eligible patients in CCR, HSCT following blinatumomab is a potential option. Clinical trial information: NCT01466179, NCT01207388.

Patients with on-study HSCT in CCR.

	MT 103 -203 N=74[b] n (%)	MT 103 -211 N=34 n (%)
Characteristics		
Age, n (%), yrs		
≤35	26 (35)	19 (56)
>35 to 55	29 (39)	9 (26)
>55	19 (26)	6 (18)
Median (range)	43 (18, 67)	31 (18, 65)
Donor		
Related, n (%)	19 (26)[a]	8 (23)
Unrelated, n (%)	53 (72)	23 (68)
Matched, n (%)	20 (27)	9 (26)
Unmatched	23 (31)	10 (29)
Unknown, n (%)	6 (8)	3 (9)
Cord	4 (5)	1 (3)
Unknown, n (%)	2 (3)	3 (9)
Conditioning regimen		
Myeloablative	32 (43)	15 (44)
Reduced intensity/nonmyeloablative	35 (47)	12 (35)
Unknown	7 (20)	7 (21)
100-day mortality after HST, n (%)[c]	5 (7)	4 (12)
Outcomes		
Median OS from HSCT, months		
Age ≤35 yrs	NE	NE
Age >35 yrs	25.7	15.9
Median RFS from HSCT, months		
Age ≤35 yrs	NE	16.4
Age >35 yrs	15.5	15.9

NE, not estimable. [a] 1 haploidentical. [b] 74 patients received on-study HSCT in CR; Ph+ and patients not in CR at treatment start excluded. [c] No VOD-related deaths. Study Sponsored by Amgen.

7045 Poster Session (Board #105), Mon, 8:00 AM-11:30 AM

Feasibility of HSCT vs consolidation therapy for AML patients aged 60-75 in CR1: A randomized phase III, multicentre EBMT study. *First Author: Dietger Niederwieser, Universitatsklinikum Leipzig AoR, Abt. Hamatologie und internistische Onkologie, Leipzig, Germany*

Background: AML has a particularly dismal prognosis in the elderly population. The OSHO, HOVON, SAKK and the French AML study groups performed a randomized phase III study comparing Hematopoietic Stem Cell Transplantation (HSCT) to conventional chemotherapy in these patients. **Methods:** Patients aged 60 – 75 years with AML CR1 (except FAB M3) were registered after induction(s) according to study group protocols. A donor search was initiated during consolidation. Patients with a related or matched unrelated donor were randomized within 150 days of diagnosis to receive either HSCT or non-HSCT in a 2:1 ratio. Patients in the HSCT arm were treated with Fludarabine/200 cGy total body irradiation followed by cyclosporine/mycophenolate mofetil. Patients in the non-HSCT arm continued therapy according to the study group protocols. Leukemia free survival was chosen as primary endpoint. Patients without a donor were included in the observation arm. **Results:** A total of 245 patients from 23 centers in five countries were registered and started consolidation. Sixty six patients (26.9%) exited the study before randomization because of relapse/no recovery (28), toxicities (10), consent withdrawal (10), patient choice (7), death (6) or miscellaneous reasons (5). Donors were identified for 135 (75.9%) of the 179 patients, 22.9% related and 77.0% unrelated. Ten patients with donors were allocated to the observation arm because of consent withdrawal, ineligibility, protocol violation or unknown reasons. Randomization proceeded for 125 (51,0%) patients. Of the 83 in the HSCT arm, 16 were not transplanted. Of the 42 patients in the non-HSCT arm, 6 did not receive the scheduled second consolidation and information is pending in 7. Endpoint analysis is due in 2020. **Conclusions:** The feasibility of HSCT for elderly patients with AML CR1 within 150 days from consolidation was demonstrated in a randomized European study. Donor identification and randomization was achieved for a large proportion of patients (75,9% and 51,0%). Despite a short treatment interval of $\leq$12 weeks from consolidation to HSCT/non-HSCT, relapse (n = 39) and toxicities (n = 14) were the most frequent cause of end of study. Clinical trial information: EudraCT Number 2007-003514-34.

7046 Poster Session (Board #106), Mon, 8:00 AM-11:30 AM

Impact of variant allele frequency of mutant *PTPN11* in AML: Single institution experience of 122 patients. *First Author: Mansour Alfayez, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Mutations in PTPN11, encoding tyrosine phosphatase SHP2, are present in 4-6% of AML. Largest report includes 27 patients (pts). **Methods:** Analysis included AML patients (pts) treated at MD Anderson Cancer Center between 2012 and 2017, positive for PTPN11 mutations by next generation sequencing. We evaluated baseline parameters, co-ocurring mutations,allelic burden and clinical outcome. **Results:** We identified 122 pts [62 (51%) male; median age 64.5 yrs (19-86)], among whom 64 (52.5%) treatment naïve and 58 (47.5%) salvage. In treatment naïve group, 26.6% had favorable risk (per ELN2017) [median overall survival (mOS) = 617 days (range 8-1151)], 23.4% intermediate [mOS = 336 days (Range 1-1403)] and 50% poor risk [mOS = 226 days (Range 3-540)] (P = 0.0086). Chr 3 abnormalities were present in 9 pts (14.1%), 14 pts (18.8%) had complex karyotype and 33 pts (39%) were diploid. Most common co-mutations were TET2 (51.9%), DNMT3A (33.3%), NPM1 (31.3%), and FLT3-ITD (26.6%), [Table]. Variant allelic frequency (VAF) for mutant PTPN11 with a cutoff of 0.4 further stratified poor risk AML into very poor (VAF $\geq$0.4; mOS = 194 days (Range 18-305)) and poor (VAF $<$ 0.4; mOS = 314 days (Range 3-645)), [P = 0.01; HR 6.16, CI 95% 1.5-24.6). Similarly among patients with non-diploid karyotype, the same VAF cut off stratified patient survival (p = 0.007, HR 3.27, CI 95% 1.2-8.7). In the salvage group also, VAF stratified pts for survival; [$\geq$0.4 vs $<$ 0.4 (P = 0.01, HR 5.14, CI 95% 1.48-17.8)]. **Conclusions:** We report the largest survey of PTPN11 mutations among adult leukemia patients. Reminiscent of experience with FLT3-ITD mutation, VAF appears to have impact on patient outcomes. Targeted therapies have the potential of improving outcomes.

Molecular and cytogenetics characteristics.

Characteristics	Treatment Naive (N = 64) (%)	Salvage (N = 57) (%)
TET2	28/54 (51.8)	27/46 (58.6)
RAS	14/63 (22.2)	20/56 (35.7)
KIT	8/63 (12.6)	12/55 (21.8)
FLT3-ITD	17/57 (26.5)	8/57 (14.0)
TP53	7/63 (11.1)	10/55 (18.2)
NPM1	20/64 (31.3)	7/55 (12.7)
Cytogenetics	33 (51.6)	11 (19)
Diploid		
Complex	12 (18.8)	22 (38)
Chr 3 abnormalities	9 (14.1)	15 (25.8)
-5/5q- and/or -7/7q-	13 (20.3)	21(36)

7047 Poster Session (Board #107), Mon, 8:00 AM-11:30 AM

Molecular testing during AML treatment for early prediction of clinical response. *First Author: Hong Yuen Wong, Laboratory of Myeloid Malignancies, Hematology Branch, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD*

Background: Early prediction of response in acute myeloid leukemia (AML) patients undergoing cytotoxic chemotherapy may have clinical utility. Currently, measurable residual disease (MRD) testing *after* initial chemotherapy treatment can predict relapse and survival in AML. However, it has not been established if repeat molecular or genetic testing *during* chemotherapy can offer information regarding the chemotherapy sensitivity of the leukemic clone. **Methods:** Blood from 45 adult AML patients at day 1 and 4 of induction (n = 35) or salvage (n = 10) cytotoxic chemotherapy was collected for next generation sequencing ($>$ 500x) of 49 gene regions recurrently mutated in MDS/AML (Raindance Thunderbolts™ Myeloid Panel) and quantitative real-time PCR (qPCR) assessment (*WT1*) on IRB approved protocols. **Results:** The average age was 58 (23-78); 42% achieved a complete response. A median of 4 non-synonymous coding mutations (range 0-7) were detected in 45 patients by NGS in blood from day 1 (median VAF: 28%). Only 1 patient had no such mutations detectable. White blood cell (WBC) count decreased 75% on average from 10K/ul (range 0.3-60) on day 1 to 2.3K/ul (range 0.2-26) by day 4 of chemotherapy. All mutations found on day 1 remained detectable in blood on day 4 of therapy. Remarkably, the ratio of mutated to wild-type sequence was often maintained despite three days of intensive therapy, a phenomenon not limited to DNMT3A, TET2 and ASXL1. This surprising finding did not hold for *NPM1* (present only in responders, n = 5, mean decrease -44%, range -2% to -98%) or *TP53* (present only in non-responders, n = 9, mean increase 34%, range -38% to 94%). *WT1* was overexpressed on day 1 in 31 of 34 patients tested. In evaluable patients 7 of 12 responders had a 4-fold reduction in *WT1*/*Abl1* expression by day 4 compared with 7 of 19 non-responders. **Conclusions:** Molecular testing on day 4 of AML chemotherapy is not predictive of clinical response. The stability of NGS detectable mutations in blood suggests that cytotoxic therapy may have a limited therapeutic specificity for clones containing these mutations. *WT1* qPCR was uninformative for very early MRD assessment. Further validation is required to confirm the utility of *NPM1* and *TP53* monitoring in blood during cytotoxic therapy. Clinical trial information: NCT02527447.

7048 Poster Session (Board #108), Mon, 8:00 AM-11:30 AM

Phase 1 study of selinexor plus mitoxantrone, etoposide, and cytarabine in acute myeloid leukemia. *First Author: Bhavana Bhatnagar, The Ohio State Univ Comp Cancer Ctr, Columbus, OH*

Background: Patients (pts) with relapsed or refractory (R/R) acute myeloid leukemia (AML) have limited treatment options. Selinexor (SEL), an oral inhibitor of the nuclear transport protein XPO1, has shown promising single-agent activity in clinical trials of AML and preclinical synergy with topoisomerase (topo) II inhibitors. Hence, we tested the combination of SEL plus chemotherapy with topo II inhibitor in pts with R/R AML. **Methods:** This phase 1, open-label 3+3, dose escalation study tested SEL plus mitoxantrone, etoposide, and cytarabine (MEC) in pts aged $<$ 60 years with R/R AML (NCT02299518). The primary objectives were to evaluate the safety and preliminary efficacy of this combination. Pts received MEC IV on days 1-6, and up to 6 doses of SEL, across 3 dose levels ranging from 30-55 mg/m^2 on days 1, 3, 8, 10, 15, and 17. **Results:** We enrolled 23 pts (median age 47 years); 11 were treated on the dose escalation portion. Due to dose limiting hyponatremia in 2 pts on dose level 2 (SEL 40 mg/m^2), the maximum tolerated dose was 30 mg/m^2. However, based on the totality of safety data from other SEL trials in R/R AML, we established the RP2D of SEL in pts with AML to be 60 mg. We treated an additional 12 pts with 60 mg of SEL in combination with MEC. Common grade $\geq$3 toxicities for 21 treated pts for whom all analyses are complete (2 remain on therapy) are shown in Table 1. Of 21 pts, the overall response rate was 39% with 4 pts (19%) achieving complete remission (CR), 2 (10%) with CR with incomplete count recovery, and 2 (10%) with a morphologic leukemia-free state. Five responders proceeded to allogeneic stem cell transplantation. **Conclusions:** SEL plus MEC is a feasible treatment for pts with R/R AML. Toxicities of the combination are similar to cytotoxic chemotherapy alone. Clinical trial information: NCT02299518.

Grade $\geq$3 treatment-related adverse events occurring in $\geq$10% of pts (n = 21).

Adverse Event Term	no. (%)
Anemia	16 (76.2)
Thrombocytopenia	14 (66.7)
Leukopenia	11 (52.4)
Febrile neutropenia	9 (42.9)
Lymphopenia	7 (33.3)
Neutropenia	7 (33.3)
Catheter related infection	6 (28.6)
Diarrhea	5 (23.8)
Hyponatremia	4 (19.0)
Sepsis	4 (19.0)
Fatigue	3 (14.3)
Hyperglycemia	3 (14.3)
Hypotension	3 (14.3)
Agitation	2 (9.5)
Hypophosphatemia	2 (9.5)
Nausea	2 (9.5)
Respiratory failure	2 (9.5)

7049 Poster Session (Board #109), Mon, 8:00 AM-11:30 AM

Pharmacodynamic characterization of eryaspase (L-asparaginase encapsulated in red blood cells) in combination with chemotherapy in a phase 2/3 trial in patients with relapsed acute lymphoblastic leukemia (NCT01518517). *First Author: Iman El-Hariry, Erytech Pharma, Cambridge, MA*

Background: L-asparaginase (ASNase) is a key drug in the treatment of ALL. ASNase therapy aims to lower serum asparagine (ASN) levels, but no critical minimum value for efficacy has yet been established. ASN levels are difficult to measure accurately due to *ex vivo* depletion during the time required to harvest plasma from blood samples and to quench the enzyme, even if samples are immediately processed and stored on ice. Eryaspase is an investigational product under development. Following infusion of eryaspase, ASN is actively transported into RBCs, where it is hydrolyzed by the encapsulated ASNase. **Methods:** This randomized Phase 2/3 study enrolled pts with relapsed ALL. The co-primary endpoints were the mean duration of ASNase activity $>$ 100 U/L and incidence of allergic reactions during the induction phase. Secondary endpoints were safety, complete remission (CR), pharmacokinetics (PK), and pharmacodynamics (PD). Pts (n = 80, age: 1-55 years) were randomized to eryaspase or native ASNase. **Results:** The mean duration of ASNase activity $>$ 100 U/L measured in whole blood was significantly higher with eryaspase (18.9 $\pm$ 5.3 days) compared with native ASNase (8.5 $\pm$ 6.6 days). In both treatment arms, ASN depletion $\leq$2 μM was maintained for ~7 days in 75% of pts. The mean duration of ASN depletion $\leq$2 μM was 6.0 $\pm$ 5.0 and 11.6 $\pm$ 7.3 days with eryaspase and native ASNase, respectively. Exploratory receiver operating characteristic (ROC) analysis suggested that an optimal threshold of $\leq$ 7.55 μM ASN on Day 6 correlated with CR with a positive predictive value of 0.88. **Conclusions:** The assumed requirement for prolonged ASN depletion in patients receiving ASNase therapy is likely to be an overestimation caused by *ex-vivo* depletion that is observed with free ASNase. Measurement of ASN depletion in pts treated with eryaspase are less prone to such error. Accordingly, the efficacy of encapsulated ASNase cannot be accurately compared with that of free ASNase based on ASN depletion. ASN depletion $\leq$2 μM may not be needed with eryaspase, and a level $\leq$7.55 μM correlated with CR. Clinical trial information: NCT01518517.

7050 Poster Session (Board #110), Mon, 8:00 AM-11:30 AM

Relapse prevention with second generation tyrosine kinase inhibitors for Ph +ve acute leukemia after allogenic stem cell transplantation. *First Author: Faiz K. Anwer, University of Arizona, Tuscon, AZ*

Background: Relapse after allogeneic hematopoietic stem cell transplantation (AlloHSCT) for Ph+ve acute lymphoblastic leukemia (Ph+ ALL) remains the major cause of treatment failure. Use of tyrosine kinase inhibitors (TKIs) for post-transplant maintenance is not well defined. **Methods:** Database search using PubMed, Cochrane library, and Embase was performed on 08/10/2017 yielding 861 articles, 17 articles met inclusion criteria (n = 502). **Results:** Patients in seven prospective trials (n = 224) received imatinib post-transplant (PT) either prophylactically or pre-emptively for median duration of 3-12 months, at dose of 200–600 mg. Imatinib yielded a better overall survival (OS) (1.7 to 5-year OS was 30-86.7%), disease free survival (DFS) (30–81.5%) and low relapse rate (13 – 31.5%). Chen et al, in 2012 reported 52.4% higher OS (p = 0.0) with imatinib. Five retrospective trial patients (n = 221) received TKI PT either prophylactically or pre-emptively for median duration of 1-11 months, at dose of 300–800mg. TKI prophylactically led to better OS (1-year OS-100%, 2-year OS-66.7%), DFS (20-100%) and with the 3-year relapse rate of 63.6%. Three prospective trial patients (n = 28) received nilotinib PT prophylactically for a median duration of 0-20 month, at dose of 200-300 mg. Nilotinib prophylactically had a better OS (2-year OS was 69%, and mOS was 35.5 months) and DFS (56% in one study and median 34.1 months in another). Two retrospective trial patients (n = 29) received post-AlloHSCT dasatinib for median duration of 11-15 months, at dose of 50-100 mg. Patients who received dasatinib had a better OS (3-year 87% in one study, and median OS was 22 months in another study) and DFS (88%). **Conclusions:** Post-transplant prophylactic or maintenance TKIs in Ph+ ALL showed increase in OS, DFS and decrease in relapse rates. Limited data appears to favor a prophylactic rather than a pre-emptive strategy. In retrospective trials, use of dasatinib reported increase 3-year OS-87% whereas imatinib 3-year OS was 40% is post-transplant patients. The second generation TKIs have better outcomes in comparison to imatinib although further studies are needed to assess this fact definitively.

7051 Poster Session (Board #111), Mon, 8:00 AM-11:30 AM

Comparison of somatic mutations profiles from next-generation sequencing (NGS) of cell-free DNA (cfDNA) versus bone marrow (BM) in acute myeloid leukemia (AML). *First Author: Rita Elias Assi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NGS of cfDNA is a novel non-invasive strategy to define mutational profiles in many solid tumors, and can be used for real-time molecular monitoring of treatment and detection of resistance or disease recurrence. We examined the feasibility of cfDNA NGS in AML and compared mutation profiles to a BM NGS panel at multiple time points during therapy. **Methods:** Plasma cfDNA was collected and analyzed using a capture-based NGS assay (Qia275) targeting 275 genes. BM NGS was performed on DNA extracted from the sample in CLIA-certified molecular diagnostics laboratory for the detection of somatic mutations in the coding sequence of 28 or 81 genes. NGS profiles from cfDNA and BM were analyzed with an established bioinformatics pipeline to identify somatic variants. **Results:** 24 patients (pts) with median age of 42 years (24-61) were prospectively enrolled and 13 had serial cfDNA and BM samples for testing. NGS analysis of cfDNA detected a median of 3 deleterious somatic mutations (range 1-22) (allele frequency (AF) $>$ 0.1%, passing bioinformatic quality filters) with AF ranging from 1.5-96.5%. When matched to common mutations in both NGS panels, cfDNA harbored a median of 3 new mutations (1-8) in 83% (20/24) of pts, not detected in BM NGS panel. BM and cfDNA NGS detected identical mutations in 1/24 (4%) pt while BM NGS detected additional mutations in 3/24 (13%) pts where NGS cfDNA failed to do. Of the 20 pts on whom complete remission samples are available, 17 (85%) had a median of 3 alterations (2-8) by cfDNA including actionable mutations not detected by BM NGS. **Conclusions:** NGS of cfDNA is feasible in AML and successfully detects prior and novel mutations when BM sequencing shows absence of these mutations in a matched panel of genes. The discrepancies between BM and cfDNA mutation profiles seen in many pts may reflect leukemic evolution or intra-leukemic heterogeneity. Plasma cfDNA for genomic profiling is a promising and non-invasive strategy and further investigation of its utility is warranted in AML.

7052 Poster Session (Board #112), Mon, 8:00 AM-11:30 AM

Comparison of blast clearance in peripheral blood and day 14 bone marrow biopsy for evaluation of disease response after 7+3 induction in acute myeloid leukemia (AML). *First Author: Fahrettin Covut, Department of Medicine, Cleveland Clinic, Cleveland, OH*

Background: Peripheral blast clearance (PBC) and blast clearance in day 14 bone marrow biopsy (D14BM) are commonly used for early assessment of disease response after 7+3 induction in patients with AML. We compared both techniques in predicting disease response. **Methods:** We identified newly diagnosed AML patients (pts) between 2003 and 2016 at our institution. All pts underwent D14BM after median of 13 days (range: 12 - 17) from initiation of 7+3 induction and recovery bone marrow biopsy between days 28 and 42. PBC was defined as percentage of absolute count reduction after induction. Eventual outcome of induction was defined per Cheson criteria. Risk groups were determined by combining cytogenetic and molecular data based on the NCCN guidelines. Logistic regression analysis was performed to identify independent factors associated with complete remission (CR) at recovery biopsy. **Results:** Among 183 AML pts, 48 (26.2%) underwent early re-induction after D14BM, whereas 135 (73.8%) pts were observed without re-induction. Among observed pts, 105 (77.8%) pts had CR at recovery biopsy. On univariate logistic regression analysis, good/intermediate-risk versus poor-risk by cytogenetic and molecular data (OR 2.98, 95% CI 1.07 – 9.17, p = 0.042), per 1 g/dL increase in hemoglobin at diagnosis (OR 1.34, 95% CI 1.06 – 1.73, p = 0.015), day-3 PBC $>$ 85% (OR 9.21, 95% CI 2.74 - 37.41, p = 0.0006), $<$ 5% blast in D14BM (OR 5.10, 95% CI 1.93 - 13.63, p = 0.0009) and $\leq$10% cellularity in D14BM (OR 5.55, 95% CI 2.16 - 14.64, p = 0.0004) were more likely to achieve CR at recovery biopsy. On multivariate logistic regression analysis, only day-3 PBC $>$ 85% (OR 32.81, 95% CI 4.09 – 669.3, p = 0.004) was significantly associated with achieving CR at recovery biopsy. Day-3 PBC $>$ 85% was more sensitive (75% vs 44%) but less specific (75.4% vs 87.6%) compared to D14BM blast $<$ 5% in predicting CR at recovery biopsy. **Conclusions:** In our cohort, day-3 PBC $>$ 85% was only independent factor associated with CR. Our study suggests that PBC might be useful early non-invasive tool to evaluate disease response compared to blast clearance in D14BM, in patients with circulating blasts before initiation of 7+3 induction.

7053 Poster Session (Board #113), Mon, 8:00 AM-11:30 AM

Validation of the ELN-2017 risk classification in younger adult patients (pts) with AML. *First Author: Prajwal Boddu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The revised 2017 European Leukemia Net (ELN) classification of AML divides patients into 3 prognostic risk categories, with additional factors such as *FLT3*-ITD allele ratio (AR) considered for risk stratification. We evaluated the prognostic utility of ELN-2017 in comparison with ELN-2010 in younger pts with AML treated in our institution. **Methods:** Pts (< 60 years) who received idarubicin plus high dose cytarabine (IA) - based induction chemotherapy for newly diagnosed AML were reviewed. Cox regression analyses were fitted with baseline prognostic factors, including cytogenetic and molecular mutation status, with receipt of allogeneic transplant (SCT) as a time-dependent covariate. **Results:** According to ELN-2017 criteria, the number of pts in the favorable (fav), intermediate (int), and adverse (adv) categories were 198 (28%), 335 (47%), and 185 (26%), respectively. Overall survival (OS) at 5 years (yrs) in the fav, int, and adv groups was 57%, 37%, and 19%, respectively. In comparison, the 5-yr OS probabilities in the fav (n = 192), int-1 (n = 76), int-2 (n = 276), and adv (n = 185) ELN-2010 categories were 59%, 32%, 39%, and 15%, respectively. Although ELN-2010 historically distinguishes prognosis into int-1 and int-2 categories in younger pts, this difference was nullified in our cohort probably due to the use of high dose cytarabine (int-2 vs. int-1: HR 0.61 [0.37 - 1.01]; p = 0.06). By cox-regression, SCT was associated with decreased risk of mortality only in int and adv AML, but not in the fav subgroup. To evaluate whether *FLT3*-ITD AR impacted prognosis, we compared the two groups (*FLT3*-ITD^{low} and *FLT3*-ITD^{high} based on AR cut-off of 0.5) and found no significant differences in survival between these groups, in patients with *NPM1* mutated AML (p = 0.40) or in those with wild type *NPM1* treated with either with IA alone [n = 55] (p = 0.61) or in combination with FLT3 inhibitors [n = 16] (p = 0.73). **Conclusions:** The ELN-2017 more accurately distinguishes prognosis by replacing the ELN-2010 int-1 and int-2 groups with a single int category. Prognostic significance of the *FLT3*-ITD AR needs further evaluation. SCT should be considered in the post remission setting in IR and adv risk AML pts.

7054 Poster Session (Board #114), Mon, 8:00 AM-11:30 AM

Outcomes of patients with nucleoplasmin 1 (NPM1) mutated acute myeloid leukemia (AML) treated with hypomethylating agents (HMAs). *First Author: Mahesh Swaminathan, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Presence of NPM1 mutations (MU) is associated with improved outcomes in younger pts with AML treated with high doses of cytarabine. The outcomes of pts with NPM1 mutated AML treated with HMAs is unknown. It is important as HMAs are becoming standard of care in older pts with AML not candidates for intensive therapy. We investigated the outcomes of such group of pts treated with either azacitidine or decitabine or combinations at a single institution. **Methods:** We retrospectively analyzed outcomes of NPM1 mutated AML pts referred to a single institution from 2010 to 2017 treated with HMAs as monotherapy or in combination. **Results:** We identified 63 pts with median age of 68 (26-91); 34 pts (54%) were female. The median number of prior therapies was 0 (0-3). A total of 58/63 pts (92%) had available cytogenetics (CG). Thirty-seven pts (64%) had favorable, 20 (34%) had intermediate and 1 had adverse (2%) CG. All pts had NPM1 MU and 26 pts (41%) also had DNMT3A MU and 21 (33%) had FLT3-ITD. The overall response rate (ORR) was 75% (n = 47) [CR-30 (48%), CRp-5 (8%) and HIP-12 (19%)]; 73% in pts who received HMAs as monotherapy (n = 22) and 76% in combination therapy (n = 41). The median overall survival (OS) was 11.63 months and the relapse-free survival was 18.27 months. The ORR for pts with FLT-3 wild-type and FLT-3-ITD MU was 81% and 62% respectively, with median OS of 19.39 and 10.07 months, respectively. Thirty pts (48%) had MRD assessment available; 19 (63%) were negative and 11 (37%) were positive. Nine pts (14%) had NPM1 MU analysis at the time of response; 4 (44%) had no MU. Eleven pts (17%) had bone marrow transplant, of that 8 (73%) are alive; 3 (27%) died in CR, CRp and progressive disease due to sepsis, unknown cause and multi-organ failure (MOF) respectively. Two pts (3%) had early death due to MOF; 4 (6%) died, 2 from MOF and 2 from an unknown cause. **Conclusions:** This analysis indicates that although response rates are high in NPM1 mutated AML when treated with HMAs, survival maybe shorter than that reported with ara-C based therapies. Ara-C based therapy should therefore be used when possible but HMAs are an option. FLT-3 MU status is important for prognosis and may improve when adding FLT-3 inhibitor.

7055 Poster Session (Board #115), Mon, 8:00 AM-11:30 AM

Timed sequential therapy with high-dose cytarabine and mitoxantrone as an effective and safe induction regimen for acute myeloid leukemia. *First Author: Melissa L. Larson, Rush University Medical Center, Chicago, IL*

Background: Traditionally, patients eligible for induction chemotherapy for AML are treated with the "7+3" regimen, which includes standard doses of infusional cytarabine and an anthracycline, with historical CR rates of 50-60%. We conducted a retrospective analysis of an alternate induction regimen. Based on timed sequential therapy, it consists of a 2-day treatment with high dose cytarabine, which improves remission rates when used in induction, and dose intensified anthracycline therapy, which improves outcomes in younger patients. We present the analysis of the regimen and the response rates of patients based on risk stratification, history of prior MDS and age. **Methods:** 382 patients were treated from 1998-2015. The treatment consisted of 2 doses of cytarabine 2gm/m^2 (1.5 gm/m^2 for patients aged greater than 70 years) IVPB over 3 hours given 12 hours apart followed by one dose of mitoxantrone 30 mg/m^2 IVPB over 1 hour on days 1 and 5. Data regarding cytogenetics and MDS history was collected for each patient. IWG remission criteria were used to determine remission status. **Results:** Median age of the patients was 58 years (range 17-85). 205 were male; 177 were female. 25 patients had favorable risk; 200 had intermediate risk; 157 had unfavorable risk. A history of MDS was noted in 83 patients. 212 patients were under the age of 60 years; 170 were aged 60 years or older. The overall CR rate (CRR: CR+CRi+CRp) for all patients was 68.5%. The complete remission rates based on risk karyotypes were favorable 96%, intermediate 77%, and unfavorable 53%. Patients with no prior MDS had a CRR of 72.6% compared to 53% for patients with a history of MDS. Patients younger than 60 years had a CRR of 72.2% compared to 63.5% for aged 60 years or older. The 30 day induction death rate was 2.4%. **Conclusions:** This two-day induction regimen is a safe and effective treatment for *de novo* AML. There is a high response rate, particularly in patients with favorable and intermediate risk karyotypes, with a low rate of early mortality. The high response rates and tolerability noted with this regimen provides a platform for further clinical trials to enhance outcome by combining with novel targeted therapies for AML.

7056 Poster Session (Board #116), Mon, 8:00 AM-11:30 AM

Post-transplant cyclophosphamide (PT-Cy) based haploidentical transplantation (haploHCT) versus matched sibling (MSD) or matched unrelated donor (MUD) reduced intensity conditioning (RIC) HCT for diffuse large b-cell lymphoma (DLBCL): A CIBMTR and EBMT analysis. *First Author: Mehdi Hamadani, CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI*

Background: The outcomes of DLBCL patients undergoing PT-Cy based haploHCT have not been compared to those receiving MSD or MUD HCT **Methods:** Adult (≥18yr) DLBCL pts (n = 1438) undergoing RIC allogeneic HCT during 2008-15 were identified in the CIBMTR or EBMT registries. Pts were divided into 4 groups; haploHCT, MSD, MUD with (w) ATG/campath (A-C) and MUD without (w/o) A-C. Overall survival (OS) was primary endpoint. Secondary endpoints included acute (a) and (c) GVHD, non-relapse mortality (NRM), relapse/progression (R/P) and progression-free survival (PFS). **Results:** The baseline characteristics are shown in Table. The cumulative incidence of day 180 grade 3-4 aGVHD and 1 year cGVHD was 7%, 11%, 13% and 19% (p < 0.001) and 15%, 41%, 23% and 48% (p < 0.001) in the haploHCT **v** MSD **v** MUD w A-C **v** MUD w/o A-C groups, respectively. The 3 year post HCT univariate outcomes for the haploHCT, MSD, MUD w A-C and MUD w/o A-C cohorts were as follows: NRM (22% v 17% v 26% v 30%), R/P (41% v 47% v 38% v 34%), PFS (38% v 37% v 36% v 37%) & OS (46% v 50% v 43% v 46%). On multivariate analysis (MVA) compared to haploHCT, MSD (RR 3.1), MUD w A-C (RR 2.0) and MUD w/o A-C (RR 4.0) were associated with significantly higher risk of cGVHD (p < 0.001). Relative to haploHCT the 3 other groups did not have a significantly different R/P risk, but compared to MSD, the MUD w A-C pts had a significantly higher R/P risk (RR 1.45; p = 0.0008). MVA showed no significant difference between the 4 cohorts in terms of NRM (p = 0.08), PFS (p = 0.45) and OS (p = 0.53). **Conclusions:** Survival outcomes are comparable between RIC MSD, MUD and PT-Cy based haploHCT in DLBCL. cGVHD was significantly lower with haploHCT.

	HaploHCT (N 132)	MSD (N 525)	MUD w A-C (N 403)	MUD w/o A-C (N 378)
Median age (range)	58 (20-75)	55 (19-73)	55 (19-75)	56 (23-73)
Male sex	86	323	259	218
KPS ≥90	96	325	249	216
HCT-CI ≥ 3	36	137	85	125
Median time from diagnosis to HCT, mos	22	26	24	28
% with Prior autoHCT	42	55	59	61
Chemosensitive @ HCT (%)	108 (72)	398 (75)	312 (77)	304 (80)
Marrow graft	100	10	30	20
GVHD prophylaxis				
PT-Cy+CNI+MMF	132	-	-	-
CNI+other	-	525	403	378
Median follow up, mos	49	48	49	39

7057 Poster Session (Board #117), Mon, 8:00 AM-11:30 AM

Development and validation of a risk assessment tool for symptomatic BKV infection. *First Author: Ala Abudayyeh, Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BKV, is a member of the family Polyomaviridae. BKV has been associated with increased morbidity and mortality secondary to late hemorrhagic cystitis, ureteral stenosis, and nephropathy. In our retrospective published study of 2477 SCT patients, 38.1% had developed renal impairment, and BKV viruria was present in 25%. In addition, BKV was found to be an independent predictor of chronic kidney disease and poor survival. Using the same cohort we derived a risk grading system to quantify risk of symptomatic BKV without having to use a complex statistical model and further validated it with another retrospective cohort of 442 allogeneic SCT patients. We hypothesize that our risk grading system will accurately identify the patients at risk of symptomatic BKV at day 30 post allogeneic stem cell transplant. **Methods:** Using the three variables *(conditioning regimen, HLA donor status, & underlying cancer diagnosis)* that were significant predictors for symptomatic BKV derived from our initial study, *we* developed a risk scoring system, using the methods described by Sullivan and colleagues. A nomogram of the sub distribution hazard model with death as a competing risk was constructed as a visualizing aid to obtain predicted probability of BK infection manually. We further stratified the patients based on their risk score into low, moderate, and high risk using 33th percentile of the risk score as the cutoff point, and into low and high risk using 99th percentile of the risk score as the cutoff points **Results:** The risk score was significantly associated with symptomatic BKV ($P < 0.0001$). Specifically, at 30-days post STC, the Low risk (≤ 7) patients had 9% chance of developing symptomatic BKV, while the high risk top 1% (9 patients) of the population had 56% of developing symptomatic BKV. This was confirmed in the cohort of 442 allogeneic SCT patients. **Conclusions:** We have created and validated a grading system for symptomatic BKV to predict risk at day 30 post allogeneic SCT. Using this grading system we would hope to identify high risk patients for BKV and treat prophylactically using BKV Cytotoxic T cell therapies and prevent reactivation which is highly associated with increased morbidity, mortality, and kidney function decline.

7058 Poster Session (Board #118), Mon, 8:00 AM-11:30 AM

Cyclophosphamide (Cy) pharmacogenetics (PGx) in allogeneic stem cell transplant (SCT) patients (pts) receiving Cy, fludarabine, total body irradiation and post-transplant Cy (FluCyTBI-postCy). *First Author: Jai Narendra Patel, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC*

Background: Cy is the backbone for many SCT conditioning regimens and is used post-SCT to prevent graft vs. host disease (GVHD). It has been proposed that genetic polymorphisms impact Cy exposure and clinical outcomes; however, no PGx studies have been performed in pts receiving FluCyTBI-postCy. **Methods:** Germline DNA from SCT pts receiving FluCyTBI-postCy was genotyped using a custom Ion AmpliSeq™ PGx Panel for polymorphisms in: *ALDH1A1* (*2), *ALDH3A1* (Pro329Ala), *GSTA1* (135T > C), *GSTM1* (null), *GSTP1* (Ile105Val, Ala114Val), *CYP2B6* (*2, *4, *5, *6, *18, *22), *CYP2C8* (*2, *3), *CYP2C9 (*2, *3, *8, *11), *CYP2C19 (*2, *3, *17), *CYP3A4* (*1B, *22), and *CYP3A5* (*3, *6, *7). Phenotypes (poor [PM], intermediate [IM], normal [NM], and rapid metabolizers [RM]) were inferred based on literature. Cy 14.5 mg/kg IV was given on days -6 & -5 pre-SCT, and 50 mg/kg on days +3 & +4 post-SCT. Univariate logistic regression was used to investigate the association between polymorphisms and any grade cardiotoxicity, hemorrhage cystitis [HC], liver toxicity, and/or acute GVHD up to day +100. Univariate Cox proportional hazards regression was used to investigate the association between polymorphisms and overall [OS] & progression-free survival [PFS]. **Results:** In 59 evaluable pts, the median age was 57 (24-77), 61% were male, 73% received haploidentical SCT and 27% matched related donor SCT. The table summarizes significant findings ($P < 0.05$). **Conclusions:** Several genes involved in the activation (*CYPs*) and inactivation (*ALDHs* & *GSTs*) of Cy and its metabolites were associated with SCT outcomes and toxicities. Prospective studies exploring the combined effects of these genes on outcomes are needed to validate findings.

Phenotype	Gene	HR/OR	95% CI	P-value
OS	*ALDH3A1* IM v PM	0.22	0.06-0.82	0.024
	CYP3A5 NM v PM	5.67	1.20-26.7	0.028
	CYP3A4 NM v IM	0.17	0.05-0.63	0.008
	RM v IM	0.22	0.05-0.92	0.038
PFS	*CYP3A4* NM v IM	0.14	0.04-0.45	0.001
	RM v IM	0.18	0.05-0.66	0.009
	CYP2C8 NM v IM	0.48	0.24-0.97	0.039
Cardiotox	*GSTP1* IM v PM	0.19	0.04-0.82	0.031
	NM v PM	0.09	0.01-0.45	0.007
HC	*ALDH1A1* NM v IM	0.09	0.004-0.65	0.036
Liver tox	*CYP2C8* NM v IM	0.23	0.05-0.83	0.038

7059 Poster Session (Board #119), Mon, 8:00 AM-11:30 AM

Effect of donor type in patients with AML or MDS undergoing reduced intensity hematopoietic cell transplant. *First Author: Nahid Rashid, Washington University in Saint Louis, Saint Louis, MO*

Background: Haploidentical (haplo) hematopoietic cell transplants (HCT) are a promising option for patients. Overall survival (OS) is comparable in patients receiving haplo vs matched unrelated donor (MUD) HCT. We are specifically interested in patients receiving peripheral blood (PB) HCT with a reduced intensity conditioning (RIC). Studies comparing AML/MDS patients who received only PB HCT and RIC are lacking. Based recent data, we hypothesized that enhanced graft-versus-leukemia effect may lead to lower relapse in RIC haplo verus MUDs. **Methods:** Our study included patients aged $\geq$ 18 undergoing MUD or haplo-HCT at Washington University between January 2010 and September 2017. Data was retrospectively collected via chart review. The primary outcome was OS, compared via the Kaplain-Meier method. Secondary outcomes included the cumulative incidence of relapse, treatment-related mortality (TRM), acute graft-versus-host disease (aGVHD), neutrophil (NE) and platelet engraftment (PE), analyzed via the method of Fine and Gray. **Results:** Our study included patients aged $\geq$ 18 undergoing MUD or haplo-HCT at Washington University between January 2010 and September 2017. Data was retrospectively collected via chart review. The primary outcome was OS, compared via the Kaplan-Meier method. Secondary outcomes included the cumulative incidence of relapse, treatment-related mortality (TRM), acute graft-versus-host disease (aGVHD), neutrophil (NE) and platelet engraftment (PE), analyzed via the method of Fine and Gray. **Conclusions:** There is no significant difference in OS, PFS, relapse, or TRM in haplo versus MUD between the two groups. This indicates that haplo are a reasonable alternative to MUD in patients receiving RIC. More data needs to be collected to determine if there is a significant difference in outcomes favoring haplo over MUD.

	Haplo	MUD	p value
1 year			
OS	49% (36 -61%)	42% (33 – 50%)	0.63
Relapse	38% (26 – 50%)	29% (21 – 36%)	0.14
TRM	22% (12 – 31%)	34% (26 – 42%)	0.08
Day + 30			
NE	88% (81 – 95%)	94% (90 – 98%)	< 0.001
Day +100			
aGVHD (II-IV)	17% (8 – 26%)	10% (5 – 15%)	0.14
aGVHD (III-IV)	7% (1 – 13%)	6% (2 – 11%)	0.52
PE	75% (66 – 85%)	85% (79 – 91%)	< 0.001

7060 Poster Session (Board #120), Mon, 8:00 AM-11:30 AM

Efficacy and safety of moxetumomab pasudotox (moxe) in adult patients (pts) with relapsed/refractory hairy cell leukemia (HCL) in relation to drug exposure, baseline disease burden, and immunogenicity. *First Author: Denison Kuruvilla, MedImmune, Mountain View, CA*

Background: Moxe is an immunotoxin targeting CD22 on B cells leading to cell death. The objectives of this analysis were to characterize the pharmacokinetics (PK) and evaluate the exposure-efficacy/safety of moxe in pts with HCL. **Methods:** Data from two HCL studies (Ph1: 49 pts dosed at 5, 10, 20, 30, 40 & 50 μg/kg IV; Ph 3: 80 pts dosed at 40 μg/kg IV) were pooled to develop a population PK model. The model derived C_{max} and AUC were then used to evaluate the exposure-efficacy/safety relationship in the 2 studies independently due to differences in bioactivity of materials (Ph1 50 μg/kg was bioactive equivalent to Ph3 40 μg/kg). Efficacy endpoints included complete response (CR), durable CR (Ph3 only) and objective response rate (ORR). Safety parameters included hemolytic uremic syndrome (HUS), capillary leak syndrome (CLS), ≥Gr 2 increased creatinine (CRE), and Gr 3/4 adverse events (AE). **Results:** Moxe PK was linear from 5-50 μg/kg with PK well-described by a 1-compartment model. Day 1 clearance (CL) was higher than for later doses (22 vs 4 L/hr), attributed to CD22+ B cell depletion with repeated dosing. Ph3 pts with anti-drug antibody (ADA) titers > 10240 had ~4-fold increase in CL. High CL was associated with high baseline B cells. High baseline B cells/low PK were associated with lower response rate, but clinical benefit was still observed. In Ph3, rates of CR and durable CR were 56-58% and 50-53% in high (≥median) PK exposure group vs 31-34% and 14-17% in the low PK exposure group. In Ph1, rate of CR was 67-71% in high vs 46-50% in low PK exposure groups. Pts with ADA titer > 10240 had lower CR and durable CR, but clinical benefit was still observed. Pts with high PK exposure had higher incidence of CLS and CRE in Ph3 but not in Ph1. HUS incidence in both studies was low and was not evaluated further. Pts with high PK exposure in Ph1 had higher rates of Gr 3/4 AE. Incidence of Gr 3/4 AE in Ph3 40 μg/kg was consistent with that of Ph1 50 μg/kg. **Conclusions:** Moxe CL decreased with repeated dosing, consistent with B cell depletion. ADA titer > 10240 increased CL by ~4-fold. Pts with high PK exposure had better response but had a slightly higher incidence of Gr 3/4 AE. Clinical trial information: NCT01829711 and NCT00586924.

7061 Poster Session (Board #121), Mon, 8:00 AM-11:30 AM

Pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of moxetumomab pasudotox (Moxe), an immunotoxin targeting CD22, in adult patients (Pts) with relapsed or refractory hairy cell leukemia (HCL). *First Author: Kemal Balic, MedImmune, Mountain View, CA*

Background: Moxe is a recombinant immunotoxin that specifically binds to CD22 on the B cell surface and internalizes leading to cell death. The PK, PD, and immunogenicity of moxe were evaluated in a pivotal study (NCT01829711) in pts with HCL. **Methods:** Eighty pts were enrolled and received moxe (40 μg/kg IV) on days 1, 3, and 5 of each 28-day cycle. Samples were collected for assessments of PK, circulating CD19+ B cell counts and immunogenicity. PK parameters were estimated by non-compartmental approach. B cell counts were evaluated by flow cytometry. Immunogenicity testing utilized a tiered strategy: screen, neutralization followed by characterization of domain specificity (*Pseudomonas* exotoxin A [PE38], CD22) and titer. **Results:** Moxe concentrations peaked shortly after infusion followed by rapid elimination in a monophasic fashion (half-life = 1.38 hr; clearance = 44.6 mL/hr/kg). PK exposure increased from Dose 1 to Dose 3, likely due to post-treatment depletion of B cells expressing CD22. Moxe caused rapid and sustained depletion of circulating CD19+ B cells (mean 89% reduction from baseline on day 8). PK exposure revealed an inverse relationship with baseline CD19+ B cells. Higher PK exposures were significantly associated with low baseline CD19+ B cell counts. After dosing, CD19+ B cells were almost fully depleted and a weakened relationship with PK was observed. Anti-drug antibody (ADA) incidence and prevalence rates were 66% and 88%, respectively. Neutralizing antibodies (Nab) were detected in 84% of total pts. Among Nab+ pts, 99% and 54% of ADA exhibited specificity to PE38 and CD22 binding domains, respectively. Median titers were generally low at baseline but increased with time. Reduced PK exposure was observed at later cycles (≥ Cycle 3), consistent with increasing titer levels. **Conclusions:** Moxe exhibited rapid clearance and was highly immunogenic, as expected for a bacterial immunotoxin. This CD22 targeted therapy elicited rapid and potent B cell depleting activity in pts with HCL. Overall, these properties support moxe as a promising new approach for the treatment of relapsed/refractory HCL. Clinical trial information: NCT01829711.

7062 Poster Session (Board #122), Mon, 8:00 AM-11:30 AM

Cross-intolerance with bosutinib after prior tyrosine kinase inhibitors (TKIs) in patients (pts) with Philadelphia chromosome–positive (Ph+) leukemia: Phase 1/2 study update. *First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy*

Background: Bosutinib has a distinct adverse event (AE) profile vs other TKIs used to treat Ph+ leukemia. **Methods:** Pts with chronic phase (CP) chronic myeloid leukemia (CML; n=403) or accelerated/blast phase CML or Ph+ acute lymphoblastic leukemia (ADV; n=167) previously treated with imatinib ± dasatinib and/or nilotinib received bosutinib (starting dose 500 mg QD) in a phase 1/2 study (NCT00261846). Cross-intolerance (AEs leading to discontinuation of both prior TKI and bosutinib) and AEs causing prior TKI intolerance and recurring as grade 3/4 AEs with bosutinib were assessed after ≥4 y of follow-up. **Results:** In imatinib-intolerant and dasatinib-intolerant pts, respectively, 18% and 24% in the CP CML group and 18% and 5% in the ADV group had cross-intolerance with bosutinib, which was most commonly due to hematologic AEs (Table). Cross-intolerance in imatinib-intolerant pts with CP CML due to AEs common with imatinib was low (rash 6%; diarrhea 10%; edema/fluid retention 0; myalgia 0); cross-intolerance due to pleural effusion was low in dasatinib-intolerant pts with CP CML (13%) and dasatinib-intolerant ADV pts (0). No deaths occurred due to cross-intolerance. **Conclusions:** Cross-intolerance with bosutinib was low and largely due to hematologic AEs, supporting bosutinib use in pts with Ph+ leukemia intolerant to prior TKIs, including those with intolerance due to rash or diarrhea. Clinical trial information: NCT00261846.

Cause of intolerance*	n	Bosutinib discontinuation due to same AE n (%)	Same grade 3/4 AE with bosutinib n (%)
CP CML			
Imatinib intolerance			
Any AE	120†	21 (18)	39 (33)
Thrombocytopenia	27	7 (26)	17 (63)
Neutropenia	21	2 (10)	7 (33)
Rash	18	1 (6)	2 (11)
Anemia	14	0	6 (43)
Edema	12	0	0
Diarrhea	10	1 (10)	3 (30)
Hematologic toxicity	7	4 (57)	5 (71)
Vomiting	7	1 (14)	1 (14)
Fatigue	7	1 (14)	0
Nausea	6	0	0
Fluid retention	5	0	0
Myalgia	5	0	0
Dasatinib intolerance			
Any AE	50	12 (24)	18 (36)
Pleural effusion	16	2 (13)	3 (19)
Thrombocytopenia	8	4 (50)	8 (100)
Pancytopenia	6	0	0
ADV			
Imatinib intolerance			
Any AE	22†	4 (18)	8 (36)
Thrombocytopenia	7	4 (57)	6 (86)
Dasatinib intolerance			
Any AE	21†	1 (5)	10 (48)
Pleural effusion	7	0	2 (29)
Thrombocytopenia	5	1 (20)	5 (100)

* Causes in ≥5 pts shown † Pts with known causes shown

7063 Poster Session (Board #123), Mon, 8:00 AM-11:30 AM

Long-term treatment-free remission (TFR) following frontline (1L) nilotinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP): ENESTfreedom 144-wk results. *First Author: Jerald P. Radich, Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: ENESTfreedom (NCT01784068) is a phase 2 study evaluating TFR following 1L nilotinib in newly diagnosed CML-CP pts. We previously reported 48- and 96-wk TFR rates of 51.6% and 48.9%. Long-term data (144-wk; data cutoff, Oct 11, 2017) on TFR durability are now available. **Methods:** Pts with $MR^{4.5}$ (*BCR-ABL1* ≤ 0.0032% on International Scale [$BCR\text{-}ABL1^{IS}$]) and ≥ 2 y of 1L nilotinib entered a 1-y consolidation phase; pts with sustained deep molecular response were eligible for TFR. Treatment was restarted after loss of major molecular response (MMR; $BCR\text{-}ABL1^{IS}$ ≤ 0.1%). Results are from the 144-wk analysis, in which all pts completed ≥ 144 wk of TFR, restarted nilotinib, or discontinued the study. **Results:** At data cutoff, 89 of 190 pts entering the TFR phase remained in TFR (144-wk TFR rate: 46.8%, 95% CI 39.6-54.2%). 94 pts (49.5%) discontinued TFR due to loss of MMR (91 restarted nilotinib), and 7 (3.7%) discontinued TFR for other reasons. 4 pts in TFR at 96 wk were no longer in TFR at 144 wk (3 had first loss of $MR^{4.5}$ within 8 wk in TFR). Of 91 pts who restarted nilotinib, 90 (98.9%) and 84 (92.3%) regained MMR and $MR^{4.5}$, respectively (1 discontinued the study without MMR, 5 discontinued with MMR but not $MR^{4.5}$, 1 remained in reinitiation phase with MMR but not $MR^{4.5}$). Of 84 pts who regained $MR^{4.5}$, 70 (83.3%) had stable $MR^{4.5}$ 48 wk later, 11 (13.1%) discontinued the study < 48 wk after regaining $MR^{4.5}$, and 3 (3.6%) remained in reinitiation phase with < 48 wk of follow-up after regaining $MR^{4.5}$. No pt had disease progression. 10 pts died (consolidation, 2; TFR, 1; reinitiation, 4; discontinuation, 3), none of causes attributable to CML. 144-wk treatment-free survival rate was 48.7% (95% CI 41.4-55.6%). Among 94 pts remaining in TFR for > 96 wk, any-grade musculoskeletal pain–related AE rates were 16.0%, 40.4%, 9.6%, and 4.3% in the consolidation phase and first, second, and third 48 wk of TFR, respectively; cardiovascular event rates were low across these periods. **Conclusions:** These results suggest the durability and safety of TFR following 1L nilotinib, with a 144-wk TFR rate of 46.8%. There were no disease progressions, and musculoskeletal pain appeared transient. Clinical trial information: NCT01784068.

7064 Poster Session (Board #124), Mon, 8:00 AM-11:30 AM

Intensive chemotherapy (IC) versus hypomethylating agents (HMA) for the treatment of younger patients with myelodysplastic syndrome (MDS) and elevated bone marrow blasts. *First Author: Paolo Strati, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The AZA-001 trial has shown a survival advantage for patients with high-risk MDS treated with HMA as compared to IC. However, this study was conducted mainly in an older population. **Methods:** We retrospectively analyzed the characteristics and outcomes of patients with MDS, younger than 60 years of age, with ≥ 10% bone marrow blasts who received frontline treatment with HMA or anthracycline-cytarabine-based IC at our institution between 10/1993 and 12/2017. **Results:** One-hundred and six patients were included in the study, 57 treated with HMA and 49 with IC. Use of IC was associated with shorter time to response (1 vs 2 months; $p < 0.001$) and higher overall response rate (ORR; 82% vs 60%, p = 0.02). On univariate analysis (UA) age younger than 50 (p = 0.03) and use of IC (p = 0.02) were associated with ORR, but on multivariate analysis (MVA) only use of IC maintained its association (OR 4.3, 95% CI 2-9.1; $p < 0.001$). Rates of treatment discontinuation secondary to early death or toxicity were comparable; 31% of patients on HMA and 33% on IC proceeded to stem cell transplant (SCT). After a median follow-up of 15 months (range, 1-178 months), 38 (51%) out of 74 patients lost their response, and median response duration (RD) was 19 months (range, 1-166 months). Factors associated with longer RD on UA were lack of unfavorable cytogenetics (p = 0.04), consolidation with SCT in first remission (p = 0.009) and use of IC (p = 0.03); on MVA, use of IC maintained its association (HR 2.9, 95% CI 1.4-5.8, p = 0.03). Eight (8%) patients transformed to acute myeloid leukemia during frontline treatment, 7 (12%) on HMA and 1 (2%) on IC (p = 0.07). At most recent follow-up, 65 (61%) patients died, median overall survival was 21 months (range, 1-178 months) and was significantly longer for patients treated with IC (43 vs 15 months; p = 0.05). **Conclusions:** IC is more effective than HMA for younger patients with MDS and bone marrow blasts ≥ 10%, irrespective of other baseline characteristics. Strategies combining targeted agents with either HMA or IC should be investigated, to determine whether this advantage will be maintained.

7065 Poster Session (Board #125), Mon, 8:00 AM-11:30 AM

PU.1 and JDP2 expression in myelodysplastic syndromes to predict treatment response and leukemia transformation. *First Author: Kristian Boasman, University of Lincoln, Lincoln, United Kingdom*

Background: Myelodysplastic syndromes (MDS) are malignant disorders leading to acute leukaemia (AML). Recent breakthroughs identified down-regulation of PU.1 in high risk MDS and AML, with work within NPM1 mutated AML cells showing PU.1 relocates in the cytoplasm causing differentiation arrest. Microarray analysis in PU.1 overexpressing K562, revealed Jun Dimerization Protein 2 (JDP2), downstream to PU.1 was significantly suppressed. In this study we investigated PU.1 and JDP2 expression during different stages of MDS progression/AML evolution and in patients responding to Azacitidine. **Methods:** Gene expression of PU.1 and JDP2, in total bone marrow and selected CD34+ cells, from 12 newly diagnosed MDS patients stratified according to IPSS-R (6-low, 3-intermediate, 3-high risk), 2 AML and 10 controls was undertaken. Samples were enriched for the mononuclear fraction by Ficoll separation and RNA analysed by RT-PCR for PU.1 and JDP2 expression. Protein expression was analysed by western blot. Results obtained were compared with Bloodspot MDS gene expression data. PU.1-knockdown was performed in K562 using PU.1 short interfering RNAs. **Results:** We revealed PU.1 and JDP2 are down regulated in MDS patients. PU.1 and JDP2 expression inversely correlates with disease progression, consistently reducing in IPSS-R groups. Investigating PU.1 and JDP2 expression data in MDS vs normal samples from a large Bloodspot pool confirmed our findings. To understand if JDP2 suppression is a direct result of reduced PU.1 we performed PU.1-knockdown. This revealed only a partial reduction in JDP2 expression suggesting a more complex regulatory mechanism. PU.1 and JDP2 expression levels in CD34+ cells, significantly and progressively reduces towards AML transformation. Furthermore, we demonstrated a significant upregulation in PU.1 and JDP2 expression in patients achieving a response to Azacitidine, suggesting PU.1/JDP2 could be targets of this drug. **Conclusions:** PU.1 and JDP2 expression correlates with patient's prognosis and leukaemia transformation in MDS, highlighting a potential role as new diagnostic and prognostic markers in MDS.

7066 Poster Session (Board #126), Mon, 8:00 AM-11:30 AM

Omacetaxine mepesuccinate for patients with higher-risk MDS and CMML after failure of hypomethylating agents: A phase II clinical trial. *First Author: Gabriela Sanchez-Petitto, University of Texas Health Science Center at Houston, Houston, TX*

Background: Hypomethylating agents (HMAs) are the standard of care for patients (pts) with higher-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML); however, outcomes after HMA failure are poor. We designed a phase II trial to evaluate omacetaxine mepesuccinate (OM) in pts with MDS and CMML after HMA failure. **Methods:** Eligible pts were $>$ 18 years of age, and had intermediate-1- or higher-risk MDS or CMML by the International Prognostic Scoring System (IPSS) and/or bone marrow (BM) blasts 5-30%, that had not responded to, progressed on, or relapsed after HMA therapy. OM was given at 1.25 mg/m^2 SQ every 12 hours for 3 days on a 28-day cycle, until progression or unacceptable toxicity. Primary endpoints were overall response rate (ORR) and overall survival (OS). **Results:** From 6/2015 to 11/2017, 42 pts were enrolled. Median age was 76 years (range, 61-87); 8 pts (19%) had CMML. 17 pts (40%) had adverse-risk cytogenetics, and 19 pts (45%) had received 2 or more prior therapies. Median BM blasts was 10% (range, 2-20%). The median duration of follow-up was 25 months, and the median number of cycles of OM received was 3 (range, 1-23). The ORR was 33%; 3 pts achieved CRp, 10 achieved CRi and 1 achieved HI with a median number of cycles to best response of 2 (range, 1-9 cycles). Response rates for pts with MDS and CMML were 35% (12/34) and 25% (2/8), respectively. Response rates for pts with diploid and adverse-risk cytogenetics were 58% (7/12) and 24% (4/17), respectively (P = 0.057). Of the 14 responders, 5 remain on study, 6 relapsed, 2 died while in response, and 1 was lost to follow-up. The median OS was 7.5 months, and the 1-year OS rate was 25%. The median RFS was 4.9 months, and the 1-year RFS rate was 14%. Two pts are alive with ongoing response after $\geq$2 years of treatment; both had MDS with diploid cytogenetics and a *RUNX1* mutation. Overall, the treatment was well-tolerated. Among 39 pts who received $\geq$2 cycles of OM, 8 (21%) required dose reduction. The 30-day and 60-day mortality rates were 10% and 14%, respectively. **Conclusions:** In patients with MDS and CMML with prior HMA failure, OM resulted in an ORR of 33% with a median OS of 7.5 months. Some pts had long-term responses to OM. Clinical trial information: NCT02159872.

7067 Poster Session (Board #127), Mon, 8:00 AM-11:30 AM

A pilot trial of anti-KIR antibody with or without 5-azacitidine for myelodysplastic syndrome. *First Author: Fevzi Firat Yalniz, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Experimental and clinical data suggest that enhancement of NK cell activity by a surrogate of KIR blockage improves the outcomes in myeloid malignancies. Lirilumab (LIRI) is a human IgG4 monoclonal antibody that blocks KIR/HLA-C interaction and augments NK cell activity. We designed a phase 2 study to evaluate the safety and efficacy of LIRI as a single agent and in combination with 5-Azacitidine (AZA) in patients (pts) with myelodysplastic syndrome (MDS). **Methods:** Adult pts with MDS of any risk who had not received prior therapy with a hypomethylating agent, adequate performance status (ECOG $\leq$ 2) and organ function were included. Lower risk MDS pts (low and intermediate-1 by IPSS) were given LIRI at the dose of 3 mg/kg in every 4 weeks. Higher risk MDS pts received AZA at the dose of 75 mg/m^2 on days 1-7 in combination with LIRI 3 mg/kg on day 7 of 28 day cycle. Responses were evaluated on day 28 of course 1 and afterwards every 3 months or as indicated according to IWG-2006 criteria. **Results:** A total of 10 pts including 8 with higher and 2 with lower risk MDS were enrolled. The median age was 70 years (range, 50-84) and 40% of pts had complex cytogenetics. All pts had baseline next generation sequencing and frequently identified mutations included TP53 (n = 5), TET2 (n = 3) and NRAS (n = 2). The median follow up was 5 months (range, 3-15) and pts received a median of 4 (range, 2-13) and 9 (range, 5-14) cycles of treatment with AZA plus LIRI and single agent LIRI, respectively. Two pts achieved complete remission (CR), 5 marrow CR and 3 had stable disease. Two achieved cytogenetic CR (20%) and 4 had hematologic improvement. Reasons for study discontinuation included disease progression (n = 4), stem cell transplantation (n = 3) and toxicities (myocarditis, non-therapy related, n = 1). The median duration of CR/mCR responses were 3 months (range, 1-5). Grade 3/4 toxicities included 3 episodes of neutropenic infections, 2 pneumonia, 2 infectious colitis and 1 elevated bilirubin. Nine serious adverse events reported of which 6 possibly related to LIRI. **Conclusions:** LIRI either as a single as well as in combination with AZA was well tolerated in pts with MDS. A large scale multicenter study is warranted to confirm our findings. Clinical trial information: 02599649.

7068 Poster Session (Board #128), Mon, 8:00 AM-11:30 AM

The impact of clonal size on the revised international prognostic scoring system (R-IPSS) in myelodysplastic syndromes (MDS) with a single cytogenetic abnormality. *First Author: Omar Alkharabsheh, Mayo Clinic, Rochester, MN*

Background: Cytogenetics is the backbone of the R-IPSS for MDS, contributing the most points (0 to 4) to the total scoring system. The current R-IPSS cytogenetics does not factor in the clone size or the number of abnormal metaphases. The International System for Human Cytogenetic Nomenclature (ISCN) in 2016 defined the clone by the presence of a structural rearrangement in at least 2 metaphases or 3 metaphases in case of monosomies. **Methods:** This is a retrospective study from the Mayo Clinic records for patients with confirmed MDS by a hematopathology review. Analysis included patients with adequate karyotyping of 20 metaphases only. Patients were divided into 3 groups (grp) based on their R-IPSS cytogenetics category (Intermediate, Poor and Very Poor). Patients with a single abnormal clone only were included. The size of the abnormal clone was calculated by dividing the number of abnormal metaphases by 20. The overall survival (OS) of each R-IPSS grp with different clonal percentage was compared to the diploid cytogenetics (DC) group. The Good and Very good R-IPSS cytogenetics were excluded. Survival estimates were calculated by Kaplan-Meier curves and log-rank testing using JMP v.13. **Results:** Of 1301 patients, 36.5% (n = 475) had a DC, 49% (n = 637) had an abnormal karyotype and 15% (n = 189) had no available cytogenetic results. Of those with abnormal karyotype, 58% (n = 372) had a single clone. Of those with a single clone, 70% (n = 260) had a single chromosomal abnormality. The OS of the 3 groups was statistically different and consistent with their R-IPSS score. OS was higher in the DC group (OS = 54 months, n = 474) compared to the Intermediate (OS = 30.5 months, n = 121), Poor (OS = 21.1 months, n = 49), and Very poor (OS = 8.7 months, n = 75), $p < 0.005$ for all grps. The clone size had no impact on overall survival above 5% when combining the 3 grps, the lowest threshold to make statistical conclusions was 10% (p = 0.01). **Conclusions:** The clonal percentage of any abnormality detected by conventional karyotype did not affect OS in patients with MDS that have an R-IPSS risk of intermediate or above. Therefore, any chromosomal abnormality should be included in the R-IPSS cytogenetics.

7069 Poster Session (Board #129), Mon, 8:00 AM-11:30 AM

Characteristics and outcomes of myelodysplastic syndrome (MDS) with chromosome (chr)3q abnormalities. *First Author: Mansour Alfayez, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Balanced and unbalanced chr 3q21;q26.2 abnormalities result in aberrant expression of the oncogene ecotropic viral integration site 1 implicated in leukemogenesis, and correlate with poor outcomes in acute myeloid leukemia (AML). These abnormalities occur in < 1% of MDS. **Methods:** We retrospectively reviewed the baseline characteristics of MDS patients (pts) with inv(3)(q21q26)/t(3;3)(q21;q26)/unbalanced abnormalities, diagnosed between 2000 and 2017, and assessed its impact on treatment response, overall survival (OS) and transformation to AML. **Results:** 56 patients [53% male; median age 66.5 yrs (29-85)] were included. 21 (38%) had therapy-related MDS and 51 (91%) were High/Very High risk by IPSS-R. Isolated Chr 3q21-26 abnormalities were seen in 18 (32%) pts; 38 (68%) had additional abnormalities the most common being chr 7 (24 pts (63%)). The median number of additional chr alterations per pt was 2 (1–25). Common molecular markers were *TP53* (8/19; 42%), *ASXL1* (2/6; 33%), *RAS* (5/44; 11%), *RUNX1* (3/6; 50%) and *PTPN11* (3/9; 33%). Of 34 pts received HMA-based therapy, 29% achieved CR/CRi/CRp compared to 40 % (4/10) in non-HMA group (8 pts received high intensity chemotherapy, including 2 pts with SCT) (p = 0.7); the median duration of response was 5.5 months (mos) in HMA-treated pts vs 19.25 mos in non-HMA group (p = 0.057). The median OS was 13.2 mos in the HMA-treated group vs 7.5 mos in non-HMA based therapy, showing a trend of higher early mortality in the latter (p = 0.042; HR 1.3, 95% CI 0.6-3.0). Stratified by IPSS-R, OS was 11.2 mos, 13.8 mos and 21.1 mos in Very High, High and Intermediate risk group; respectively (p = 0.03). Of the 48 pts with available follow-up, AML transformation was seen in 27 pts (56%): 23/35 (66%) in HMA-treated and 4/13 (31%) in non-HMA group (median time to transformation: 5.5 mos vs 4.75 mos, respectively; p = 0.4). **Conclusions:** MDS with chr 3q21;26.2 abnormalities is an aggressive disease with high risk of transformation to AML. Additional cytogenetic abnormalities are common including –7/7q, and relationship with specific molecular abnormalities is unclear. Treatment with HMA does not seem to affect survival or transformation to AML and novel therapeutic approaches are needed.

7070 Poster Session (Board #130), Mon, 8:00 AM-11:30 AM

Effect of enforced expression of *cxcl8* by hematopoietic stem and progenitor cells on niche interactions and hematopoietic progenitor cells in adult zebrafish. *First Author: Bradley Wayne Blaser, Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: *Cxcl8* is an angiogenic chemokine that is highly expressed in a subset of patients with MPN or clonal hematopoiesis of indeterminate potential (CHIP), a finding which is associated with poor outcomes. Our recent work has discovered a novel role for *cxcl8* and its receptor, *cxcr1*, in supporting colonization of hematopoietic stem and progenitor cells (HSPCs) within the sinusoidal endothelial cell niche of the embryonic zebrafish known as the caudal hematopoietic territory (CHT). We hypothesized that enforced expression of *cxcl8* by HSPCs would alter HSPC-niche interactions and expand HSPCs in adults. **Methods:** Expression of *cxcl8* was enforced in zebrafish HSPCs by microinjecting DNA constructs containing the HSPC-specific *Runx1+23* enhancer/promoter element into HSPC (*Runx1+23:mCherry*) or endothelial cell (*kdrl:mCherry*) reporter zebrafish. Time lapse fluorescence video microscopy and single-cell tracking was performed on embryonic zebrafish HSPCs within the CHT niche. Kidney marrow was harvested from adult zebrafish and hematopoietic cell populations were identified by flow cytometry. **Results:** Enforced expression of *cxcl8* by HSPCs nearly doubled the amount of time they resided within the CHT when compared to expression of GFP as a control (3.8 ± 0.5 vs 2.1 ± 0.3 h, p = 0.005, N = 108 tracked cells). Enforced expression of *cxcl8* increased the percent of time individual HSPCs spent closely interacting with a single group of CHT endothelial cells by 30% (87% vs 57%, p = 0.001). Flow cytometric analysis of whole kidney marrow in adult zebrafish at 3 months of age showed that *cxcl8* expression caused a skewing of the hematopoietic progenitor cell:lymphoid cell ratio in favor of the progenitor compartment (1.96 ± 0.15 vs 1.61 ± 0.10, p = 0.048). **Conclusions:** Taken together, these data support a model in which pre-malignant HSPC clones aberrantly express *cxcl8*, acquire a selective advantage over normal clones through enhanced interactions with the endothelial cell niche, and progress over time to a neoplastic state.

7071 Poster Session (Board #131), Mon, 8:00 AM-11:30 AM

Impact of ruxolitinib in myelofibrosis post allogeneic stem cell transplant: A pilot study. *First Author: Joyson Poulose, Penn State Hershey Medical Center, Hershey, PA*

Background: Allogeneic stem cell transplant (SCT) is the only potentially curative treatment for intermediate and high-risk myelofibrosis (MF). The use of Ruxolitinib (Rux) in the pre-SCT setting has demonstrated significant improvements in constitutional symptoms and splenomegaly. However, the optimal time of starting Rux and the effects of post-SCT Rux maintenance are still unclear. **Methods:** We analyzed outcomes of patients diagnosed with MF at our center who never received Rux (Cohort A), received only pre-SCT Rux (Cohort B), and received post-SCT Rux (Cohort C) between 6/2012 and 6/2017. **Results:** This study analyzed 16 patients, 11 male and 5 female, with median age of 59 years (range 47-72) at the time of SCT. The MF scores ranged from 2 to 3 (WHO Grade) at diagnosis. All patients had constitutional symptoms and splenomegaly at diagnosis except 1 who had prior splenectomy. There were 3 patients in cohort A, 9 patients in cohort B, and 4 patients in cohort C (3 patients received both pre- and post-SCT Rux; 1 received only post-SCT Rux). The median duration of Rux pre-SCT was 8 months (5-20); the mean duration of Rux post-SCT was 20 months (4-32). A JAK2V617F mutation was detected in all patients in cohort A, 7 patients in cohort B, and 3 patients in cohort C. All patients received reduced intensity conditioning regimen. The median time (days) for neutrophil engraftment (ANC>500) was 17 (13-18) in group A, 15 (0-74) in group B, and 12.5 (12-16) in group C. The median time (days) to transfusion independence was 148 (118-1140), 72 (11-105), and 24.5 (13-101) for patients in cohorts A, B, and C respectively. CMV/EBV viremia was detected in 8 patients before day 100, 3 of them in cohort A. Grade II-III acute GVHD was seen in all patients in cohort A and 4 patients in cohort B, but none in cohort C. The median spleen size reduction post-SCT was 17% in cohort A, 11% in cohort B, and 32% in cohort C. At the time of last follow up, an overall response was seen in 4 patients in cohort B, 2 with CR. All patients in cohort C achieved a CR and are alive. No one in group A achieved a remission. **Conclusions:** In this pilot study, patients treated with Rux pre- and post-SCT showed better outcomes and fairly good tolerability. Further studies on a larger patient population are warranted.

7072 Poster Session (Board #132), Mon, 8:00 AM-11:30 AM

The effect of pre-transplant JAK 1/2 inhibitors on outcomes of myelofibrosis patients who receive allogeneic stem cell transplant. *First Author: Kathleen Miller, Harvard Medical School, Boston, MA*

Background: The use of JAK 1/2 inhibitors (JAKi) for myelofibrosis (MF) treatment is becoming commonplace, but their impact on outcomes after hematopoietic stem cell transplant (SCT) is not well studied. We conducted a retrospective analysis of 132 patients who underwent SCT for primary or secondary MF at two partner institutions to assess the impact of receiving pre-SCT JAKi on several outcomes, including overall survival (OS), progression free survival (PFS), and GVHD-free and relapse-free survival (GRFS). **Methods:** 132 patients with MF who received allogeneic SCT between 2004 and 2017 at Massachusetts General Hospital or Dana Farber Cancer Institute were identified. The use of this data was approved by the local Institutional Review Board. We limited our final analysis to the 116 patients who were intermediate-1 (41) and intermediate 2 risk (75) by DIPSS prior to SCT, as there were very few patients in the high or low risk groups. Cox proportional hazard regressions were fit to estimate the association between the use of pre-SCT JAKi and OS, PFS, and GRFS after SCT, adjusting for baseline ECOG performance status, conditioning intensity and DIPSS status. **Results:** Of the 116 DIPPS-intermediate patients in the study, 41 received a JAKi prior to SCT and 75 patients did not. Patients who received pre-SCT JAKi had increased OS (75% vs 41%) and increased PFS (73% vs 44%) but not in GRFS (17% vs 14) in unadjusted analysis. In models adjusted for baseline ECOG performance status, conditioning regimen intensity, and DIPPS status, the use of JAKi prior to SCT was associated with a marginally-significant improvement in PFS [hazard ratio (HR) = 0.54, 95% CI 0.27 – 1.07, p = .075] and OS [HR = 0.53, 95% CI 0.26 – 1.07, p = .077], and was not associated with an improvement in GRFS [HR = 0.77, CI 0.49 – 1.23, p = .28]. **Conclusions:** Our data suggest that the use of JAKi prior to SCT may improve survival outcomes for patients with MF intermediate risk 1 or 2 who undergo SCT. However, further investigation with a larger sample size is needed to better understand the effect of pre-SCT JAKi use on patient outcomes after SCT. Future investigation should also focus on the use of post-SCT JAKi given their exhibited activity for GVHD.

TPS7073 Poster Session (Board #133a), Mon, 8:00 AM-11:30 AM

Phase 3, randomized, placebo-controlled trials evaluating glasdegib in combination with intensive or nonintensive chemotherapy in patients with untreated acute myeloid leukemia. *First Author: Jorge E. Cortes, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Glasdegib is an oral Hedgehog pathway inhibitor with clinical activity in patients (pts) with untreated AML or higher-risk MDS, and improved survival when combined with low-dose cytarabine (AraC) in unfit pts with AML. BRIGHT AML1019 comprises two Phase 3, randomized (1:1), double-blind trials evaluating glasdegib 100 mg once daily (QD) or placebo (PBO) + chemotherapy in untreated adult AML (NCT03416179). The protocol includes 2 parallel, simultaneous trials: 1 with intensive chemotherapy (IC) and 1 with nonintensive chemotherapy (nIC). **Methods:** Both trials include pts aged ≥18 y with untreated AML (WHO 2016), including AML evolved from MDS or antecedent hematologic disease, or secondary AML. Key exclusions: inadequate organ function, acute promyelocytic leukemia, active CNS leukemia. Assignment to IC or nIC trial is per Investigator. In the IC trial, 400 pts are randomized (1:1) to glasdegib 100 mg QD or PBO on Day 1 and continue for up to 2 y or until post consolidation minimal residual disease (MRD)-negative status. Glasdegib or PBO are administered with 7+3 induction (AraC 100 mg/m^2 IV for 7 days + daunorubicin 60 mg/m^2 for 3 days); induction 2, if needed, will use 7+3 or 5+2. Consolidation consists of single-agent AraC 1 or 3 g/m^2 IV over 3 h twice daily on Days 1, 3 and 5 every 28 days for ≤4 cycles; eligible patients may receive hematopoietic stem cell transplant. In the nIC trial, 320 pts are randomized (1:1) to glasdegib 100 mg QD or PBO, each with azacitidine 75 mg/m^2 daily SC or IV for 7 days, in 28-day cycles. Treatments continue until disease progression, unacceptable toxicity, withdrawal or death. In both trials, glasdegib and PBO continue regardless of chemotherapy dose modifications/delays. The primary endpoint is overall survival. Secondary endpoints include response, time to and duration of response, event-free survival, safety, patient-reported outcomes and pharmacokinetics. Clinical trial information: NCT03416179.

TPS7074 Poster Session (Board #133b), Mon, 8:00 AM-11:30 AM

AGILE: A phase 3, multicenter, randomized, placebo-controlled study of ivosidenib in combination with azacitidine in adult patients with previously untreated acute myeloid leukemia with an IDH1 mutation. *First Author: Eytan Stein, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Acute myeloid leukemia (AML) is a hematologic malignancy with limited treatment options for patients who are ineligible for intensive chemotherapy, corresponding to a median overall survival ≤1 year (Dombret et al. 2016). Mutations in isocitrate dehydrogenase 1 (*IDH1*) occur in 6–10% of AML cases (Xu et al. 2017). Ivosidenib (IVO; AG-120) is a first-in-class, oral, targeted inhibitor of the mutant IDH1 (mIDH1) enzyme that has demonstrated robust clinical activity and a manageable safety profile as a single agent in patients with AML. A phase 1 study of IVO in combination with azacitidine (AZA) is ongoing (NCT02677922). As of September 11, 2017, 11 treatment-naïve patients with mIDH1 AML have been treated with IVO 500 mg QD + AZA 75 mg/m^2 subcutaneously (SC) for 7 days in a 28-day schedule (DiNardo et al. ASH 2017). Patients have been treated for a median of 3 cycles (range 1–13) and adverse events are consistent with the AML monotherapy experiences of IVO and AZA. One case of IDH differentiation syndrome has been reported. The objective response rate (ORR) was 8 of 11 patients, including 4 patients who achieved a complete remission (CR). **Methods:** AGILE is a global, randomized, double-blind, placebo-controlled trial in patients with previously untreated mIDH1 AML who are candidates for nonintensive treatment (NCT03173248). 392 patients are being randomized 1:1 to receive either IVO 500 mg QD + AZA 75 mg/m^2 SC or intravenously for 7 days in 28-day cycles, or matched placebo + AZA. Randomization is stratified by region and by *de novo* versus secondary AML. Key eligibility criteria include patients with previously untreated mIDH1 AML (according to WHO criteria) who are not candidates for or not willing to receive intensive chemotherapy, ECOG performance status 0–2, and no prior treatment with a hypomethylating agent or mIDH1 inhibitor. The primary outcome measure is overall survival, and key secondary outcome measures include event-free survival, CR rate, CR + CR with partial hematologic recovery (CRh) rate, and ORR. AGILE is currently open for enrollment globally. Clinical trial information: NCT03173248.

TPS7075 Poster Session (Board #134a), Mon, 8:00 AM-11:30 AM

A phase 3, trial of gilteritinib, as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with *FLT3*-ITD$^+$ AML. *First Author: Mark J. Levis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: *Fms*-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutations in acute myeloid leukemia (AML) are a common indication for allogeneic hematopoietic stem cell transplant (HSCT) in first complete remission (CR1). Despite HSCT, relapses are common and cure rates are limited thereafter. The use of FLT3 inhibitors as post-HSCT maintenance therapy has not been prospectively evaluated. Gilteritinib is a highly selective, potent FLT3/AXL inhibitor with robust activity and favorable tolerability in relapsed/refractory AML. Several gilteritinib trials in AML include single arm post-HSCT gilteritinib maintenance therapy to establish the feasibility of this strategy. This trial will compare the safety and efficacy of 2-year maintenance therapy with gilteritinib versus placebo in patients with *FLT3*-ITD$^+$ AML in CR1 after allogeneic HSCT. **Methods:** This Phase 3, randomized, double-blind, placebo-controlled multicenter trial (NCT02997202; Blood and Marrow Transplant Clinical Trials Network Protocol 1506), to be conducted at 149 sites worldwide, will enroll 532 adult subjects (aged ≥18 years) with *FLT3*-ITD$^+$ AML in CR1 who are ≥30 days and ≤90 days from scheduled allogeneic HSCT. Of these 532 subjects, 346 subjects who have achieved successful engraftment without uncontrolled graft-versus-host disease (GVHD) or other serious toxicity will be randomized (1:1; stratified by conditioning regimen intensity, time from HSCT [Day 0] to randomization [30–60 days vs 61–90 days], and presence of minimal residual disease [MRD] in the pre-transplant bone marrow sample) to receive oral gilteritinib (120 mg) or matching placebo as maintenance therapy for 2 years. The primary endpoint is relapse-free survival (RFS) in the two treatment arms; RFS will be assessed from the time of randomization to the time of death or morphologic leukemia relapse (as defined by Revised IWG criteria). Overall survival is a key secondary endpoint. Other endpoints include safety/tolerability, non-relapse mortality, event-free survival, incidences of acute/chronic GVHD, and MRD. As of January 30, 2018, 47 patients have been enrolled and 11 have been randomized. Clinical trial information: NCT02997202.

TPS7076 Poster Session (Board #134b), Mon, 8:00 AM-11:30 AM

An open-label, first-in-human, dose escalation study of a novel CD3-CD123 bispecific T-cell engager administered as a single agent by intravenous infusion in patients with relapsed or refractory acute myeloid leukemia, B-cell acute lymphoblastic leukemia, or high risk myelodysplastic syndrome. *First Author: Nicolas Boissel, Hôpital Saint-Louis, Paris, France*

Background: Persistence of leukemic stem cells is an important cause of relapse in patients with acute myeloid leukemia (AML). CD123 (α-chain of the interleukin-3 receptor) is highly expressed on myeloid leukemic stem cells and blasts, and is present on B-cell acute lymphoblastic leukemia (B-ALL). With the goal of developing a therapeutic molecule active against leukemic stem cells and blasts, a novel bispecific T-cell engager (TCE) has been engineered incorporating the proprietary Cross-Over-Dual-Variable-Domain (CODV) format, a fully humanized Fc-silenced IgG1 backbone, and variable domains from two antibodies, targeting CD3 (T-cell co-receptor) and CD123, respectively. In nonclinical experiments, the TCE exhibited T-cell mediated cytotoxic activity against AML cells in vitro and in mouse models. **Methods:** This first-in-human trial will enroll patients with relapsed or refractory AML, B-ALL, or high risk myelodysplastic syndrome. The trial is starting at the minimum anticipated biological effect level (MABEL) dose, followed by an intrapatient dose escalation to a steady-state dose. The drug will be administered intravenously on a weekly basis with specific precautions to prevent and mitigate cytokine release syndrome. One patient will be treated at each of the first two dose levels, while subsequent dose levels will enlarge to a 3+3 design. Patients will be assessed for response, safety, and pharmacodynamic and pharmacokinetic endpoints. The primary objective of the dose escalation study is to determine a recommended phase 2 dose for a subsequent expansion cohort.

TPS7077 Poster Session (Board #135a), Mon, 8:00 AM-11:30 AM

Phase 3 study of first line pevonedistat (PEV) + azacitidine (AZA) versus single-agent AZA in patients with higher-risk myelodysplastic syndromes (HR MDS), chronic myelomonocytic leukemia (CMML) or low-blast acute myelogenous leukemia (AML). *First Author: Mikkael A. Sekeres, Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Background: PEV is a first-in-class small molecule inhibitor of NEDD8-activating enzyme, with single-agent clinical activity in patients with relapsed/refractory AML (Swords et al. *Br J Haematol* 2015;169:534–43). In preclinical AML models, PEV in combination with AZA resulted in synergistic antitumor activity compared with either agent alone (Visconte et al. *Leukemia* 2016;30:1190–4). A phase 1b study reported that PEV+AZA was well tolerated and showed clinical activity in patients ≥60 years with untreated AML (Swords et al. *Blood* 2018; Epub). These results provided the rationale for this phase 3 study to compare the efficacy and safety of PEV+AZA versus single-agent AZA as first line treatment for patients with HR MDS, CMML, or low-blast AML. **Methods:** This is a global, multicenter, randomized, controlled, open-label, phase 3 study (NCT03268954). Eligible patients (N = ~450 planned) are adults with a confirmed diagnosis of HR MDS, CMML, or low-blast AML with no prior treatment, who are ineligible for intensive chemotherapy and/or allogeneic stem cell transplantation and do not have acute promyelocytic leukemia or a history of central nervous system involvement by AML. Patients are stratified by IPSS-R risk group (MDS/CMML) and low-blast AML, and randomized 1:1 to receive PEV 20 mg/m^2 intravenously on days 1, 3, and 5, plus AZA 75 mg/m^2 (intravenous or subcutaneous) on days 1–5, 8, and 9, or AZA alone, in 28-day cycles until progression, transformation to AML, or unacceptable toxicity. Primary endpoints are overall response rate by cycle 6 and event-free survival; overall survival is a key secondary endpoint. Other secondary endpoints include survival rates at 6 months and 1 year; rate/duration of response; time to AML transformation; rate of complete remission (CR); time to first CR or partial remission; rate of hematologic improvement; rate/duration of red blood cell and platelet transfusion independence; time to relapse, progression, or death; pharmacokinetics; and health-related quality of life. Recruitment is currently ongoing. Clinical trial information: NCT03268954.

TPS7078 Poster Session (Board #135b), Mon, 8:00 AM-11:30 AM

A phase 3, randomized study of pracinostat (PRAN) in combination with azacitidine (AZA) versus placebo in patients ≥18 years with newly diagnosed acute myeloid leukemia (AML) unfit for standard induction chemotherapy (IC). *First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: AML is associated with poor survival rates in patients ineligible for IC or stem cell transplant due to advanced age, comorbidities, and/or disease risk factors. Non-intensive therapies, including the hypomethylating agent AZA, are frequently used in this setting; however, response rates/survival remain dismal. Pre-clinical studies in myeloid malignancies indicate that inhibition of DNA hypermethylation and histone deacetylation induces re-expression of silenced genes in a synergistic fashion. In a Phase 2 study in AML patients ≥65 years not eligible for IC, PRAN, a novel oral histone deacetylase (HDAC) inhibitor, in combination with AZA showed promising efficacy (Garcia Manero, Blood 2016) with a 64% overall response rate and 19.1 months median overall survival. **Methods:** This phase 3, randomized, double-blind study (NCT03151408) is evaluating the efficacy and safety of PRAN plus AZA in patients ≥18 years with newly diagnosed AML unfit to receive IC. Ineligibility for induction CT is based on either 1) age ≥75 years or 2) age < 75 years plus a protocol-defined comorbidity. A total of 500 patients (randomized 1:1 to either PRAN + AZA or placebo + AZA) are planned to be enrolled at ~130 study centers worldwide. Randomization is stratified by cytogenetic risk (intermediate vs. unfavorable-risk) and ECOG Performance Status (0-1 vs. 2). Treatments are administered as 28-day cycles, with PRAN/placebo given orally 3x/week for 3 weeks followed by one week off and AZA administered for 7 days of each cycle. Study treatment is to be continued until disease progression or unacceptable toxicity. A minimum of 6 cycles may be required to achieve a CR. The primary endpoint is overall survival; secondary endpoints include morphologic and cytogenetic CR rates, CR without minimal residual disease and transfusion independence. Overall survival will be tested for superiority of PRAN using the stratified log-rank test at the alpha = 0.025 level of significance (one-sided). Enrollment opened in July 2017. Clinical trial information: NCT03151408.

TPS7079 Poster Session (Board #136a), Mon, 8:00 AM-11:30 AM

Trial in progress: An open-label, multicenter, phase 3b study to assess the safety and efficacy of midostaurin in patients (pts) aged ≥ 18 y with newly diagnosed (ND) *FLT3*-mutated acute myeloid leukemia (AML) who are eligible for 7+3 or 5+2 chemotherapy (chemo). *First Author: Adolfo Fuentes, Novartis Pharmaceuticals Corporation, East Hanover, NJ*

Background: *FLT3* mutations, found in ≈30% of pts with AML, are associated with a poor prognosis. Midostaurin is a multikinase inhibitor that targets FLT3 and other kinases involved in AML pathogenesis. In the phase 3, randomized, placebo-controlled RATIFY trial, midostaurin + chemo significantly improved OS and EFS in adults (aged 18-59 y) with ND *FLT3*-mutated AML. The chemo regimen in RATIFY was 7+3 induction (1-2 cycles of cytarabine [Ara-C] 200 mg/m^2/d on d1-7 + daunorubicin 60 mg/m^2/d on d1-3) and consolidation (≤4 cycles of Ara-C 3000 mg/m^2/d every 12 h on d1, 3, 5). Midostaurin + chemo was approved in the United States and Europe for pts aged ≥18 y with ND *FLT3*-mutated AML. However, many institutions use different chemo regimens as the standard of care (SOC). The aim of this new study is to assess the safety and efficacy of midostaurin 50 mg bid in combination with different SOC chemo regimens and as single-agent maintenance. **Methods:** CPKC412A2408 (NCT03379727) is an open-label, single-arm, multicenter, phase 3b study in adults aged ≥18 y and fit for chemo with ND AML per WHO 2008 classification, ECOG performance status of ≤2, and a documented *FLT3* internal tandem duplication or tyrosine kinase domain mutation (estimated enrollment, 300). Pts must start their first induction chemo cycle with 7+3 (Ara-C 100-200 mg/m^2/d on d1-7 + daunorubicin 60-90 mg/m^2/d or idarubicin 12 mg/m^2/d on d1-3) or 5+2 (a reduced-dose regimen with these agents) per investigator's discretion and enroll by d7 of the first induction cycle. Once pts start on 7+3 or 5+2, they may not switch. Pts will receive consolidation with Ara-C, with dose per investigator's choice. Midostaurin 50 mg bid will be administered on d8-28 of each 28-d induction and consolidation cycle and daily for ≤12 cycles of maintenance. Pts will discontinue the study if not in complete remission (CR) or CR with incomplete hematologic recovery (CRi) at the end of induction or consolidation or if they receive a stem cell transplant. The primary and secondary endpoints are safety and the proportion of pts achieving CR/CRi, respectively. Clinical trial information: NCT03379727.

TPS7081 Poster Session (Board #137a), Mon, 8:00 AM-11:30 AM

Clinical development of asciminib (ABL001) in chronic myeloid leukemia (CML): A randomized phase 3 study vs. bosutinib. *First Author: Michael J. Mauro, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Several tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 ATP-binding site are available to treat CML. However, new options are needed for patients (pts) with resistance/intolerance to these TKIs or who do not achieve treatment goals with them. Asciminib is a novel, potent and specific BCR-ABL1 inhibitor that targets the myristoyl pocket (Wylie, *Nature* 2017). Due to its distinct binding site, asciminib maintains activity against BCR-ABL1 mutants that confer resistance to ATP-binding site TKIs and offers the possibility for combination therapy with these TKIs. It therefore has the potential to address unmet needs in CML, including use in pts for whom ATP-binding site TKIs have failed or for combination with these TKIs in earlier lines, and in Philadelphia chromosome–positive acute lymphoblastic leukemia. In an ongoing phase 1 study in pts with resistance/intolerance to ≥ 2 TKIs (Hughes, *Blood* 2016 [abst 625]), asciminib has been well tolerated; 42% of pts achieved a major molecular response (MMR) by 12 mo with single-agent twice-daily asciminib. A recommended dose for asciminib monotherapy was identified for pts without T315I mutations (40 mg twice daily); in separate cohorts, dosing in select pt groups and combination dosing with ATP-binding site TKIs continues to be evaluated. Now, a phase 2 study of asciminib add-on therapy in pts without a deep molecular response on long-term frontline imatinib is planned, and a randomized phase 3 study of asciminib monotherapy vs bosutinib (an ATP-binding site TKI approved for third-line therapy) in the third or later line is enrolling. Here we describe this ongoing, open-label, phase 3 study (NCT03106779). **Methods:** Pts with CML in chronic phase (planned enrollment, N = 222) are randomized 2:1 to receive asciminib 40 mg twice daily or bosutinib 500 mg once daily. Eligible pts are ≥ 18 y old, previously treated with ≥ 2 TKIs, with failure/intolerance to the previous TKI, and have *BCR-ABL1*^{IS} ≥ 1%. Pts with T315I or V299L mutations are excluded. MMR rate at 24 wk will be compared between arms (primary objective). The 96-wk MMR rate, progression-free and overall survival, safety, tolerability, and asciminib pharmacokinetics will also be evaluated. Clinical trial information: NCT03106779.

TPS7082 Poster Session (Board #137b), Mon, 8:00 AM-11:30 AM

Phase 1b study of venetoclax in combination with azacitidine in patients with treatment-naïve higher-risk myelodysplastic syndromes. *First Author: Chun Yew Fong, Austin Health/Olivia Newton-John Cancer Research & Wellness Centre, Heidelberg, Australia*

Background: Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis leading to cytopenias and potentially transform to acute myeloid leukemia (AML). Treatment (tx) with hypomethylating agents (HMAs) is the standard of care for patients (pts) with tx-naïve higher-risk (HR) MDS who are not candidates for intensive chemotherapy/allogeneic stem cell transplant. Currently, azacitidine (AZA) is the only drug shown to prolong survival in tx-naïve HR MDS. However, ~50% of pts treated with HMA alone do not derive clinical benefit. Venetoclax (VEN) is a potent, orally bioavailable BCL-2-specific inhibitor, VEN plus AZA has demonstrated a tolerable safety profile and promising efficacy in elderly pts with tx-naïve AML (incl. secondary AML) ineligible for intensive chemotherapy. Preclinical data indicate activity of VEN in HR MDS (Jilg, 2016). Thus, the unmet medical need in HR MDS as well as relevant clinical data with VEN in AML provide a rationale for assessing VEN plus AZA in pts with tx-naïve HR MDS. **Methods:** This open-label, Phase 1b dose-escalation study evaluates VEN in combination with AZA for tx-naive HR MDS (NCT02942290) and consists of 2 portions, an initial dose-escalation (~24 pts) and a safety expansion (~20 pts) at the recommended Phase 2 dose (RPTD). Key eligibility criteria are no prior therapy for MDS, an overall International Prognostic Scoring System score of $\geq$1.5 (Int-2 and HR), bone marrow blasts $\geq$5% and $<$ 20%, and ECOG score of $\leq$2. VEN will be administered at starting dose level of 100 mg daily for 14 days/cycle (28 days) and may be escalated up to 400 mg for subsequent dose-level cohorts. AZA will be administered at the standard dose (75 mg/m^2) for 7 days/cycle. Primary study objectives are to assess safety and pharmacokinetics, and to determine the RPTD and dosing schedule of VEN plus AZA. Secondary objectives incl. rates of overall response, hematologic improvement, transfusion independence, and cytogenetic response, as well as duration of response, progression-free survival, overall survival, and time to transformation to AML. Exploratory objectives include patient-reported outcomes and translational biomarkers of response and resistance. Clinical trial information: NCT02942290.

TPS7083 Poster Session (Board #138a), Mon, 8:00 AM-11:30 AM

A phase 2, multicenter, open-label study of the safety and efficacy of luspatercept in subjects with myeloproliferative neoplasm (MPN)-associated myelofibrosis and anemia with or without RBC transfusion dependence. *First Author: Ruben A. Mesa, UT Health San Antonio Cancer Center, San Antonio, TX*

Background: Anemia is an important complication of MPN-associated myelofibrosis. There are few effective therapies other than RBC transfusions, and responses to other therapies are typically brief. Anemia and RBC transfusion dependence are independent adverse prognostic and predictive variables for survival. Luspatercept is a fusion protein consisting of a modified type IIB activin receptor linked to the Fc domain of human IgG1. Luspatercept acts as an erythroid maturation agent by binding specific TGFβ superfamily ligands such as GDF11, blocking their inhibitory effect and leading to increased RBC production. Luspatercept ameliorated anemia in preclinical models and preliminary data have shown it is effective and well tolerated in subjects with lower-risk myelodysplastic syndromes and anemia, with or without RBC transfusion dependence. **Methods:** Eligible subjects have MPN-associated myelofibrosis, are aged $\geq$18 y, and have anemia (hemoglobin $<$ 9.5 g/dL) or RBC transfusion dependence (defined as receiving 2–4 U RBC/28 d averaged over 84 d). There are 3 cohorts: (1) cohort 1: 20 subjects with anemia only, no ruxolitinib received in the past 112 d; (2) cohort 2: 20 subjects with RBC transfusion dependence, no ruxolitinib; and (3) cohort 3: 30 subjects with anemia or RBC transfusion dependence receiving a stable ruxolitinib dose. Luspatercept is given subcutaneously at a starting dose level of 1.0 mg/kg every 3 w for 8 cycles. The primary endpoint is anemia response, defined as a hemoglobin increase of $\geq$1.5 g/dL from baseline or RBC transfusion independence for $\geq$84 d. Responders can continue therapy in an extension phase. Secondary endpoints include time to response, response duration, health-related quality of life, and safety. Response rates with 95% confidence interval will be calculated. The statistical analyses are descriptive. Enrollment began November 2017. Clinical trial information: NCT03194542.

TPS7084 Poster Session (Board #138b), Mon, 8:00 AM-11:30 AM

Clinical activity, safety and tolerability of ASN002, a dual JAK/SYK inhibitor, in patients with non-Hodgkin lymphoma (NHL), myeolfibrosis (MF), chronic lymphocytic leukemia (CLL) and solid tumors. *First Author: Stefan K. Barta, Fox Chase Cancer Center, Philadelphia, PA*

Background: ASN002 is a novel, potent inhibitor of Janus Kinases (JAK) and Spleen Tyrosine Kinase (SYK). Pre-clinical studies indicate that ASN002 has low nM IC50s against SYK and JAK, decreases proliferation in ibrutinib-resistant cell lines, and suppresses tumor growth in rodent xenograft models of NHL and other hematologic malignancies. **Methods:** This Phase 1/2 clinical trial in patients with solid tumors and hematologic malignancies evaluated escalating ASN002 oral doses of 10, 20, 30, 40, 50 and 75 mg BID and 80 and 120 mg QD. Phase 1 allowed patients with solid tumors or hematologic malignancies; Phase 2 allows only patients with mantle cell lymphoma (MCL), myelofibrosis (MF), Peripheral T-cell Lymphoma (PTCL) and Chronic Lymphocytic Leukemia (CLL). Endpoints include safety, tolerability, pharmacokinetics, serum markers of inflammation, and response using Lugano criteria (NHL), IWG-MRT (MF), or IWG-CLL. **Results:** Forty-six patients have enrolled in the study at doses of 10 –75 mg BID and 80-120 mg QD. All patients had multiple prior lines of treatment (range: 2 – 8). ASN002 was well tolerated at doses up to 75 mg BID. The DLT at 100 mg BID was Grade 3 infection. 75 mg BID was the recommended Phase 2 dose. Most drug-related adverse events were Gr 1/2 (e.g. headache, fatigue). Steady-state systemic exposure was high (C_{max}, AUC (0-12h)) and increased in a dose related manner up to 100 mg BID. Robust reduction of inflammatory markers CRP, IL-18, MIP1β, VCAM-1, TNFR2 was observed at all dose levels. Stable disease (9+ months) in a patient with primary peritoneal cancer, about 50% reduction in target lesions at 3 months in a FL patient, stable disease and reduction of pruritus in a PTCL patient after 2 months, and significant disappearance of skin lesions in another PTCL patient after one month were observed. Early improvement in symptoms within 2 weeks of treatment in MF has also been reported in an ongoing patient. Accrual of patients continues. Conclusions: ASN002 was safe and well tolerated. Encouraging preliminary evidence of efficacy in NHL and MF patients was observed. Updated and detailed results will be presented. Clinical trial information: NCT02440685.

7500 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

RELEVANCE: Phase III randomized study of lenalidomide plus rituximab (R^2) versus chemotherapy plus rituximab, followed by rituximab maintenance, in patients with previously untreated follicular lymphoma. *First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immunochemotherapy induction followed by rituximab maintenance is the standard of care in previously untreated symptomatic FL. Phase II studies of chemo-free combination immunotherapy with lenalidomide and rituximab (R^2) show promising activity. **Methods:** RELEVANCE is a global, randomized, phase III trial (NCT01650701) of R^2 vs R-chemo followed by rituximab in previously untreated grade 1-3a FL patients requiring therapy according to GELF criteria. Lenalidomide dose was 20 mg/d, d2-22/28 for 6-12 cycles (c), continued in responders at 10 mg/d for a total of 18 c. Rituximab dose was 375 mg/m^2 weekly c1 and d1 c2-6 and continued in responders for 12 additional c (q8wk). R-chemo was given per investigator's choice of standard R-CHOP, R-bendamustine (R-B), or R-CVP, followed by 12 c of rituximab (q8wk). Co-primary endpoints of CR/CRu at 120 wk and PFS (50% interim analysis by 1999 IWG) are reported here. **Results:** As of 31May2017, 1030 patients with high tumor burden were randomized to R^2 (n = 513) and R-chemo (n = 517; 72% R-CHOP, 23% R-B, 5% R-CVP); baseline characteristics were similar in both groups. At a median follow-up of 37.9 mo, superiority for R^2 over R-chemo was not established for both co-primary endpoints (Table). Toxicity profiles for R^2 vs R-chemo differed, with higher grade 3/4 lab (34% vs 50%) and febrile (2% vs 6%) neutropenia with R-chemo, and higher grade 3/4 cutaneous events (7% vs 1%) with R^2. SPMs were reported in 7% R^2 and 9% R-chemo patients and grade 5 AEs were 1% for both. 69% R^2 and 71% R-chemo patients completed treatment. **Conclusions:** In the first randomized phase III comparison of a chemo-free regimen vs standard R-chemo followed by rituximab maintenance in previously untreated FL, R^2 showed similar efficacy and a different safety profile to R-chemo. Clinical trial information: NCT01650701.

Primary efficacy results of R^2 vs R-chemo in previously untreated FL.

	R^2 (n = 513)	R-chemo (n = 517)	*P* value
CR/CRu at 120 wk			
By IRC	48%	53%	0.13
By Inv	55%	58%	0.38
PFS			
R^2 vs R-chemo: HR (95% CI) by IRC	1.10 (0.85, 1.43)		0.48
R^2 vs R-chemo: HR (95% CI) by Inv	0.94 (0.73, 1.22)		0.63
2 y (IRC/Inv)	84%/84%	87%/83%	—
3 y (IRC/Inv)	77%/77%	78%/78%	—
OS at 3 y	94%	94%	—

7501 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Acalabrutinib in patients (pts) with Waldenström macroglobulinemia (WM). *First Author: Roger Owen, St. James's University Hospital, Leeds, United Kingdom*

Background: Bruton tyrosine kinase (BTK) is a clinically validated target in WM. Acalabrutinib is a highly selective, potent, covalent BTK inhibitor that we evaluated in a Phase 2 study of pts with treatment-naive (TN) or relapsed/refractory (R/R) WM. **Methods:** Pts with TN or R/R WM received 100 mg acalabrutinib BID (or 200 mg QD [n=6], later switched to 100 mg BID) in 28-day cycles until progressive disease (PD) or intolerance. The primary endpoint was investigator-assessed overall response rate (ORR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety and PK. **Results:** One hundred six pts (14 TN and 92 R/R) were treated; median age was 69 y (range 39-90); 94% had ECOG PS $\leq$1; median serum IgM was 3615 mg/dL (range 291-9740). R/R pts had a median of 2 prior therapies (range 1-7). At a 25-mo median follow-up, 7 (50%) TN and 70 (76%) R/R pts remain on treatment. Discontinuations were primarily due to PD (TN 0 pts; R/R 9 pts), adverse events (AEs; TN 3; R/R 3), and investigator decision (TN 2; R/R 4). BTK occupancy and PK parameters were consistent with previous acalabrutinib studies. Efficacy outcomes are listed in the Table. Common AEs (any grade) were headache (39%), diarrhea (31%), contusion (29%), and dizziness (25%). Common Gr 3/4 AEs were neutropenia (16%), pneumonia (7%), anemia, increased ALT, and hyponatremia (each 5%). Atrial fibrillation occurred in 3 pts (1 Gr 3). Bleeding events occurred in 57% of pts (commonly contusion [29%] and epistaxis [13%]); 4 events were Gr 3/4: epistaxis, hematuria, dysfunctional uterine bleeding, and retinal hemorrhage. There were 5 Gr 5 events: pneumonia, glioblastoma multiforme, esophageal carcinoma, myocardial ischemia, and intracranial hematoma. **Conclusions:** Acalabrutinib is a highly effective treatment for WM with durable responses and limited toxicity. Clinical trial information: NCT02180724.

Modified 3rd Intl workshop on WM criteria (Kimby 2006).

	TN (n=14)	R/R (n=92)
ORR (≥ minor response [MR]), n (%)	13 (93)	86 (94)
95% CI	66, 100	86, 98
Major response rate (≥ partial response [PR])	11 (79)	72 (78)
95% CI	49, 95	68, 86
Complete response	0	0
Very good PR	1 (7)	29 (32)
PR	10 (71)	43 (47)
MR	2 (14)	14 (15)
24-mo rate, % (95% CI)		
DOR	90 (47, 99)	84 (73, 90)
PFS	90 (47, 99)	82 (72, 88)
OS	92 (54, 99)	89 (80, 94)

7502 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL). *First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ibr, a first-in-class, once-daily BTK inhibitor, is approved in the US and EU for CLL treatment, including del17p. Early studies support synergistic antitumor activity with combined ibr and ven, a BCL-2 inhibitor approved by FDA for relapsed del17p CLL. Single-agent ibr lead-in may lower tumor lysis syndrome (TLS) risk by debulking prior to adding ven. PCYC-1142 (CAPTIVATE) is a multicenter, phase 2 study of ibr + ven (I+V) in first-line CLL (NCT02910583) evaluating if remission with undetectable minimal residual disease (MRD(-)) after I+V can provide pts treatment holidays. **Methods:** Treatment-naïve pts <70 y with active CLL/SLL by IWCLL criteria receive single-agent ibr (420 mg/d PO) lead-in (3 x 28 d cycles) before initiating ven ramp-up to 400 mg/d PO. MRD (<0.01% by flow) is assessed in peripheral blood (PB) after 6 cycles I+V. MRD and response in bone marrow (BM) are assessed after 12 cycles I+V with planned randomization and intervention based on MRD status. **Results:** 163 pts were enrolled (median 58 y; 14% del17p; 15% del11q; 33% longest lymph node diameter [LDi] ≥5 cm). The first 14 pts enrolled for safety run-in completed ≥6 cycles I+V (median treatment duration, 9.9 mo ibr, 7.2 mo ven). No dose-limiting toxicities occurred during safety run-in; response was seen in 14/14 (CR confirmed in 1/5 early BM; 13/14 PR); PB was MRD(-) in 9/11 assessed pts. 97 pts (including 14 safety run-in pts) completed ibr lead-in plus ≥1 dose of ven (I+V Exposed). AEs in ≥20% of I+V Exposed pts were diarrhea (39%), fatigue (23%), nausea (23%) and arthralgia (21%); grade ≥3 AEs in ≥3% were neutropenia (10%), hypertension (3%) and thrombocytopenia (3%). No clinical TLS occurred; lab TLS was seen in 1/163 pts. In I+V Exposed pts with baseline LDi ≥5 cm, LDi decreased to <5 cm in 19/30 pts (63%) after ibr lead-in. TLS risk shifted from high to medium/low in 17/22 pts (77%); overall, proportion of high-risk TLS decreased from 23% at baseline to 3% after ibr lead-in. **Conclusions:** Early data show promising activity of I+V oral regimen with MRD(-) response in 82% in first-line CLL. Safety was consistent with AE profiles of single-agent ibr or ven. The protocol-specified efficacy analysis in the first 30 pts will be presented. Clinical trial information: NCT02910583.

7503 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Randomized phase III study comparing an early PET driven treatment de-escalation to a not PET-monitored strategy in patients with advanced stages Hodgkin lymphoma: Final analysis of the AHL2011 LYSA study. *First Author: Olivier Casasnovas, CHU Le Bocage Service d'Hématologie Clinique, Dijon, France*

Background: Escalated BEACOPP (BEA) improves PFS but not OS in pts with advanced HL compared to ABVD and is associated to a higher risk of hematological toxicity, secondary leukemia and infertility. PET performed after 2 cycles of BEA (PET2) might identify a population with a better outcome suitable for de-escalation treatment without impairing the disease control. **Methods:** AHL 2011 (NCT01358747) was designed to evaluate in 16 to 60 y HL pts with stage III, IV or high risk IIB, a treatment strategy driven by PET after 2 BEA cycles, delivering 4 cycles of ABVD for PET2 negative pts and 4 cycles of BEA for PET2 positive pts. This PET driven strategy (arm B) was randomly compared to a standard treatment delivering 6 cycles of BEA (arm A). The allocation of treatment in the experimental arm was based on the central review of PET2 interpreted according to Deauville criteria. PFS was the primary endpoint with a hypothesis of non-inferiority of the PET driven arm compared to the standard arm. **Results:** 823 pts were registered including 413 and 410 pts in the arms A and B respectively. Pts characteristics were well balanced in both arms. PET2 positivity rate was similar in arms A (12%) and B (13%). Based on PET2 results, 346 (84%) pts received 4 cycles of ABVD and 51 (12%) 4 additional cycles of BEA in the experimental arm. The treatment toxicity was significantly higher in pts receiving 6 cycles of BEA compared to those who received 2 cycles of BEA + 4 cycles of ABVD with more frequent grade ≥3 AE (anemia (11% vs 2%), leukopenia (85% vs 74%), thrombocytopenia (44% vs 15%), and sepsis (7% vs 3%)) and SAE (45% vs 28% ($p < 10^{-4}$). With a median follow up of 50 months, the 5y-PFS was similar in the standard (86.2%) and the PET driven arms (85.7%; p = 0.68). PET2 positivity was related to a significantly lower 5y-PFS compared to PET2 negative pts (70.7% vs 88.9%; $p < 0.0001$). OS was similar in both arms. **Conclusions:** PET performed after 2 cycles of BEA can be safely used to guide subsequent treatment and supports the response-adapted strategy delivering ABVD for pts with negative PET2 reducing the treatment-related immediate toxicity without impairing the disease control. Clinical trial information: NCT01358747.

7504 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Activity and tolerabilty of the first-in-class anti-CD47 antibody Hu5F9-G4 with rituximab tolerated in relapsed/refractory non-Hodgkin lymphoma: Initial phase 1b/2 results. *First Author: Ranjana H. Advani, Stanford Cancer Institute, Stanford, CA*

Background: Targeted non-cytotoxic therapies are needed in relapsed/refractory (r/r) NHL. Hu5F9-G4 (5F9) is a first-in-class humanized antibody targeting CD47, a protective "don't eat me" signal on cancers, that stimulates tumor cell phagocytosis and an anti-tumor T cell response. Preclinically, 5F9 synergizes with rituximab to eliminate lymphoma by enhancing Fc receptor-mediated antibody-dependent cellular phagocytosis. This trial is the first to explore clinical activity of an anti-CD47 antibody+ rituximab. **Methods:** This Phase 1b/2 enrolled r/r NHL patients in a 3+3 dose escalation design (NCT02953509). A 1 mg/kg 5F9 priming dose with higher weekly maintenance doses was used to mitigate on-target toxicities, specifically anemia. Maintenance doses were escalated from 10 to 30 mg/kg with standard dose rituximab. **Results:** 22 heavily pre-treated patients with r/r DLBCL (n = 15) and FL (n = 7) were enrolled in Phase 1b. Patients had a median of 4 prior therapies (range 2-9), 90% were rituximab-refractory. 5F9+ rituximab was well-tolerated. Common treatment-related AEs were chills (41%), headache (36%), anemia (32%), and fever (27%). All were grade 1-2 except 3 G3 AEs (chills, fever, anemia). Prime/maintenance 5F9 dosing significantly mitigated on-target anemia, a mostly first dose effect with spontaneous recovery. Only 2 patients required a one-time transfusion. The MTD was not reached up to 30 mg/kg weekly of 5F9 dosing. > 90% CD47 receptor occupancy was achieved on peripheral blood cells, showing high target saturation. A Phase 2 dose of 30 mg/kg 5F9 Q2 weeks after cycle 1 was selected. Across all doses, the ORR was 50%, 32% achieved CR. %ORR/CR was 40/27 in DLBCL and 71/43 in FL, respectively. As of 1/16/2018, 90% of responding patients continued in response (4.4 month median follow up), including 1 patient for 13+ months. **Conclusions:** 5F9 + rituximab is a novel immunotherapy that inhibits a key macrophage/cancer checkpoint. It is well tolerated with no MTD reached and has promising clinical activity in rituximab-refractory DLBCL and FL patients including multiple CRs. Phase 2 cohorts are ongoing in indolent lymphoma and DLBCL Clinical trial information: NCT02953509.

7505 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL. *First Author: Jeremy S. Abramson, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Lisocabtagene maraleucel (liso-cel; JCAR017) is a CD19-directed 4-1BB CAR T cell product administered in defined composition at a precise dose of CD8 and CD4 CAR T cells. A multicenter seamless design pivotal phase 1 trial of liso-cel in R/R B-NHL (NCT02631044) has enrolled; long-term follow up of the nonpivotal cohort will be presented here. **Methods:** Pts with R/R DLBCL, PMBCL, FL3B, or MCL and adequate organ function are eligible. Treatment includes lymphodepletion with fludarabine and cyclophosphamide, followed by liso-cel. Multiple dose levels (DLs) and administration schedules were evaluated; DL2 (10^8 CAR T cells) was chosen for the pivotal cohort. The nonpivotal FULL dataset includes all pts in the DLBCL cohort (DLBCL NOS, PMBCL, FL3B) treated with liso-cel at all DLs; CORE dataset includes only pts meeting inclusion criteria for the pivotal cohort, including DLBCL NOS (de novo or transformed from FL) and high grade lymphoma. Study objectives include safety, PK, and antitumor response. **Results:** As of Oct 9, 2017, 91 pts were treated and evaluable for safety, 88 for efficacy. Pt characteristics were previously reported (Abramson ASH 2017). CRS was seen in 35% of pts; a single pt (1%) developed grade 3-4 CRS. Neurotoxicity (NT) developed in 19% of pts including 12% grade 3-4; all but one event resolved at time of data snapshot. Median onset of CRS and NT was 5 and 10 days respectively. Nineteen pts (21%) received tocilizumab and/or dexamethasone. Long term safety, including B cell aplasia, infections, and cytopenias, will be reported. Best ORR in FULL and CORE was 74% (65/88) and 80% (52/65), respectively; best CR was 52% (46/88) in FULL and 55% (36/65) in CORE. A higher rate of durable response at DL2 was observed in the CORE population, with 6-month ORR and CR of 50% and 50% (7/14) vs 40% (8/20) and 30% (6/20) at DL1. Long term efficacy, including 6-/12-month follow up from ~95/~55 pts, will be reported. **Conclusions:** Liso-cel shows durable responses in pts with heavily pretreated R/R DLBCL and trends toward more durable responses at DL2. Observed acute toxicities have been manageable at all DLs tested and long-term safety from the nonpivotal cohort will be reported. Clinical trial information: NCT02631044.

7507 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR) in relapsed/refractory (r/r) FL and DLBCL. *First Author: Laurie Helen Sehn, BC Cancer Agency, Vancouver, BC, Canada*

Background: Pola is an antibody-drug conjugate targeting CD79b+ cells in B-NHL. Early results led to FDA breakthrough therapy status and EMA PRIME designation. We now report combined results for safety and efficacy from the randomized r/r FL and DLBCL cohorts of a phase 1b/2 study (ClinicalTrials.gov NCT02257567). **Methods:** 80 FL and 80 DLBCL transplant-ineligible patients (pts) were randomized 1:1 to pola 1.8 mg/kg + BR (B: 90mg/m^2 x 2 days; R: 375mg/m^2) or BR for 6 cycles (q28 days FL, q21 days DLBCL). Primary endpoint: PET-CR, 6–8 weeks after treatment end, by independent review committee (IRC) using modified Lugano criteria. **Results:** For FL pts (pola+BR *v* BR), median age was 65 *v* 63 years, both arms had median 2 prior therapies, 41% *v* 42% were refractory to last therapy, and 64% *v* 37% had FLIPI 3–5. At 24 Oct 17, median follow up was 15 months. DLBCL characteristics and follow up were previously described (Sehn, ASH 2017). The most common grade 3–5 AEs higher in pola+BR *v* BR were cytopenias, febrile neutropenia, and infections. SAEs higher in pola+BR *v* BR were febrile neutropenia (FL, DLBCL) and infection (FL). Grade 5 AE rates were similar between treatment arms: 5% (FL) and 18% (DLBCL). PET-CR and PFS were similar between FL arms. In DLBCL, pola+BR showed significantly higher PET-CR rates (p = 0.012) and longer median (m) PFS (p < 0.0001) and mOS (p = 0.0008) (Table). In DLBCL, longer PFS and OS were seen for pola+BR in 2nd-line (2L), 3rd-line plus (3L+), relapsed, and refractory pts. mPFS (pola+BR *v* BR [months]): 2L (11.1 *v* 3.7), 3L+ (6.0 *v* 2.0), relapsed (11.1 *v* 5.1), refractory (6.0 *v* 1.9). mOS: 2L (not reached [NR] *v* 5.9), 3L+ (11.5 *v* 3.8), relapsed (NR, NR), refractory (11.5 *v* 3.8). **Conclusions:** The toxicity of pola+BR was manageable. In FL, pola+BR did not improve PET-CR rate; longer follow up is necessary to assess survival. In contrast, in DLBCL, pola+BR led to significantly higher PET-CR rates and notably longer PFS and OS *v* BR regardless of prior treatment status. Clinical trial information: NCT02257567.

Efficacy (ITT).

	FL		DLBCL	
	Pola+BR (N = 39)	BR (N = 41)	Pola+BR (N = 40)	BR (N = 40)
IRC PET-CR, %	69	63	40	15
Median PFS, months (95% CI)	17 (13.4, NR)	17.3 (12.5, NR)	6.7 (4.9, 11.1)	2 (1.5, 3.7)
Median OS, months (95%CI)	NR	NR	11.8 (9.5, NR)	4.7 (3.7, 8.3)

7508 Oral Abstract Session, Sun, 9:45 AM-12:45 PM

High, durable minimal residual disease negativity (MRD–) with venetoclax + rituximab (VenR) in relapsed/refractory (R/R) CLL: MRD kinetics from phase 3 MURANO study. *First Author: Peter Hillmen, St James's University Hospital, Leeds, United Kingdom*

Background: Survival with chemoimmunotherapy is associated with MRD–, but the importance of MRD with targeted agents and in R/R setting remains unclear, mostly due to low MRD– rates. In MURANO, VenR showed superior PFS (hazard ratio 0.17) and peripheral blood (PB) and bone marrow (BM) MRD– vs bendamustine + R (BR) in R/R CLL pts. We now report MRD kinetics. **Methods:** Pts randomized to VenR for 6 mo. followed by single-agent Ven ≤1.5 y, or BR for 6 mo. PB samples serially collected and BM at end of combination treatment (EOCT; Mo. 9) or at best response; MRD analyzed centrally by ASO-PCR and/or flow cytometry; MRD–: < 1 CLL cell/10^4 leukocytes. **Results:** Higher concordance in MRD– between BM and PB in VenR (45/50 [90%]) vs BR (3/10 [30%]) in pts with paired samples. Thus, we focus on PB MRD and outcome. Best MRD– rates were higher with VenR (84% vs 23% in BR), and were independent of high-risk factors only for VenR: del(17p), IGVH unmutated and mutated TP53 (present vs non-present: 83% vs 87%, 82% vs mutated 89% and 73% vs unmutated 88% respectively). PB MRD kinetics for VenR are shown in Table. Among 121/194 (62%) pts on VenR and MRD– at EOCT: 100 (83%) maintained MRD– and were PFS free at median follow-up (f/u) of 13.8 (5.6–23.0) mo.; 2 developed PD; 2 died (unrelated); 2 developed Richter's (with one MRD+ directly before); and 15 (12%) converted to confirmed MRD+ (2 serial assay positive) at median MRD+ f/u of 5.6 (0.03–11.2) mo. (1 MRD ≥10^{-2} with PD, 14 MRD 10^{-4}– < 10^{-2} with 2 PD, 1 death and 11 PFS free). MRD kinetics by arm will be presented graphically. **Conclusions:** Robust PB MRD and high concordance with BM MRD with VenR confirms value of PB MRD for correlation with clinical outcome. VenR achieves high, early, deep, durable PB MRD–regardless of risk features, unlike BR. Some reemergence of MRD+, mainly intermediate level, is seen only in a small number of pts, and may not lead to clinical PD, consistent with PFS benefit observed. Clinical trial information: NCT02005471.

VenR MRD kinetics.

	Assessment timepoint, mo.				
N = 194, %	4*	9†	12	15	18
Negative: < 10^{-4}	45	62	60	57	60
Positive					
Intermediate: 10^{-4}– < 10^{-2}	25	19	16	10	18
≥10^{-2}	6	5	4	4	5
Assay failure	2	1	1	10	1
Missing or progressive disease/death/withdrew	22	13	19	19	16

*1st assessment †EOCT

7509 Poster Discussion Session; Displayed in Poster Session (Board #146), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Romidepsin activity in T follicular helper(TFH)-phenotype PTCL versus non TFH treated on the same clinical trials. *First Author: Paola Ghione, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Histone-deacetylase inhibitors are active agents for peripheral T-cell lymphomas (PTCL). Anecdotally, angioimmunoblastic T-cell lymphoma (AITL) may respond better to romidepsin than PTCL-NOS. The cell of origin of AITL and a subset of PTCL-NOS are understood to originate from a follicular helper T-cell (TFH). We characterized PTCL-NOS in terms of TFH phenotype and analyzed responses to romidepsin in AITL, TFH-PTCL, and non-TFH-PTCL. **Methods:** We analyzed 41 patients with PTCL treated with romidepsin alone or in combinations at MSKCC between 7/2012 to 1/2018. We re-reviewed the pathology of all PTCL-NOS to identify TFH-PTCL. We estimated survival with Kaplan-Meier method and differences in survival with Log-Rank. Differences between groups were estimated with Mann Whitney and Fisher's Exact tests. **Results:** Patients characteristics are in the table. Median FU was 43.6 months. Patients received romidepsin after at least one line of prior therapy (range 1-5) as single agent in 21 (11 TFH, 10 non-TFH), or combination in 20 (13 TFH, 7 non-TFH) with duvelisib, lenalidomide or lenalidomide+carfilzomib. Three PTCL-NOS were TFH, 2 PTCL-NOS were re-classified as AITL. Romidepsin therapies had 58% ORR in TFH compared to 30% in non-TFH (p = 0.11). Median time-to-progression was 6 months for TFH vs 2months for non-TFH (p = 0.0046, HR 0.31, 95% CI 0.14–0.70). Six patients sufficiently responded to romidepsin to proceed to alloSCT (5 TFH, 1 non-TFH). **Conclusions:** Our results suggest that romidepsin, and combinations, may have superior activity in TFH-PTCL compared to non-TFH. If this observation is confirmed in prospective studies, it could help in the development of subtype-specific PTCL therapy.

	TFH(n = 24)		Non TFH(n = 17)		p
Gender (M/F)	10 (42%)/14 (58%)		4 (23%)/13 (77%)		0.32
Age	67 years (36–75)		58 years (32–83)		0.21
Median prior therapies	1 (1-5)		1 (1-5)		NS
Median time-from-diagnosis, months	8 (3-38)		9 (3-67)		0.91
Ann Arbor					
I-II	4 (16%)		2 (12%)		0.99
III-IV	20 (84%)		15 (88%)		
IPI at romidepsin start					
0-2	9 (37%)		7 (41%)		> 0.99
3-5	15 (63%)		10 (59%)		
Response	ORR	CR	ORR	CR	
Overall	14 (58%)	7 (29%)	5 (30%)	2 (12%)	0.11
Single agent (n = 21)	4 (36%)	1 (9%)	1 (10%)	1 (10%)	0.31
Combinations (n = 20)	10 (77%)	6 (46%)	4 (57%)	1 (14%)	0.61

7510 Poster Discussion Session; Displayed in Poster Session (Board #147), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Tenalisib, a dual PI3K δ/γ inhibitor: Safety and efficacy results from an on-going phase I/Ib study in relapsed/refractory T-cell lymphoma. *First Author: Yasuhiro Oki, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Tenalisib is a novel, next generation, highly specific, dual equi-potent PI3K δ/γ inhibitor. Early results demonstrated an acceptable safety profile with encouraging clinical activity in relapsed/refractory TCL (NCT02567656). **Methods:** An open-label, Phase 1/1b study consists of dose escalation cohorts followed by two expansion cohorts enrolling patients with peripheral TCL (PTCL) and with cutaneous TCL (CTCL). The primary objective is to determine the MTD, and to describe the safety and pharmacokinetic profiles. The secondary objectives are assessment of the overall response rate (ORR) and duration of response (DoR). Responses were evaluated for PTCL and CTCL based on IWG criteria (Cheson 2007) and the mSWAT respectively. **Results:** As of January 10, 2018, a total of 55 patients (27 PTCL and 28 CTCL) have been enrolled. 19 patients across dose escalation (200 mg - 800 mg BID) and 36 patients in dose expansion (at MTD, 800 mg BID Fasting) were enrolled and the results presented are the pooled data across both parts. At the time of analysis, safety assessment of 55 patients receiving at least one dose of Tenalisib demonstrated an acceptable safety profile. The most common drug related AEs were transaminitis, diarrhea, and fatigue. Related Grade ≥ 3 AE (≥ 5%) includes transaminitis (20%) and rash (5%). These events were reversible and managed by withholding study drug. Seven of 14 patients who had transaminitis were treated with steroids and only one patient discontinued therapy due to a drug related transaminitis. Drug related SAEs were pyrexia, elevated INR, sepsis, and diplopia secondary to neuropathy. Efficacy assessments of the 32 evaluable patients receiving at least two cycles of tenalisib showed an ORR of 47% (15/32, 3 CR, 12 PR and 10 SD). Indication specific analysis showed an ORR of 50% (7/14, 3 CR, 4 PR) in PTCL and 44% (8/18, 8 PR) in CTCL. Twelve patients discontinued treatment due to a rapid progression before the first efficacy assessment. **Conclusions:** Tenalisib shows acceptable safety and encouraging clinical activity in relapsed/refractory TCL. Recruitment in the expansion cohort is close to completion. Clinical trial information: NCT02567656.

7511 Poster Discussion Session; Displayed in Poster Session (Board #148), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

The dual SYK/JAK inhibitor cerdulatinib demonstrates rapid tumor responses in a phase 2 study in patients with relapsed/refractory B- and T-cell non-Hodgkin lymphoma (NHL). *First Author: Paul A. Hamlin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cerdulatinib is a selective, potent inhibitor of SYK, JAK1, JAK3, and TYK2. Preclinical and clinical data suggest that combined SYK/JAK inhibition may have activity in B- and T-cell NHL. SYK is a key regulator of BCR signalling (upstream of BTK and PI3K), and is also expressed in T-cell lymphomas. Preclinical studies suggest it may be an oncogenic driver in PTCL. Frequent activating JAK/STAT mutations are observed in B and T cell NHL. A phase 1 dose escalation study of cerdulatinib in 43 patients with r/r CLL and NHL was completed in 2016. Complete inhibition of SYK and JAK was well tolerated and consistent antitumor activity was seen in CLL and FL. **Methods:** This phase 2a study intended to confirm the safety and efficacy of cerdulatinib dosed 30 mg orally BID in patients with r/r B- and T-cell lymphoma. Dose reductions were permitted to a minimum of 15mg BID. Response was assessed by Lugano Classification criteria. **Results:** 99 patients enrolled (FL: 36, CLL/SLL: 28, PTCL: 18, marginal zone lymphoma: 8, aggressive: 5, Waldenstrom's macroglobulinemia: 4). Median age is 68 (42-93) and median # of prior therapies is 3 (1–13). 30 patients had prior BTK, PI3K or BCL-2 inhibitor therapy. The most common AEs of any grade are diarrhea (42%), fatigue (36%), and nausea (32%). Grade 3+ AEs occurring in ≥5% patients are neutropenia (18%), lipase increase (15%), pneumonia (12%), diarrhea (10%), and fatigue (7%). 5 patients have had Grade 5 infections considered related to study drug (3 of 5 in the CLL cohort). The target PK range has been achieved with an average SSCmin of ~0.8 μM. Broad activity seen: 61% ORR in CLL/SLL, 50% in FL, and 43% in PTCL (4 CRs, 2 PRs in 14 patients). The first PTCL patient achieved a CR and is on drug at 11 months. Responses typically occurred after 2 cycles of treatment. Durable PRs have occurred in patients who relapsed on BTK inhibitor (CLL, 5+ months, WM, 7+ months, FL, 12 months), venetoclax (SLL, 18+ months), and tenalisib (PTCL, 3+ months) therapy. Updated PK/PD, safety and efficacy will be presented. **Conclusions:** The cerdulatinib phase 2 dose of 30 mg BID demonstrates good tolerability and efficacy in heavily pre-treated r/r B and T cell NHL. Clinical trial information: NCT01994382.

7512 Poster Discussion Session; Displayed in Poster Session (Board #149), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Durability of response to venetoclax (VEN) in patients with CLL relapsed/refractory to ibrutinib and/or idelalisib. *First Author: John C. Byrd, The Ohio State University, Division of Hematology, Columbus, OH*

Background: Therapies are urgently needed for patients (pts) with CLL relapsed/refractory (R/R) to BCRi. We report outcomes for the full trial population from an ongoing phase 2 trial with VEN monotherapy, including the impact on detectable minimal residual disease (MRD). **Methods:** Pts with CLL R/R to ibrutinib and/or idelalisib received 400 mg daily VEN after initial dose ramp up. Results are from a data cut on 28Nov2017. **Results:** Pts (N = 127) had received a median of 4 prior therapies (1 – 15). Del(17p) was noted in 40% (50/126) and 28% (34/122) of pts had mutated *TP53*. After a median of 17 (.1 – 36) months on VEN, the best overall response rate was 66% (84/127; CR/CRi – 10%, nPR/PR – 56%) per investigators (INV) and 70% (89/127) by independent review committee (IRC). Per INV (median follow up, 16 [.03 – 33] months), estimated median progression-free survival (PFS) was 25 months (18-month rate, 66%); neither median duration of response (18-month rate: 75%) nor median overall survival (18-month rate: 88%) was reached. 36/77 pts assessed (47%; 28% [36/127] by intent to treat) had undetectable blood MRD, 9/26 assessed were also undetectable in marrow (2 CR/CRi, 7 PR). Median PFS was longer for pts with undetectable MRD in blood vs positive (not reached vs 21.9 months; HR, .148 [.04 – .49], p= .0019). 64 pts discontinued VEN, most commonly for CLL progression (n = 35; median time, 10 months [.1 – 29]), AEs (n = 8), and Richter's transformation (n = 6; median time, 13 months [4 – 19]). Common any-grade AEs were GI AEs (diarrhea [50%], nausea [49%]) and cytopenias (anemia [43%], neutropenia [41%], thrombocytopenia [28%], decreased white blood cell count [28%]). **Conclusions:** Based on longer follow up, VEN monotherapy demonstrates robust activity, with good tolerability in pts with CLL R/R to ibrutinib and/or idelalisib. Though most pts achieved PR, outcomes appear durable with undetectable MRD. Clinical trial information: NCT02141282.

	Last prior BCRi					
	Ibrutinib n = 91		Idelalisib n = 36		N = 127	
n (%)	INV	IRC	INV	IRC	INV	IRC
ORR	59 (65)	64 (70)	25 (69)	25 (69)	84 (66)	89 (70)
CR	5 (6)	0	2 (6)	0	7 (6)	0
CRi	4 (4)	1 (1)	2 (6)	0	6 (5)	1 (1)
nPR	3 (3)	0	0	0	3 (3)	0
PR	47 (52)	63 (69)	21 (58)	25 (69)	68 (54)	88 (69)
SD	21 (23)	27 (30)	9 (25)	11 (31)	30 (24)	38 (30)
PD	5 (6)		2 (6)		7 (6)	
Early discontinuation	6 (7)		0		6 (5)	

7513 Poster Discussion Session; Displayed in Poster Session (Board #150), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Comparison of different phase II studies using sequential combinations of targeted agents for treating chronic lymphocytic leukemia. *First Author: Von Tresckow Julia, Department I of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany*

Background: The German CLL study group (GCLLSG) performed three similar phase-II-trials combining a CD20-antibody, ofatumumab (O) or obinutuzumab (G, for GA-101), with ibrutinib (I) or venetoclax (A) in an all-comer population of treatment-naïve or relapsed/refractory CLL patients (pts). **Methods:** In all 3 trials, pts with high tumor burden received optional bendamustine debulking (BD). Subsequent induction therapy consisted of 6 cycles of I plus O (BIO trial), or I plus G (BIG) or A plus G (BAG). Induction therapy was followed by a maintenance phase using the same drugs until achieving a minimal residual disease (MRD) negative complete remission or up to 24 months. The primary endpoint was the overall response rate (ORR) at the end of induction; secondary endpoints were MRD and safety. **Results:** 66 pts each were enrolled in the 3 trials. Pts with < 2 induction cycles were excluded from the analysis as per protocol, resulting in 65, 61 and 63 evaluable pts in BIO, BIG and BAG, respectively. The primary endpoint was met in all trials. BD achieved an ORR of 61 % across all trials. During combination therapy one fatal adverse event occurred in each trial; during induction 46 SAEs occurred in BIO, 29 in BIG and 59 in BAG. Patients characteristics and major results are shown in the Table. **Conclusions:** The sequential combination concept shows very good efficacy and tolerability. BD reduced the number of IRR. Combination therapies with G seemed more efficient when compared to O. Additionally, combining A plus G seemed to evoke deeper responses than I plus G. Clinical trial information: NCT02689141, NCT02401503 and NCT02345863.

	BIO	BIG	BAG
Patients (N)	65	61	63
Median age (years)	61	66	59
Prior therapies (median)	1.5	1.0	2.0
TP53 mutations or del(17p)	21 (32%)	13 (21%)	17 (28%)
CLL-IPI high or very high risk	42 (67%)	41 (67%)	38 (63%)
Response			
ORR	60 (92%)	61 (100%)	60 (95%)
Complete remission (CR)	0	0	5 (8%)
Clinical CR or CR with incomplete recovery of the marrow	20 (31%)	28 (46%)	20 (32%)
MRD negative (< 10-4) after induction	9 (14%)	29 (48%)	55 (87%)
Infusion related reactions during induction (CTC gr. 1 4)			
with BD	17 (33%)	13 (29%)	13 (28%)
without BD	8 (57%)	10 (59%)	7 (37%)
Tumor lysis syndrome during induction (CTC gr. 1 4)			
with BD	0	1 (2%)	1 (2%)
without BD	0	0	1 (5%)

7514 Poster Discussion Session; Displayed in Poster Session (Board #151), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Depth of response and progression free survival in CLL patients on ibrutinib. *First Author: Audrey Sigmund, The Ohio State University, Department of Internal Medicine, Columbus, OH*

Background: While it has been established that attainment of a complete response (CR) after chemoimmunotherapy improves progression free survival (PFS), this has not been proven with the BTK inhibitor ibrutinib (IB). Most patients (pts) receiving IB achieve a partial response (PR) at best, and multiple trials have focused on deepening responses. Here we investigate the association of depth of response at one year and PFS in CLL pts on IB. **Methods:** This was a retrospective study of pts with CLL enrolled in 4 sequential clinical trials of IB as a single agent or in combination with ofatumumab at the Ohio State University. Response was evaluated by two independent investigators using International Workshop on CLL 2008 guidelines if bone marrow was available; if no marrow was available, clinical response was used. A landmark analysis was performed at response assessment at 12 +/- 2 months. PFS was calculated from this response assessment to progression or death. The method of Kaplan-Meier and Cox models were used to estimate PFS. **Results:** The cohort was comprised of 237 pts enrolled between July 19, 2010 and March 24, 2014 with median number of prior therapies 3 (range 0-13). Median age was 65; 82% IGVH unmutated, 36% with del(17p), and 54% with complex karyotype. At month 12 assessment, 5% of pts had CR, 3% CR with incomplete marrow recovery (CRi), 77% PR, 12% PR with lymphocytosis, and 3% stable disease. With a median follow-up of 48 months, the median PFS was 52 months (95% CI: 42-70) with no significant difference among response groups (p = 0.23). However, PR pts with lymph nodes (LN) ≥3cm had significantly higher risk of progression than pts with LN < 3cm (median PFS 42 vs. 68 months; hazard ratio = 1.6, p = 0.03 from multivariable model). **Conclusions:** There was no significant difference in PFS between CR and other response groups. However, a significant difference was found in PR pts with LN ≥3cm vs. LN < 3cm. This suggests that, unlike with chemoimmunotherapy, attainment of a CR with IB is not critical, however, those patients with significantly enlarged nodes after 1 year of therapy have shorter PFS. Combination therapy studies without the goal of therapy discontinuation may focus on elimination of bulky nodal disease rather than attainment of CR for all patients.

7515 Poster Discussion Session; Displayed in Poster Session (Board #152), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Two years rituximab maintenance vs. observation after first line treatment with bendamustine plus rituximab (B-R) in patients with marginal zone lymphoma (MZL): Results of a prospective, randomized, multicenter phase 2 study (the StiL NHL7-2008 MAINTAIN trial). *First Author: Mathias J. Rummel, Department of Haematology and Oncology, Justus-Liebig Universität, Giessen, Germany*

Background: Rituximab (R) maintenance is part of a standard treatment for follicular lymphoma. In MZL, however, it is not yet common practice. In this study we compared the effect of 2 years of R maintenance vs. observation after first-line treatment with B-R in patients with previously untreated MZL. **Methods:** Patients had stage II (bulky disease > 7 cm), III, or IV disease. Nodal and splenic MZL were included but not MALT lymphomas. Primary endpoint was progression free survival (PFS). Secondary endpoints included response rates, overall survival (OS), and toxicity. For induction patients were treated with up to 6 cycles of B-R plus 2 additional R cycles. Only patients responding to B-R were then randomized to either R maintenance (q 2 months for 2 years) or observation. **Results:** Median time of follow-up after registration was 76 months at the time of this analysis (February 2018). 119 patients with a median age of 65 years were evaluable for response. 108 (91%) responded to B-R induction, with 23 patients (19%) achieving a complete remission. Of 104 randomized patients, 53 (51%) were randomized to R maintenance and 51 (49%) to observation. Median age of randomized patients was 64 years, patient characteristics and toxicity were similar for both groups. PFS was superior for 2 years of R maintenance, with the median not yet reached vs. 92.2 months for observation (hazard ratio (HR) 0.35, 95% CI 0.17 – 0.76, p = 0.008). The OS rate at 6 years was 92% for R maintenance vs. 86% for observation. The difference in OS was not statistically significant (HR 0.52, 95% CI = 0.20 – 1.39). **Conclusions:** Our results demonstrate a statistically significant PFS improvement of a 2-year R-maintenance vs. observation after B-R induction in patients with MZL. Clinical trial information: NCT00877214.

7516 Poster Discussion Session; Displayed in Poster Session (Board #153), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Response rate to lenalidomide plus rituximab (R^2) as independent of number of prior lines of therapy: Interim analysis of initial phase of MAGNIFY phase IIIb study of R2 followed by maintenance in relapsed/refractory indolent NHL. *First Author: David Andorsky, Rocky Mountain Cancer Centers, US Oncology Research, Boulder, CO*

Background: In the relapsed/refractory (R/R) setting for indolent non-Hodgkin lymphoma (iNHL), duration of response (DOR) to and types of prior therapy are important factors in predicting outcomes to subsequent therapy. Lenalidomide plus rituximab (R^2) has shown promising efficacy and tolerability in multiple NHL studies. This report explores the association between prior number of therapies and response to R^2. **Methods:** MAGNIFY (NCT01996865) is a phase IIIb, multicenter, global study of R/R NHL patients, including follicular lymphoma (FL) grade 1-3a and marginal zone lymphoma (MZL). Patients receive 12 cycles of R^2 (lenalidomide 20 mg/d, d1-21/28 + standard rituximab). Patients with stable disease or better are then randomized 1:1 to maintenance with R^2 vs rituximab alone. This analysis focuses on the initial period before randomization (12 cycles R^2) for patients with <2 (<2L) vs ≥2 lines (≥2L) of prior systemic anti-lymphoma therapies. **Results:** As of May 1, 2017, 232 patients with FL gr1-3a (n = 186) and MZL (n = 46) were enrolled for the initial treatment period. Overall, median age was 66 years (range 35-91) and 89% were stage III/IV. Patients received a median of 2 prior systemic treatments (31% ≥3) and 97% received prior rituximab-containing regimens. Analyzed subgroups included 43% <2L (n = 99) and 57% ≥2L (n = 133) with generally similar baseline characteristics. In efficacy-evaluable patients, the overall response rates (70% and 66%) and complete response (51% and 36%) were similar in <2L and ≥2L patients. Median time to response was 2.8 months (range, 2-12) for both groups. For <2L and ≥2L groups, 1-year rates for PFS were 68% and 70%, and DOR were 77% and 81%, respectively. The most common grade ≥3 treatment-emergent adverse events for <2L and ≥2L patients, respectively, were neutropenia (29%; 37%), thrombocytopenia (10%; 6%), and leukopenia (4%; 7%). **Conclusions:** R^2 therapy showed favorable activity and tolerable safety profiles in patients who had R/R FL and MZL, regardless of the number of prior anti-lymphoma therapies. Enrollment in MAGNIFY is ongoing. Clinical trial information: NCT01996865.

7517 Poster Discussion Session; Displayed in Poster Session (Board #154), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Role of ofatumumab (OFA) maintenance treatment in relapsed chronic lymphocytic leukemia (CLL): Final analysis of PROLONG study. *First Author: Marinus Van Oers, Department of Hematology, Academic Medical Center, Amsterdam, the Netherlands, on behalf of the HOVON CLL Working Group, Amsterdam, Netherlands*

Background: An interim analysis of the PROLONG phase 3 study in patients (pts) with CLL showed a significant increase in progression free survival (PFS) with OFA maintenance without unexpected side effects (van Oers, et al, 2015). Here, we present the final analysis of the study. **Methods:** Pts in complete or partial remission after 2nd or 3rd line treatment for CLL were randomized 1:1 to OFA (300 mg followed 1 week later by 1000 mg every 8 weeks for up to 2 years) or to observation (Obs) arm. The primary endpoint was investigator-assessed PFS. Secondary endpoints included time to next treatment (TTNT), overall survival (OS), and safety. **Results:** Overall, 480 pts were randomized to either OFA arm or Obs arm. Baseline characteristics were similar between the 2 arms. Median duration of OFA treatment was 608 days. Median follow-up was 40.89 months (mo). Median PFS was 34.17 mo for OFA (95% confidence interval [CI]: 29.70, 38.01) and 16.89 mo (95% CI: 12.98, 20.37) for Obs (Hazard ratio [HR] = 0.55; 95% CI: 0.43, 0.70; $P < 0.0001$) arm. Median TTNT was 37.36 mo (95% CI: 30.55, 42.61) for OFA and 27.56 mo (95% CI: 23.52, 32.62) for Obs (HR = 0.72; 95% CI: 0.57, 0.91; $P < 0.0044$). The OS data although not yet mature, do not show a difference (HR = 0.99; 95% CI: 0.72, 1.37). Death rate was similar in both the arms (32% in OFA vs. 29% in Obs). Adverse events (AEs) were reported in 92% of pts in OFA arm vs. 82% in Obs arm; 62% of pts in OFA arm had ≥grade 3 AEs vs. 51% in Obs arm. Serious AEs (SAEs) were reported in 48% of pts in OFA vs. 46% in the Obs arm. Most common (> 5% of all pts) ≥grade 3 AEs were neutropenia (OFA: 23% vs Obs: 10%), pneumonia (OFA: 13% vs Obs: 12%), febrile neutropenia (OFA: 6% vs Obs: 4%), and pyrexia (OFA: 5% vs Obs: 2%). Due to AEs, 12% of pts discontinued OFA permanently. Up to 60 days after the last treatment, there were 5 SAEs leading to death in the OFA arm vs 7 in the Obs arm; none were considered to be related to the study drug. **Conclusions:** This final analysis confirmed the results of the interim analysis, the treatment effect of maintenance OFA was maintained with more mature data. A significant clinical benefit was observed in pts with relapsed CLL after OFA maintenance. Treatment was well tolerated without unexpected toxicities. Clinical trial information: NCT01039376.

7518 Poster Discussion Session; Displayed in Poster Session (Board #155), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Acalabrutinib combined with PI3Kδ inhibitor ACP-319 in patients (pts) with relapsed/refractory (R/R) B-cell malignancies. *First Author: Paul M. Barr, Wilmot Cancer Institute, University of Rochester, Rochester, NY*

Background: Acalabrutinib, a selective, covalent inhibitor of Bruton tyrosine kinase (BTK), was evaluated in combination with the PI3Kδ inhibitor ACP-319 in pts with R/R B-cell malignancies. **Methods:** Pts with ≥1 prior therapy & ECOG PS ≤2 received oral acalabrutinib 100 mg bid and ACP-319 in escalating doses (25/50/100 mg bid; Part 1) or 50 mg bid (expansion cohort; Part 2) until progressive disease or unacceptable toxicity. The primary endpoint was safety (including dose-limiting toxicity [DLT; Part 1]). Secondary endpoints were PK/PD, overall response rate (ORR), duration of response (DOR) & progression-free survival (PFS). **Results:** Part 1 pts (8 CLL/SLL, 3 FL, 3 MCL, 3 diffuse large B-cell lymphoma [DLBCL], 1 WM) had median age 65 y (range 48-77) & ECOG PS ≤1. One pt had a DLT in the ACP-319 50-mg group (maculopapular rash [MR]); 2 had DLTs in the 100-mg group (MR; febrile neutropenia, diarrhea & pneumonitis). The maximum tolerated dose for Part 2 was ACP-319 50 mg bid with acalabrutinib 100 mg bid. Pts with CLL/SLL were switched to acalabrutinib monotherapy in 2016 due to reduced benefit:risk ratio with added ACP-319. Herein, 25 DLBCL pts (3 in Part 1, 22 in Part 2) were analyzed; by IHC (Hans algorithm), 9 had germinal center B-cell (GCB) & 16 had non-GCB DLBCL. Median age was 70 y (range 55-90); median no. of prior therapies was 2 (range 1-5). Common AEs (≥40%) were increased AST/ALT (48%/52% [Grade ≥3, 28%/20%]), diarrhea (52% [12%]), fatigue (40% [0%]) & rash (40% [12%]); 22 pts discontinued (5/7 due to AEs with acalabrutinib/ACP-319); no deaths were due to AEs. ORR is in Table. ACP-319 exposure was dose proportional with higher/variable exposure to an inactive metabolite. Acalabrutinib exposure was slightly higher at ACP-319 100 (vs 25/50) mg. Median BTK occupancy at trough was 95%; p-AKT inhibition was ACP-319 dose dependent. **Conclusions:** The combination of acalabrutinib + ACP-319 was tolerable with manageable AEs; in DLBCL, response rate was high in non-GCB pts. Clinical trial information: NCT02328014.

	DLBCL	
	GCB n=9	Non-GCB n=16
ORR (≥ PR), n (%)	0	10 (63)
95% CI		35, 85
CR	0	4 (25)
PR	0	6 (38)
Median, mo		
Time on study (range)	2.4 (0.8, 10.4)	4.0 (0.8, 29.7)
DOR (95% CI)	–	NR (1.8, NR)
		range, 0.03+ – 18.4+
PFS (95% CI)	1.8 (1.7, 10.4)	5.5 (1.6, NR)

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7519 Poster Discussion Session; Displayed in Poster Session (Board #156), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Initial results of a dose escalation study of a selective and structurally differentiated PI3Kδ inhibitor, ME-401, in relapsed/refractory (R/R) follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). *First Author: Jacob Drobnyk Soumerai, Massachusetts General Hospital, Boston, MA*

Background: ME-401, an oral tyrosine kinase inhibitor highly selective for PI3Kδ was studied in a phase 1b trial for patients (pts) with R/R FL or CLL/SLL. The starting dose was based on pharmacokinetic and pharmacodynamic data from a study in healthy volunteers. **Methods:** Eligible adult pts had ECOG ≤2, no prior PI3K therapy, and no prior progression of disease (POD) on BTK therapy. ME-401 was given once daily on days 1-28 of 28-day cycle until POD or unacceptable toxicity. All pts received PJP prophylaxis and CMV monitoring was mandatory. At least 6 evaluable pts were treated at each dose level, with option to expand to 12 pts for efficacy assessment. Dose limiting toxicities (DLT) were assessed up to Day 56. Response was assessed after Cycles 2 and 6. **Results:** 31 pts (21 FL, 10 CLL/SLL) received ME-401 and 30 were evaluable for DLT: 12 at 60 mg, 12 at 120 mg, and 6 at 180 mg. Median age was 65 (range: 47-79), 14/30 (47%) pts received ≥2 prior therapies, and 9/21 (43%) pts with FL had POD < 24 months after initial chemoimmunotherapy (POD24). Of 29 pts evaluable for response, the overall objective response rate was 83% (24/29), with 75% (15/20) in FL, including 9/9 (100%) with POD24, and 100% (9/9) in CLL/SLL, occurring by Cycle 2 in 20/24 responders. No DLTs were reported and escalation above 180 mg was closed given frequent responses across lower dose levels. With a median follow-up of 20 weeks (range: 2-53 weeks) 3 pts had POD at 8, 14 and 17 weeks after starting therapy. Five pts discontinued MEI-401 due to adverse events (AEs): rash (n = 3), colitis (n = 1), and cardiomyopathy (n = 1), and 2 pts discontinued for personal reasons. Most common AEs (all grades/grade ≥3) were diarrhea (32%/16%), fatigue (29%/0%), cough (29%/0%), rash (29%/10%), and nasal congestion (26%/0%). All grade ≥3 AEs were reported in Cycle 3 or later. **Conclusions:** ME-401 was well tolerated with high early response rates among R/R FL and CLL/SLL pts. No DLTs were reported. An alternative dosing (ME-401 days 1-7 of 28-day cycle starting with Cycle 3) is being evaluated, including dosing ME-401 at 45 mg and at 60 mg in combination with rituximab. Clinical trial information: NCT02914938.

7520 Poster Discussion Session; Displayed in Poster Session (Board #157), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 1:15 PM-2:30 PM

Phase I/II clinical trial of ibrutinib and buparlisib in relapsed/refractory diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. *First Author: Connie Lee Batlevi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Bruton's tyrosine kinase (BTK) and PI3K inhibitors synergize effectively in both in vitro and in vivo models of B-cell non-Hodgkin lymphoma (Griner, et al, PNAS, 2014; Erdmann et al, Blood, 2017). We report on a phase I/II clinical trial of ibrutinib (BTK inhibitor) and buparlisib (pan-PI3K inhibitor) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL). **Methods:** Patients (pts) were eligible if they had relapsed/refractory DLBCL, FL, or MCL, ECOG ≤2, and adequate organ function. Ibrutinib and buparlisib were given daily by mouth on a 28-day cycle with dose reductions permitted after cycle 1 unless a DLT was noted. Tumor response was based on a modified Lugano classification with CRs requiring FDG-PET resolution and ≥ PR by CT. **Results:** 37 pts were enrolled (DLBCL N = 14, FL N = 5, MCL N = 18) with median prior systemic therapies being 3 for DLBCL (range 1-7), 2 for FL (all had 2 prior regimens), and 1 for MCL (range 1-3). Ibrutinib 560 mg and buparlisib 80 mg was selected for dose expansion cohort based on rash and diarrhea requiring dose reductions. Thirty-six pts were evaluable for toxicity while 1 pt was not evaluable for progression within one week of therapy. Grade 3/4 adverse events related to therapy included rash (22%), hyperglycemia (16%), diarrhea (11%), hypertension (11%), anorexia (8%), mood changes (8%), ALT elevation (5%), lipase elevation (5%), anemia (5%), and hyponatremia (5%). Five pts discontinued buparlisib but continued ibrutinib for neurocognitive toxicities related to buparlisib. Thirty-five pts were evaluable for response with best overall response rate (ORR) as follows: DLBCL 31% (N = 13, 3 CR, 1 PR), FL 20% (N = 5, 1 CR), MCL 88% (N = 17, 11 CR, 4 PR). **Conclusions:** Combination of BTK and PI3K inhibition such as ibrutinib and buparlisib demonstrate a reasonable safety profile and promising clinical activity, especially in MCL. Long term follow-up and correlative analysis of tumor targeted sequencing and cell free DNA analysis is ongoing. Clinical trial information: NCT02756247.

7521 Poster Session (Board #158), Mon, 8:00 AM-11:30 AM

Prognostic role of beta-2 microglobulin (B2M) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) patients (pts) treated with ibrutinib (ibr). *First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: B2M is often elevated in pts with CLL and correlates with disease stage and burden. Normalization of B2M at 6 mo during ibr treatment was associated with improved progression-free survival (PFS) (Thompson et al 2016). We evaluated B2M changes over time, factors associated with B2M normalization, and correlations between B2M status and PFS in pts with R/R CLL treated with ibr. **Methods:** Data were pooled from 2 clinical trials of single-agent ibr (420 mg/d) in pts with R/R CLL. Pts in RESONATE were randomized 1:1 to ibr or ofatumumab. All pts in RESONATE-17 received ibr. Univariate (UVA) and multivariate (MVA) analyses were used to examine baseline (BL) factors associated with B2M normalization. PFS from time of the 6-mo B2M visit was compared based on B2M status; exploratory analyses evaluated PFS by 9-, 12-, and 15-mo B2M status. **Results:** In the combined ibr population (N = 339), BL elevated B2M (79% ≥3.5 mg/L; median 5.4 mg/L), del17p (61%), and unmutated *IGHV* (58%) were common; 15% had del11q, and 25% had creatinine clearance (CrCl) < 60 mL/min. Pts had a median of 2 prior lines of therapy. Median B2M decreased rapidly, by ~40% at 3 mo, in all patients. Overall, 50% of pts normalized B2M during ibr. Median time to B2M normalization was 17 mo and was non-significantly shorter for pts with del17p vs without del17p (14 vs 26 mo; *P*= 0.220). In UVA, BL B2M < 3.5 mg/L, age < 65 y, and CrCl ≥60 mL/min were significantly (*P*≤0.0002) associated with B2M normalization at 6 mo, while del17p was not significant. In MVA, BL B2M < 3.5 mg/L (*P*= 0.0002) and CrCl ≥60 mL/min (*P*= 0.034) were significant factors. PFS did not differ when assessed by 6-mo B2M normalization status (HR 0.699 [95% CI 0.452, 1.080]; *P*= 0.105), nor by 12- or 15-mo B2M status, but was significantly different by 9-mo B2M status (HR 0.579 [95% CI 0.366, 0.915]; *P*= 0.018); median PFS was not reached in either group. For B2M normalization at 9 mo, CrCl was significant in MVA, but age and BL B2M were not. **Conclusions:** Pts treated with ibr had a rapid decrease in median B2M regardless of BL parameters. BL B2M < 3.5 mg/L and CrCl ≥60 mL/min were associated with B2M normalization at 6 mo in MVA. B2M normalization status at 9, but not 6, mo predicted PFS. Clinical trial information: NCT01578707 and NCT01744691.

7522 Poster Session (Board #159), Mon, 8:00 AM-11:30 AM

Achievement of complete remission (CR) as an endpoint for patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib. *First Author: Paolo Strati, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Achievement of a deep response with chemoimmunotherapy associates with prolonged survival in patients with CLL. However, it remains unclear whether this is a desirable endpoint also for patients treated with ibrutinib, who generally achieve partial remissions (PR) rather than CRs. **Methods:** We analyzed the characteristics and outcomes of patients with CLL enrolled in a phase 2 study (NCT02007044) of frontline or salvage continuous ibrutinib therapy, with or without 6 cycles of Rituximab, at our institution between 12/2013 and 10/2016. Progression-free survival (PFS) was defined as time from treatment initiation to disease progression and/or death secondary to CLL-related complications. **Results:** Two-hundred and six patients were included in this study and response was achieved in 186 (99%) of 188 evaluable patients, including PR with lymphocytosis. Six (3%) patients achieved a CR with negative minimal residual disease (MRD), 40 (21%) CR with positive MRD, 3 (2%) nodular PR, 119 (63%) PR, and 18 (10%) PR with lymphocytosis. No significant differences were observed among the baseline characteristics of the 46 patients achieving CR as compared to the 140 patients achieving PR. Achievement of CR was associated with a significantly prolonged PFS (1 event out of 46 patients, 3-year PFS 97%) as compared to PR (14 events out of 140 patients; 3-year PFS 78%)(p = 0.04). None of the baseline characteristics associated with prolonged PFS. Overall, after a median follow-up of 22 months (range, 2-37 months), median PFS was not reached and 19 patients (9%) progressed and/or died of CLL-related complications. Among patients in CR, 1 (2%) with positive MRD died of metastatic melanoma, after 19 months on treatment. Among patients in PR, 13 (8%) developed progressive CLL (1 with Richter transformation), 1 (0.5%) died of metastatic colon cancer, and 4 (1%) died of severe infections. **Conclusions:** This is the first study showing that achievement of CR is a desirable endpoint for patients with CLL treated with ibrutinib, associating with prolonged PFS. Our results support the development of future combination studies, aimed at achieving higher rates of CR in patients treated with ibrutinib. Clinical trial information: NCT02007044.

7523 Poster Session (Board #160), Mon, 8:00 AM-11:30 AM

Association of *ATM* mutation and unmutated IGHV status with shorter time to first treatment (TTFT): An analysis of multigene mutation profiling and standard prognostic clinical markers in 384 treatment-naive (TN) chronic lymphocytic leukemia (CLL). *First Author: Boyu Hu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Somatic mutations (MUTs) in CLL play important roles in leukemogenesis and affect both response to treatment and survival outcomes. Correlation of somatic MUTs with TTFT remains limited. In this study, we associated somatic MUT results from a 29-gene panel and known prognostic factors with TTFT. **Methods:** DNA from either peripheral blood or bone marrow that contained ≥ 10% CLL cells from 384 TN pts underwent next generation targeted sequencing of a 29-gene panel. Concurrent clinical characteristics such as Rai/Binet staging, FISH abnormalities, cytogenetics and *IGHV* MUT were analyzed in univariable (UA) and multivariable (MVA) analyses with MUT data. TTFT was defined as time from diagnosis to initial treatment; untreated pts were censored at last follow up. **Results:** With a median follow up of 24.3 months (m), the median TTFT for all pts was 61.7m (95% CI 47-74.5m). Compared to pts with no MUTs, pts with a single MUT in *ATM* (p < 0.001), *BIRC3* (p < 0.001), *CXCR4* (p < 0.001), *NOTCH1* (p < 0.001), *SF3B1* (p = 0.02) and *SPEN* (p = 0.04) had shorter TTFT. Pts with 2-5 MUTs also had shorter TTFT by 39m compared to pts with 0-1 MUT (p < 0.001). Location of the MUT in various domains of *TP53* gene along with "hotspot" MUTs in *SF3B1* and *NOTCH1* were not associated with differences in TTFT. Additionally, del(17p) was not associated with shorter TTFT. In UA, MUT in *ATM* (p < 0.001), *NOTCH1* (p < 0.001) and *SF3B1* (p = 0.002) as well as unmutated *IGHV* (p < 0.001), del(11q) (p < 0.001) and trisomy 12 (p < 0.001) and advanced Rai (p = 0.05) and Binet (p < 0.001) stages were associated with shorter TTFT. In MVA, *ATM* MUT (p < 0.001), unmutated *IGHV* (p < 0.001) and advanced Binet stage (p = 0.01) remained significant; del(11q) was not significant in the model. **Conclusions:** Somatic MUT in *ATM* and unmutated *IGHV* are important independent prognostic factors for shorter TTFT. Other somatic MUTs, like *CXCR4* and *SPEN* whose clinical significance have not been fully elucidated, correlated to shorter TTFT although not independently. Somatic gene MUTs, especially *ATM,* are associated with disease progression in TN pts.

7524 Poster Session (Board #161), Mon, 8:00 AM-11:30 AM

Distinct immune signatures in chronic lymphocytic leukemia (CLL) and Richter's syndrome (RS). *First Author: Yucai Wang, Mayo Clinic, Rochester, MN*

Background: Immune checkpoint blockade with PD-1 inhibitor pembrolizumab was effective in RS but not CLL in a phase 2 study (NCT02332980). Analyzing the immune signatures including PD-L1 expression and T cell diversity is important for understanding the differential responses. **Methods:** 15 CLL and 14 RS patients in NCT02332980 were included. Expression of PD-L1 in lymph node (LN) was analyzed by immunohistochemistry staining. Peripheral blood (PB) and LN T cell diversity was analyzed using the ImmunoSEQ platform (Adaptive Biotechnology), which quantifies the clonailty of T cells by deep sequencing of the CDR3 region of T cell receptor (TCR). Data analysis (Student's t-test and Mann-Whiney U test) was done by GraphPad Prism (v7). **Results:** PD-L1 expression was significantly lower in CLL (n = 6) *vs* RS (n = 12) patients (mean 5.5% *vs* 22.9%, *P*= 0.003). A control CLL cohort (n = 11, Mayo CLL tissue registry) also had lower PD-L1 expression (7.7%, *P*= 0.002 *vs* RS). RS Patients progressed on ibrutinib or chemotherapy had similar PD-L1 expression (25.3% vs 19.6%, *P*= 0.416). PB TCR clonality at trial baseline was significantly lower in RS (n = 13) *vs* CLL (n = 13) patients (median 0.098 *vs* 0.342, *P*= 0.026). Patients progressed on ibrutinib or chemotherapy had similar TCR clonality (CLL: 0.34 *vs* 0.24, *P*= 0.524; RS: 0.11 *vs* 0.09, *P*= 0.534). 5 RS patients achieved an objective response (1 CR, 2 PR, 1 CMR and 1 PMR), 4 of which were after progression on ibrutinib. For CLL patients, only 1 nodal reduction was seen. 4 RS patients had prior CLL samples available for TCR analysis. 2 patients had a notable decrease of TCR clonality (0.21-0.04 and 0.17-0.03) from CLL (PB) to RS state (LN), and achieved CR and PR, respectively. 2 other patients with stable clonality (0.04-0.05 and 0.03-0.08) had SD and PMR, respectively. PB TCR clonality did not change significantly with pembrolizumab (CLL [n = 11]: *P*= 0.775; RS [n = 11]: *P*= 0.830; paired t-test). **Conclusions:** RS patients had higher expression of PD-L1 and lower TCR clonality (more diverse T cells) compared with CLL patients. The distinct immune signatures may explain their differential responses to PD-1 blockade. The dynamic changes of TCR clonality during Richter's transformation may predict a response to PD-1 blockade.

7525 Poster Session (Board #162), Mon, 8:00 AM-11:30 AM

Rapid progression of disease following ibrutinib discontinuation in patients with chronic lymphocytic leukemia. *First Author: Paul Joseph Hampel, Mayo Clinic, Rochester, MN*

Background: The clinical characteristics, management, and outcomes of patients (pts) with chronic lymphocytic leukemia (CLL) who develop rapid progression of disease following ibrutinib discontinuation are not well described. **Methods:** We identified all CLL pts at Mayo Clinic who discontinued ibrutinib therapy. Clinical symptoms, exam and radiographic findings, and laboratory changes associated with discontinuation were ascertained. **Results:** Of 281 ibrutinib treated pts, 82 (29%) discontinued therapy. Reasons for discontinuation and the median time to discontinuation include: toxicity (n = 30, 37%, 8 months), CLL progression (n = 18, 22%, 25 months), Richter's transformation (n = 9, 11%, 6 months), other (n = 11, 13%), and death (n = 14, 17%). In total, 61 pts had adequate records for review within 4 weeks after discontinuing ibrutinib. Among these, 15 (25%) had progressive worsening in > 2 clinical domains (i.e., symptoms, exam/imaging, labs) post discontinuation, including 13 pts who discontinued due to progression or transformation and 2 pts who discontinued due to toxicity or other. Clinical findings included sudden worsening of constitutional symptoms (n = 14, 93%), worsening lymphadenopathy or splenomegaly (n = 10, 67%), and increasing lactate dehydrogenase or lymphocytosis (n = 12, 80%). We defined these clinical symptoms as ibrutinib stop sequela. Next line therapy was started the next day after ibrutinib discontinuation for 6 pts, after gap in treatment in 4 pts (median 13 days, range 5-36), and overlapped with ibrutinib in 2 pts. Three pts did not receive subsequent therapy. Next line therapy included idelalisib (n = 3), venetoclax (n = 3), steroids with anti-CD20 therapy (n = 2), pembrolizumab (n = 1) and multi-agent chemotherapy (n = 3). Age, sex, *TP53* disruption, and *IGHV* mutation status did not predict the occurrence of the described worsening on univariate analysis. The median overall survival for the entire group was 35 months. **Conclusions:** Multiple ibrutinib stop sequela were seen in 1 out of 4 patients after stopping ibrutinib, occurring despite prompt next line salvage therapy. Parameters to better define the post-ibrutinib interval and optimal ways for its management are required.

7526 Poster Session (Board #163), Mon, 8:00 AM-11:30 AM

Mitigation of tumor lysis syndrome (TLS) complications with venetoclax (VEN) in CLL. *First Author: Matthew Steven Davids, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: VEN can cause rapid tumor debulking in patients (pts) with relapsed/refractory CLL. Current VEN dosing schedule with TLS prophylaxis/monitoring averts overt TLS, but further data on emergent biochemical changes during VEN initiation are needed to guide practice. **Methods:** Pts were included from phase 2 trials of VEN for CLL with del(17p) (n = 51) or prior BCRi therapy (n = 117). VEN started at 20 mg QD with ramp up to 400 mg over 5 wk. Pts were categorized as low (L) TLS risk (nodes < 5 cm and ALC < 25), medium (M; node ≥5 – < 10 cm or ALC ≥25), or high (H; node ≥10 cm or ≥5 cm and ALC ≥25). Laboratory values, AEs, and relevant concomitant medications during ramp up were analyzed. **Results:** TLS risk was categorized as 36% L, 36% M, and 27% H (see Table). 96% of pts completed ramp up; most in 5 wk. TLS AEs were reported in 4 pts (2 M; 2 H), with no clinical TLS and 1 laboratory TLS meeting Howard criteria (HC*). During VEN ramp up, 114 pts had potassium (K) > upper limit of normal (ULN) (1 K > HC); 21 were treated for rising or sustained K > ULN. 16 of these 21 had pre-VEN initiation K > ULN. 5/21 pts interrupted VEN for 1 day and all restarted VEN. 119 pts had phosphate (P) > ULN. 20 pts received P binder for P > HC during VEN ramp up and all others resolved without additional medication. Most instances were isolated; 4 pts had concurrent calcium (Ca^{2+}) or uric acid (UA) changes, and P was not treated in these cases. 70% of pts received allopurinol and 20% allopurinol and rasburicase at VEN start. 6 pts received rasburicase in addition to ongoing prophylaxis. Though 144 pts had Ca^{2+} < lower limit of normal (LLN), only 6 were treated. **Conclusions:** Despite the frequency of K > ULN, treatment was applied in 13% of pts for rising or sustained elevation, and most had pre-VEN K > ULN. Most cases of P > ULN were isolated, asymptomatic, and resolved without intervention. VEN causes rapid tumor cytoreduction consistent with analyte changes, though clinical sequelae are rare and mitigated by approved dose ramp up, TLS prophylaxis/monitoring, and timely intervention. Clinical trial information: NCT01889186, NCT02141282.

		TLS risk			
n of pts		L n = 61	M n = 61	H n = 46	All N = 168
K	> ULN	41	40	33	114
	> 6 mmol/L*	0	1	0	1
	Treated	4	10	7	21
P	> ULN	34	44	41	119
	> 1.5 mmol/L*	18	27	34	79
	Treated	1	8	11	20
Ca^{2+}	< LLN	45	58	41	144
	< 0.3 μmol/L*	0	4	4	8
	Treated	0	3	3	6
UA	> ULN	3	4	6	13
	> 476 μmol/L*	2	2	4	8
	Treated	2	1	3	6

7527 Poster Session (Board #164), Mon, 8:00 AM-11:30 AM

Economic evaluation for the US of venetoclax (VEN) versus ibrutinib (IBR) versus allogeneic hematopoietic stem-cell transplantation (HSCT) for patients (pts) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) with 17p deletion (del 17p). *First Author: Nimer Alsaid, University of Arizona College of Pharmacy, Tucson, AZ*

Background: Prior to targeted agents, HSCT was the primary treatment for R/R CLL del 17p. VEN and IBR have been shown to improve progression free (PFS) and overall survival (OS). We performed an independent economic evaluation of VEN versus IBR versus HSCT in R/R CLL del 17p from the U.S. payer perspective. **Methods:** From published trial data we constructed a life-time horizon Markov model with 3 states: PFS; progression; and death. Kaplan-Meier PFS and OS curves for VEN, IBR and HSCT were digitized, and Weibull distributions fitted. The wholesale acquisition cost of VEN and IBR were sourced from RedBook. Costs of the HSCT (procedure, pre-conditioning, post-procedural adverse events [AE]) were estimated from published prediction equations and a claims database. EQ-5D utility values were sourced from literature. AE disutility values were assumed the same for the 3 interventions. Discount of 3% was applied. The life years (LY) and quality adjusted LY (QALY) for each treatment were estimated, and the incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR) were determined. **Results:** IBR prevailed in PFS over VEN and HSCT until ~190 weeks (3.7 years) when curves crossed and VEN prevailed over both IBR and HSCT. VEN prevailed in OS over IBR and HSCT over the full life time horizon. The Table below presents the BCA and PSA estimated costs and (QA)LYs gained. VEN was cost saving over IBR and HSCT and yielded higher (QA)LY gains. IBR was cost saving over HSCT and yielded higher (QA)LY gains. The ICERs and ICURs for VEN over IBR and HSCT were cost saving per (QA)LY gained. For IBR, the ICER and ICUR revealed incremental costs per LY and QALY gained. **Conclusions:** Over a life time horizon, VEN showed cost savings while achieving higher (QA)LYs over IBR and HSCT. IBR achieved higher (QA)LYs over HSCT but at incremental cost.

BCA/PSA		
ICER(cost/LY)		
VEN		
$743,840/-$705,032	IBR	
$564,054/-$565,080	$215,016/$259,077	HSCT
ICUR(cost/QALY)		
VEN		
$1,487,680/-$1,383,951	IBR	
$925,628/-$946,891	$198,476/$233,170	HSCT

7528 Poster Session (Board #165), Mon, 8:00 AM-11:30 AM

Change in tumor lysis syndrome risk after lead-in treatment in a phase 1b/2 study of obinutuzumab, ibrutinib, and venetoclax for chronic lymphocytic leukemia. *First Author: Kerry Anne Rogers, The Ohio State University, Division of Hematology, Columbus, OH*

Background: Venetoclax (VEN) is highly effective for the treatment of chronic lymphocytic leukemia (CLL). Tumor lysis syndrome (TLS) during VEN initiation is a major risk and management, including hospitalization for high risk patients, increases treatment burden and limits use. Strategies to decrease TLS risk are of interest. We reviewed our phase 1b/2 study of combination obinutuzumab (OBIN), ibrutinib (IBR), and VEN to understand how lead-in OBIN and IBR change TLS risk. **Methods:** All study patients who completed 3 cycles (C) of treatment were included. Agents were started sequentially over C1-3 with OBIN C1 (C1 D1: 100mg, C1 D2: 900mg, C1 D8, D15: 1,000mg, C2-8 D1: 1,000mg), IBR C2 (C2-14 D1-28: 420mg), and VEN C3. Risk for TLS was assessed according to the VEN US label at baseline and prior to C3. We recorded absolute lymphocyte count (ALC) and lymph node (LN) sum of the product of longest diameters (SPD) and tested for changes in TLS risk between C1 and C3 using the Wilcoxon signed-rank test. **Results:** 61 patients were included: 36 relapsed or refractory and 25 treatment naïve. ALC and LN (C1-3) and TLS risk (baseline, C3) are in Table 1. ALC significantly decreased from C1 to C3 ($p < 0.0001$) with a median change of -93.2% (range -99.6-194.5%). LN similarly decreased ($p < 0.0001$). OBIN attenuated IBR lymphocytosis with a median ALC change C2 to C3 of 2.1 (range -0.3-46.7). Twelve (20%) patients reduced TLS risk from high to medium, 26 (43%) from medium to low, and 23 (38%) had no change. There were no incidents of clinical or laboratory TLS. **Conclusions:** Lead-in OBIN and IBR decreased TLS risk in the majority of high (12/19, 63%) or medium (26/34, 76%) risk patients when reassessed prior to VEN. This strategy may improve the safety of VEN initiation, allow some initially high risk patients to avoid hospitalization, and expand settings where VEN is used. Clinical trial information: NCT02427451.

CLL burden and TLS risk (n = 61).

ALC in k/uL, median (range)	-
C1	69.7 (0.2-445.6)
C2	1.1 (0.2-10.2)
C3	3.7 (0.3-48.3)
Palpable LN SPD in cm, median (range)	-
C1	12.3 (0-235)
C2	0.5 (0-158)
C3	0 (0-47)
Baseline TLS risk, n (%)	-
High	19 (31)
Medium	34 (56)
Low	8 (13)
C3 TLS Risk, n (%)	-
High	7(11)
Medium	20 (33)
Low	34 (56)

7529 Poster Session (Board #166), Mon, 8:00 AM-11:30 AM

Management and outcomes of 222 CLL patients (pts) treated with venetoclax (VEN) in the real world. *First Author: Chadi Nabhan, Cardinal Health Specialty Solutions, Dublin, OH*

Background: VEN is an oral bioavailable BCL-2 inhibitor approved by the FDA in April 2016 for use in CLL. More data are needed to understand real world initiation, management and outcomes of CLL pts treated with VEN. **Methods:** This was a retrospective cohort study of CLL pts who initiated VEN. Investigators from 25 community centers provided pt-level data from medical records including demographics, clinical characteristics, ramp up management and outcomes. Tumor burden was assessed per FDA label, tumor lysis syndrome (TLS) was defined by Howard criteria and response was based on iwCLL criteria. The primary endpoint was response. Characteristics and outcomes were summarized by descriptive statistics. **Results:** 222 VEN pts were included, of whom 22% used VEN in combination with ibrutinib (7%) or an anti-CD20 (14%). Median age was 64 years (range 57-71); 82% had *TP53* interruption ; 84% had ≥1 prior line of therapy (median 1; range 0-6); 62% had prior kinase inhibitor (KI) use; and 4% had prior use of 2 KIs. At baseline, 11%, 49% and 40% had low, medium and high tumor burden, respectively, and 27% initiated VEN as inpatient. During ramp up, 6% had a dose interruption; no dose modifications were reported due to hematologic abnormalities. TLS events occurred in 6% of pts (n = 13) with 2 pts experiencing clinical TLS, mainly among high risk pts. 34 pts (15%) discontinued VEN, mainly due to relapse (n = 5), refractoriness (n = 9), or in setting of disease response (n = 8). Maximum dose of 400mg was achieved in 53% of pts and 46% (n = 103) were maintained at doses < 400mg following ramp up. With a median follow up of 6.1 months, ORR was 75% (CR: 26%). Median time to best response was 3 months. Responses were not negatively affected by TLS or maintenance doses < 400mg. Among 38 pts assessed for minimal residual disease (MRD) during VEN, 23 (61%) were MRD negative. Resolution of baseline lymphadenopathy, lymphocytosis, or B symptoms were reported among 93%, 95%, and 96%, respectively. **Conclusions:** In this study, most VEN-treated CLL pts completed the ramp up, few experienced a TLS /hematologic event, and responses were comparable to clinical trials. Inpatient management deviated from the FDA label suggesting opportunity to improve adherence to initiation guidance.

7530 Poster Session (Board #167), Mon, 8:00 AM-11:30 AM

A phase 2 study to assess the safety and efficacy of umbralisib (TGR-1202) in pts with CLL who are intolerant to prior BTK or PI3Kδ inhibitor therapy. *First Author: Anthony R. Mato, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Although KI therapies are generally well-tolerated, intolerance is the most common reason for discontinuation, thus representing an unmet medical need. Umbralisib (TGR-1202), a next generation PI3Kδ inhibitor, has a discontinuation rate due to adverse events (AEs) of < 10%. **Methods:** We report results from a Ph 2 study assessing the safety/efficacy of umbralisib in CLL pts who were intolerant (defined per protocol) to a prior KI within 12 mos. AEs must have resolved to ≤ GR 1 prior to umbralisib therapy. Umbralisib (800mg QD) administered until progression or toxicity. Primary endpoint is progression-free survival (PFS). **Results:** 40 pts were treated as of 2/2018 (36 BTK & 4 PI3Kδ intolerant). Baseline demographics: median (med) age 69 yrs (range 52-96), med prior therapies 2 (1-7), 55% male, ECOG 0-1 (92%), del17p (20%), del11q (23%), IGHV unmutated (60%). 80% required treatment within 6 mos of prior KI discontinuation. Most AE's leading to KI discontinuation were: arthralgia, rash (9 events each), A-fib (6), diarrhea (4), bleeding, fatigue and weight loss (3 each). AEs on umbralisib are listed in the table: GR ≥3 PI3Kδ-associated AE's were limited: AST/ALT (3%); diarrhea (7.5%); rash (3%). 4 pts discontinued umbralisib due to intolerance (rash, pneumonia, pneumonitis, pancreatitis), and 1 pt due to study noncompliance. No pt discontinued umbralisib as a result of a prior KI intolerant AE. 3 pts (7.5%) had dose reductions (headache, hematologic, and colitis) and were successfully re-challenged (colitis pt on study in PR now 12 mos). Med PFS not reached with 90% of pts progression free at a med follow up 6.5 mos (range 1–15). **Conclusions:** Umbralisib appears to be safe and effective in KI intolerant CLL pts. These are the first data to confirm that switching from KI to an alternate PI3Kδ (umbralisib) can result in disease control (PFS) without recurrence of KI intolerance toxicities. BTK mutations and CYP polymorphisms are being assessed. Clinical trial information: NCT02742090.

Umbralisib AEs (all causality) in > 15% pts (n = 40).

Adverse Events	All Grades	% All Grades	GR 3/4	% GR 3/4
Diarrhea	17	43%	3	8%
Nausea	17	43%		
Thrombocytopenia	11	28%	4	10%
Insomnia	9	23%		
Neutropenia	9	23%	7	18%
Dizziness	8	20%		
Fatigue	8	20%		
Rash	7	18%	1	3%

7531 Poster Session (Board #168), Mon, 8:00 AM-11:30 AM

B-cell acute lymphoblastic leukemia (B-ALL) in CLL patients treated with lenalidomide. *First Author: Moritz Fuerstenau, Department I of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany*

Background: The immunomodulatory drug lenalidomide (len) has shown clinical activity in CLL. It has been associated with an increased rate of second primary malignancies (SPM) in multiple myeloma (MM). In MM degradation of transcription factors Ikaros and Aiolos leads to its anti-tumor activity and T-cell activation; in CLL, its mechanism of action has not been determined yet. In our CLLM1 trial, 2 of 56 pts developed BCR-ABL positive B-ALL during or after len maintenance; there were no B-ALL cases in the placebo group. **Methods:** We screened all phase III trials using len in CLL pts for reported B-ALL cases, obtained reports of B-ALL cases in CLL from the FDA Adverse Event Reporting System (FAERS) and analysed available data for B-ALL cases in five non-len GCLLSG trials in order to estimate the incidence of B-ALL in CLL pts not exposed to len. In the 2 CLLM1 pts, PCR was performed for detection of BCR-ABL before B-ALL diagnosis and clonal relationships of B-ALL and CLL will be assessed by NGS. **Results:** In 3 phase III trials (CLLM1, CONTINUUM, ORIGIN) evaluating the use of len in CLL, a total of 846 pts were enrolled, 438 receiving len monotherapy. Five out of 438 pts (1,1%) developed B-ALL during treatment (n = 1) or after discontinuation (n = 4). No B-ALL cases were reported in the control groups including 408 pts. Of the 5 pts, 2 received len as firstline and 3 as maintenance therapy, median length of exposure was 32 months (range 15-47), median age at B-ALL diagnosis was 69 years (range 60-82). Both CLLM1 pts were categorized as 'high risk' or 'very high risk' according to CLL-IPI, 1 pt featuring a TP53 mutation, both with unmutated IGHV. BCR-ABL could not be detected at any time point before ALL diagnosis, clonal relationship of B-ALL and CLL is currently being analysed. In 2015 pts treated within 5 non-len GCLLSG trials, only 2 cases of B-ALL were identified (0,1%); this underscores the assumption that secondary B-ALL is usually a rare event in CLL. **Conclusions:** According to a large GCLLSG cohort and in accordance with published data on SPM in CLL, B-ALL is a rare event in CLL patients. In CLL patients treated with len either as firstline or maintenance therapy following chemotherapy, an increased number of B-ALL was observed, the reason for this increase is unknown.

7532 Poster Session (Board #169), Mon, 8:00 AM-11:30 AM

A U.S.-based survey: The experiences of 1147 chronic lymphocytic leukemia (CLL) patients (pts). *First Author: Brian Koffman, CLL Society Inc, Claremont, CA*

Background: The CLL literature focuses largely on the objective aspects of diagnosis (dx), active observation (AO), prognosis and management. While health care providers (HCPs) try to effectively educate and reassure pts, the literature on pts' subjective experience through the continuum of care is limited. **Methods:** We utilized an online or paper 64 question survey directed to CLL pts to capture more information on their experience with CLL. The survey was IRB-approved and took place between October-December 2017. All analyses here are descriptive in nature. **Results:** 1147 pts from 48 states completed the survey. Median age was 65 (range 28-86), 46% male, 96% Caucasian. 33% of pts do not recall education by their HCP at dx. Following education, 66% of pts report a good understanding of sources of information on CLL, 64% of disease characteristics and 62% of therapy indications. At disease progression, only 23% of pts report education from their HCPs. Effects of treatment and clinical trial opportunities are well understood by 43% and 35% respectively. At dx, 48% were told they had the "good" cancer. When AO was recommended, pts report anxiety (56%), relief (52%) and confusion (31%). 34% and 16% of pts report that discussing prognostics increased their anxiety and confusion respectively. During AO pts report fatigue (51%), enlarged nodes (47%), anxiety (39%), depression (21%), and night sweats (21%). Also during AO, 653 pts (66%) utilize herbals and other non-traditional interventions for CLL management (Table). When pts declined participation in a clinical trial, the reasons cited were preference for a "proven" treatment (38%), distance from the trial site (29%), fear (20%), and frequent imaging (20%). **Conclusions:** To our knowledge, this is the largest survey of CLL pts. Much can be learned by detailed surveying of CLL pts throughout their disease. These include previously unrecognized suboptimal interactions between the CLL pt and the HCP. Understanding how pts experience their disease is critical to improve communication between pts and their HCPs, which will ultimately advance CLL outcomes.

During AO	% used
Green tea or derivatives	60
Vitamin D	56
Prayer	36
Exercise	30
Curcumin	27
Other herbs / supplements	26

7533 Poster Session (Board #170), Mon, 8:00 AM-11:30 AM

The efficacy of duvelisib monotherapy following disease progression on ofatumumab monotherapy in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study. *First Author: Bryone J. Kuss, Flinders Medical Centre, Bedford Park, Australia*

Background: Duvelisib, an oral dual inhibitor of PI3K-δ,γ, is being developed for the treatment of hematologic malignancies, including relapsed/refractory (RR) CLL/SLL. In the Phase 3 DUO study (NCT02004522) duvelisib monotherapy demonstrated significant improvement compared to ofatumumab monotherapy (PFS 13.3 vs 9.9 mo. $p < 0.0001$; ORR 74% vs 45% $p < 0.0001$) with a manageable safety profile (Flinn, ASH 2017). Study IPI-145-12 (NCT02049515) is an open-label, optional, crossover extension study where pts with confirmed progressive disease (PD) on DUO were given the option to receive the opposite treatment. Herein we present data for the 89 pts who voluntarily rolled over following PD on ofatumumab on DUO and received duvelisib on Study IPI-145-12. **Methods:** Eligible pts were enrolled within 3 months of PD on the DUO study (excluding Richter's transformation or prolymphocytic leukemia), and maintained adequate renal and hepatic function and an ECOG PS of 0-2. Duvelisib 25 mg BID was administered until PD, intolerance, death, or study withdrawal. Responses were determined by investigators using modified IWCLL/IWG criteria. **Results:** Median age was 68 yrs (range: 39-89), 63% were male, and 90% Caucasian. Nearly half (49%) had Rai Stage III/IV or Binet Stage C, and 23% had del(17p) and/or *TP53* mutation. Median prior anticancer therapies was 3 (range: 2-8). Median exposure to duvelisib was 32 weeks on the extension study. The ORR for pts treated with duvelisib in the crossover was 73% (95% CI: 64, 82) (all PRs) compared to 28% (95% CI: 19, 37) (1% CR, 27% PR) when previously treated with ofatumumab in DUO. The median PFS for duvelisib was 15 mo. (95% CI: 10, 17) compared to 9 mo. (95% CI: 9, 11) for prior ofatumumab. **Conclusions:** In an extension study, duvelisib monotherapy achieved robust and durable responses in 89 RR CLL/SLL pts with PD following ofatumumab treatment in the DUO study (ORR: duvelisib 73%; prior ofatumumab 28%), with a longer PFS with duvelisib than prior ofatumumab (PFS: duvelisib 15 mo.; prior ofatumumab 9 mo.). These data further support duvelisib monotherapy as an effective oral treatment option for pts with RR CLL/SLL. Clinical trial information: NCT02049515.

7534 Poster Session (Board #171), Mon, 8:00 AM-11:30 AM

Improving outcomes with brentuximab vedotin (BV) plus chemotherapy in patients with newly diagnosed advanced stage Hodgkin lymphoma. *First Author: David J. Straus, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: ECHELON-1 is a phase 3 study of BV plus doxorubicin, vinblastine, and dacarbazine (A+AVD) vs ABVD as frontline therapy in untreated advanced HL (NCT01712490). G-CSF primary prophylaxis (G-PP) was administered at the investigators' discretion, and during the study was formally recommended by an independent data monitoring committee (IDMC) for patients (pts) receiving A+AVD. For pts receiving A+AVD, G-PP was associated with fewer infections and ≥ Grade 3 AEs, including neutropenia (70% without vs 29% with G-PP) and febrile neutropenia (21% vs 11%). **Methods:** Exploratory analyses assessing outcomes and exposure in pts who received G-PP on the A+AVD arm compared with those who did not were conducted. G-PP was defined as use of G-CSF by Day 5 of treatment (tx); non-G-PP pts included pts who received G-CSF secondary prophylaxis. **Results:** 1334 pts with advanced HL were randomized 1:1 to receive A+AVD or ABVD. In 662 pts treated with A+AVD, G-PP was given to 42 of 499 pts who started tx prior to, and 41 of 163 pts who started tx after the IDMC recommendation. Across tx arms, baseline characteristics were similar between the subgroups. G-PP, compared with no G-PP, was associated with a lower rate of BV dose delays (35% vs 49%) and dose reductions (20% vs 26%), and decreased hospitalization rates (pts with at least 1 hospitalization 29% vs 38%). Of the 7 neutropenia-associated deaths during A+AVD tx, none occurred in pts who received G-CSF prior to the onset of neutropenia. A+AVD with G-PP was associated with a decreased risk of a modified progression free survival event (mPFS; Connors, 2018) by 25% compared to A+AVD without G-PP and by 42% compared to ABVD. Clinical trial information: NCT01712490. **Conclusions:** Concomitant administration of G-PP with A+AVD in pts with advanced HL reduced AEs and frequency of tx delays. Though the sample size is small, G-PP with A+AVD may be associated with improved efficacy and a decrease in early, neutropenia-associated deaths; a prospective clinical trial to further assess the safety and efficacy in pts receiving G-PP with A+AVD is planned.

	A+AVD		
	With G-PP	Without G-PP	ABVD
N	83	581	670
2-year mPFS %	84.6	81.7	77.2
95% CI	73.7, 91.3	78.1, 84.8	73.7, 80.4
Hazard ratio vs ABVD	0.58	0.79	-
95% CI	0.31, 1.07	0.62, 1.02	

7535 Poster Session (Board #172), Mon, 8:00 AM-11:30 AM

Limited stage nodular lymphocyte predominant Hodgkin lymphoma (NLPHL): A subgroup analysis of the HD.6 clinical trial. *First Author: Bethany Monteith, Queen's University, Kingston, ON, CA*

Background: NLPHL is a rare subtype of Hodgkin lymphoma (HL) accounting for 5% of cases. It is rarely studied in prospective clinical trials and treatment is controversial. **Methods:** In the Canadian Cancer Trials Group HD.6 phase 3 trial, individuals with newly diagnosed non-bulky stage IA or IIA HL were randomly assigned to treatment with ABVD chemotherapy (CT) alone, or to radiation based (CMT/RT) therapy *[Meyer NEJM 2012]*. From this we identified all patients with NLPHL. A classical Hodgkin lymphoma (cHL) comparison cohort was constructed using propensity score matching 3:1 for age, sex, stage, treatment arm and number of nodal sites. Event free survival (EFS), overall survival (OS) and freedom from disease progression (FFP) were as defined in the original trial. The NLPHL cohort was analyzed according to treatment arm and compared with the cHL cohort using log-rank statistics. Secondary endpoints included toxicity and second malignancies. **Results:** Of 405 individuals enrolled in HD.6, 29 (7.2%) had NLPHL. Of these, median age at diagnosis was 42 yrs, 24 (83%) were male and 15 were assigned to RT. Median follow up was 120 months. For patients with NLPHL, 12-yr EFS for CMT/RT vs CT was 58% vs. 85% (HR 0.46, 95% CI 0.09-2.37) and FFP was 70% vs 85% (HR 0.72, 95% CI 0.12-4.33), respectively. There was one death in the CMT/RT arm; OS analysis by treatment arm was not conducted due to insufficient events. Eighty-seven pts were identified for the matched cHL cohort. 12-yr OS in the NLPHL and cHL groups was 95% and 87% (HR 3.43, 95% CI 0.44-26.5), EFS 70% and 81% (HR 0.73, 95% CI 0.30-1.76), FFP 78% and 90% (HR 0.51, 95% CI 0.17-1.57). Over the entire course of follow-up, there was 1 (3%) death in the NLPHL group due to unknown cause and 12 (14%) deaths in the cHL group – 3 treatment-related toxicity, 6 secondary malignancy, 3 other causes. **Conclusions:** We present the only prospective assessment of early-stage NLPHL treated with ABVD alone. Acknowledging limitations including small sample size, outcomes of pts with NLPHL appear very good when treated with ABVD chemotherapy alone. Clinical trial information: NCT 00002561.

7536 Poster Session (Board #173), Mon, 8:00 AM-11:30 AM

Sintilimab (IBI308) in relapsed/refractory classical Hodgkin lymphoma: A multicenter, single-arm phase 2 trial in China (ORIENT-1 study). *First Author: Yuankai Shi, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Classical Hodgkin's lymphoma (cHL), characterized by chromosome 9p24.1 alteration and PD-1 ligands overexpression, is sensitive to PD-1/PD-L1 blockage in previous studies. This study will confirm the efficacy and safety of sintilimab (IBI308), a promising anti-PD-1 monoclonal antibody, in Chinese patients with relapsed/refractory (R/R) cHL. **Methods:** ORIENT-1 (NCT03114683) is a multicenter, single-arm, phase 2 study. Patients who failed 2 or more lines of systemic therapy, including autologous hematopoietic stem cell transplantation (HSCT) were enrolled. Sintilimab was given 200 mg intravenously every 3 weeks, until disease progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint was objective response rate (ORR) assessed by independent radiological review committee (IRRC) according to 2007 IWG criteria. The cut-off date for this analysis was Feb 8, 2018. **Results:** Among 96 treated patients enrolled between Mar 30th 2017 and Nov 1st 2017, the median number of previous chemotherapies was 3 (range: 1~13). 54.2% patients received prior radiotherapy and 18.8% failed HSCT. With median treatment cycles of 9 (range: 1~14), ORR was 74.0% (71/96, 97%CI: 64.2%, 83.7%) per IRRC review. 23 patients (24.0%) achieved complete response (CR). The median duration of response has not been reached. At the time of analysis, 64 of 71 complete and partial response patients had an on-going response. The most common treatment-related adverse event (TRAE) was pyrexia (43.8%, 42/96), and 92.9% were grade 1~2. Most of pyrexia happened in the day of first infusion and recovered within 1 day. Other common TRAEs were hypothyroidism (13.5%) and TSH increase (11.5%), and all were grade 1~2. The most common grade 3~4 TRAEs were pyrexia (3.1%) and thrombocytopenia (2.1%). No patient died. **Conclusions:** Till now, ORIENT-1 study is the largest cHL study in China. Patients in our study were sensitive to sintilimab, with 74.0% ORR and 24.0% CR rate. The safety profile was consistent with the findings of other anti-PD-1 monoclonal antibodies in cHL patients. Sintilimab could be a new treatment option for R/R cHL patients in China. Clinical trial information: NCT03114683.

7537 Poster Session (Board #174), Mon, 8:00 AM-11:30 AM

Safety and efficacy of decitabine-primed anti-PD-1 (SHR-1210) treatment in patients with relapsed/refractory classical Hodgkin lymphoma. *First Author: Chunmeng Wang, Bio-therapeutic Department, Molecule & Immunology Department, Chinese PLA General Hospital, Beijing, China*

Background: More than 50% unprecedented objective clinical response rate led to a rapid approval of anti-PD-1 antibodies by FDA using in patients with relapsed/refractory classical Hodgkin lymphoma (r/r cHL). However, anti-PD-1 monotherapy can induce complete remission (CR) only in about 10% patients. Decitabine, a demethylating agent, was documented to directly boost T cell function and also possibly delay/reverse PD-1-blocked T cell exhaustion. This Phase I/II study was designed to assess the safety and efficacy of decitabine-primed anti-PD-1 (SHR-1210, a novel humanized IgG4/kappa monoclonal antibody) treatment in r/r cHL patients. **Methods:** Enrolled patients without anti-PD-1 history were 1:2 assigned into SHR-1210 monotherapy (4 mg/kg per 3 weeks) cohort 1 or decitabine (10mg/d on day 1-5) plus SHR-1210 (4mg/kg, day 8, per 3 weeks) cohort 2. Patients refractory to anti-PD-1 monotherapy were allocated into cohort 2. Safety was assessed by CTCAEv4.0, and clinical response by PET-CT referred to standard international criteria. **Results:** A total of 57 patients with heavily treated history (14-cycle median systemic treatment or with average 8-cycle anti-PD-1 monotherapy) were enrolled and 41 completed serial response evaluation by the end of Jan. 2018. The most common adverse events were clinically negligible cherry hemangioma (75% in cohort 1 and 93% in cohort 2), and unattended leukocytopenia (32% in cohort 2). Six from 13 patients in cohort 1 were evaluated as 1 CR (17%), 2 PR (34%), and 3 SD. Twenty cases from cohort 2, before enrollment were evaluated to be refractory to anti-PD-1 alone therapy, 17 were evaluated and showed 4 CR (23%), 5 PR (30%), 4 SD, and 4 PD. Eighteen of 26 patients without anti-PD-1 history before enrollment were evaluated as 12 CR (67%), 4 PR (22%), and 2 SD. So far, 88% evaluated patients had a $>$ 24-week progression-free survival. **Conclusions:** Addition of decitabine not only largely increased the CR rate of anti-PD-1 therapy in r/r cHL, but significantly reversed the resistance of anti-PD-1 therapy. Combination therapy had an acceptable safety profile. Clinical trial information: NCT02961101 and NCT03250962.

7538 Poster Session (Board #175), Mon, 8:00 AM-11:30 AM

Immune toxicity in post autologous transplant patients treated with brentuximab vedotin in combination with immune checkpoint blockade. *First Author: Catherine S. Magid Diefenbach, Perlmutter Cancer Center at NYU Langone Health, New York, NY*

Background: Emerging data suggests that checkpoint blockade therapy (CBT) subsequent to stem cell transplant (SCT) may cause significant immune-related toxicity. We evaluated whether increased patterns of immune toxicity were seen in post SCT patients treated on Arms A-F of E4412: A Phase I Study with an Expansion Cohort of the Combinations of Ipilimumab, Nivolumab and Brentuximab Vedotin in Patients with Relapsed/Refractory Hodgkin Lymphoma **Methods:** Transplant status of patients treated with brentuximab vedotin (BV) + ipilimumab (Ipi) (Arms A-C) or BV + nivolumab (Nivo) (Arms D-F) was recorded at study entry. Toxicity was graded according to CTCAE v4.0. **Results:** Eighteen of 42 patients enrolled on Arms A-F were post SCT; 15 autologous (ASCT) and 3 allogeneic (AlloSCT). There were no demographic differences between the SCT and all patients. No patients had active GVHD. In Arms A-C grade 3 toxicities (rash and allergic reaction), occurred in 20% (2/10) of SCT patients (8 ASCT, 1 AlloSCT) compared with 39% (9/23) of all patients; there were no grade 4 toxicities in SCT patients compared to 4% (1/23) of all patients. A higher incidence of grade-1-2 rash was noted in ASCT patients 70% vs 39% all patients; however there was no increase in diarrhea, arthritis, or uveitis. In Arms D-F there were no significant differences in high grade toxicities in ASCT 16% (1/6) vs. 21% (4/19) all patients; 50% (1/2) AlloSCT patients experienced grade 3 toxicity (pneumonitis, typhlitis). A second pneumonitis, grade 5, occurred in the non SCT population. There remainder of toxicities were grade 1-2 and were not significantly increased in the SCT patients. A transient and clinically insignificant elevation in transaminases was not increased in SCT 16% (3/19) compared to all patients 47% (9/19). **Conclusions:** CBT in combination with BV was well tolerated in the ASCT population, however larger studies are required to confirm this finding for AlloSCT patients. Investigation of dual CBT (Ipi + Nivo) in combination with BV in this population continues. Evaluation of the safety of CBT + BV in E4412 in the pre SCT setting is ongoing and will be combined with this data by the ASCO meeting. Clinical trial information: NCT01896999.

7539 Poster Session (Board #176), Mon, 8:00 AM-11:30 AM

Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin lymphoma (HL): Impact of cycle 2 PET result on modified progression-free survival (mPFS). *First Author: Robert W. Chen, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA*

Background: The ECHELON-1 trial demonstrated improved outcomes for patients (pts) with advanced HL who received frontline A+AVD (brentuximab vedotin, doxorubicin, vinblastine, dacarbazine) vs ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), with 2-year mPFS rates of 82% and 77%, respectively. Here we report a post-hoc analysis of mPFS outcomes and clinical characteristics by Cycle 2 PET (PET2) status per independent review facility (IRF). **Methods:** Pts were randomized 1:1 to A+AVD or ABVD on Days 1 and 15 for up to six 28-day cycles. PET scans were conducted at the end of Cycle 2 and end of treatment. PET2 results guided an optional switch to alternative therapy at the treating physician's discretion for pts with a Deauville score of 5. A switch to alternate therapy was not considered an event. The primary endpoint, mPFS, was defined as time to progression, death, or absence of a complete response with subsequent anticancer therapy, per IRF. **Results:** PET2 negativity rates (Deauville $\leq$3) were 89% (588/664 pts) in the A+AVD arm and 86% (577/670) with ABVD. Baseline characteristics were well-balanced across arms, with no significant differences in PET2– vs PET2+ pts in either arm. PET2 positivity rates (Deauville $\geq$4) were 7% (47/644) in the A+AVD arm and 9% (58/670) with ABVD; 5 total pts with a Deauville score of 5 switched to alternative frontline therapy. Subgroup analyses showed a favorable treatment effect for both subgroups in favor of A+AVD (Table 1), with 2-year mPFS (PET2– vs PET2+) of 85.2 vs 57.5% in the A+AVD arm, and 80.9 vs 42.0% in the ABVD arm. Outcomes for PET2+ pts were relatively poor in both arms, as previously reported. **Conclusions:** Overall, ECHELON-1 demonstrated a treatment effect in favor of A+AVD over ABVD. This post-hoc analysis showed a similar treatment effect on mPFS consistently in favor of A+AVD regardless of PET2 status. Clinical trial information: NCT01712490.

Summary of mPFS by PET2 Status.

	2-year mPFS (per IRF), %			
	A+AVD	ABVD	HR	P-value
Overall	82.1	77.2	0.77	0.035
95% CI	78.8–85.0	73.7–80.4	0.603–0.983	
N	664	670		
PET2–	85.2	80.9	0.774	0.070
95% CI	81.9–88.0	77.3–84.0	0.586–1.022	
N	588	577		
PET2+	57.5	42.0	0.609	0.089
95% CI	41.0–70.9	28.6–54.8	0.341–1.088	
N	47	58		

7540 Poster Session (Board #177), Mon, 8:00 AM-11:30 AM

Prognostication of older Hodgkin lymphoma (HL) patients (pts): Findings from a multicenter phase II study. *First Author: Andrew M. Evens, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Outcomes have been historically poor for older HL pts (ages $\geq$ 60 years (yr)). Furthermore, there are sparse data regarding prognostication. **Methods:** Untreated older HL pts received 2 initial doses of single agent brentuximab vedotin (Bv) 1.8 mg/kg q 3 weeks followed by 6 cycles of doxorubicin, vinblastine & dacarbazine (AVD); responding pts received 4 Bv consolidation doses. 48 pts enrolled (42 evaluable for response). Univariate (UVA) & multivariate (MVA) analyses were performed with Cox proportional hazard regression for survival. **Results:** Median age was 69 yrs (60-88); 63% male; ECOG PS 0: 40%, 1: 42%, 2: 20%; 82% stage III/IV; 60% IPS 3-7; median Cumulative Illness Rating Scale-Geriatric (CIRS-G) comorbidity score 6 (52% grade 3/4); & 12% had baseline loss of instrumental activities of daily living (iADL). 52% of pts completed all intended cycles & 65% received at least 1 Bv consolidation; the median CIRS-G for pts who completed all intended therapy vs not was 4 vs 8, respectively (P= 0.03). ORR to initial Bv was 87% (CR 30%). After AVD, ORR & CR rates were 95% and 90%, respectively. Among all 48 pts, 2 yr PFS was 85% with 94% OS. Response to the initial 2 doses of Bv (CR/PR vs SD) was associated with 2 yr PFS rates of 100% vs 50%, respectively (P= 0.002). On UVA, increasing age and CIRS-G score & loss of iADLs were significant for PFS (Table). On MVA of all factors, only iADLs loss remained significant for inferior PFS (HR 8.19, 95%CI 1.2-57.6, P= 0.03). 2 yr PFS rates based on loss of iADLs vs not were 25% vs 94%, respectively ($P<$ 0.0001) with 2 yr OS 67% vs 97%, respectively (P= 0.01). Pts with loss of iADLs received a median of 6.5 vs 12 intended cycles on study (P= 0.01); 67% vs 39% had a serious adverse event (P= 0.20); and CR rate was 60% vs 95% (P= 0.06). **Conclusions:** Outcomes for older HL pts treated with sequential Bv/AVD were overall excellent. The most dominant factor associated with divergent pt outcomes was baseline functionality, as assessed by iADLs. Clinical trial information: NCT01476410.

UVA analyses.

	PFS		
Variables*	HR	95% CI	P
Age	1.16	1.05-1.28	0.005
Female	4.97	0.96-25.7	0.06
ECOG PS	2.46	0.87-6.97	0.09
Loss iADLs	14.88	2.68-82.53	0.002
CIRS-G	1.21	1.06-1.38	0.005

*Non-significant factors: histology; EBV/EBER; albumin; stage; marrow involvement; IPS

7541 Poster Session (Board #178), Mon, 8:00 AM-11:30 AM

Brentuximab vedotin (BV) plus chemotherapy in patients with newly diagnosed advanced stage Hodgkin lymphoma (HL): North American results. *First Author: Rod Ramchandren, Barbara Ann Karmanos Cancer Institute, Detroit, MI*

Background: ECHELON-1 is a global, phase 3 study of BV plus doxorubicin, vinblastine, and dacarbazine (A+AVD) vs ABVD as frontline therapy in patients with advanced HL (NCT01712490). The primary endpoint was modified PFS (mPFS) per independent review facility (IRF) defined as progression (PD), death, or the receipt of additional treatment for patients not achieving CR at the completion of frontline therapy. A+AVD was superior to ABVD (HR = 0.77, p = 0.035) with 2-year mPFS rates of 82.1% and 77.2%; as previously reported. **Methods:** Efficacy and safety of A+AVD vs ABVD in North America (NA) was examined. mPFS in NA was a prespecified analysis. Traditional PFS by investigator, where only PD or death were counted as events, was a sensitivity analysis of the primary endpoint. **Results:** 497 pts in NA with advanced classical HL were randomized 1:1 to receive up to six cycles of A+AVD or ABVD. There was a significant improvement in mPFS by IRF and by INV for pts who received A+AVD compared with ABVD (Table). 2-year traditional PFS by INV was also improved with A+AVD. Across subgroups, a benefit for A+AVD was consistently observed, including in pts with Stage III (HR = 0.64; 95% CI: 0.33, 1.24) and Stage IV (HR = 0.55; 95% CI: 0.33, 0.94) disease. Clinical trial information: NCT01712490. Adverse event rates for A+AVD vs ABVD (all grades) were: interstitial lung disease 3% vs 10%, peripheral neuropathy, 80% vs 56%; neutropenia, 62% vs 54%; febrile neutropenia (FN), 20% vs 9%. In A+AVD pts receiving G-CSF primary prophylaxis, FN was 9%. Two NA pts died during treatment with A+AVD vs 7 with ABVD. **Conclusions:** For pts treated in NA on the ECHELON-1 trial, the absolute difference between A+AVD and ABVD at 2 years for mPFS by IRF was 10.6% and for PFS by INV was 11.7%. A prospective clinical trial is planned to confirm these safety and efficacy findings in advanced stage HL pts treated with A+AVD in the NA community setting.

	mPFS IRF		mPFS INV		PFS INV	
	A+AVD	ABVD	A+AVD	ABVD	A+AVD	ABVD
N	250	247	250	247	250	247
2-year survival (%)	84.3	73.7	86.4	73.6	88.1	76.4
HR (95% CI)	0.60 (0.40,0.90)		0.52 (0.34, 0.79)		0.50 (0.32-0.79)	
p-value	0.012		0.002		0.002	

7542 Poster Session (Board #179), Mon, 8:00 AM-11:30 AM

Long-term follow-up of brentuximab vedotin ± dacarbazine as first line therapy in elderly patients with Hodgkin lymphoma. *First Author: Jonathan W. Friedberg, University of Rochester Medical Center, Rochester, NY*

Background: Elderly patients (pts) with Hodgkin lymphoma (HL) have few treatment (tx) options and poor outcomes compared to younger pts. This phase 2, frontline, open-label trial studied brentuximab vedotin monotherapy (BV; ADCETRIS) and BV+dacarbazine (DTIC) in these pts (NCT01716806). We previously reported high response rates (92% and 100%, respectively) and complete remission rates (73% and 62%, respectively) as well as manageable safety profiles (Forero-Torres 2015, Friedberg 2017). **Methods:** Twenty-seven pts ≥ age 60 with classical HL not eligible for standard tx received 1.8 mg/kg BV; then 22 others received 1.8 mg/kg BV+375 mg/m^2 DTIC (12 cycles), then BV. Radiographic scans were done at Cycles 2, 4, 8, 12, 16 (for continued BV), end of tx, then per standard of care. Follow-up visits were every 3 months (mos). **Results:** Survival and peripheral neuropathy (PN) results are presented below. BV+DTIC resulted in 3-year (yr) PFS and OS rates of 52% and 90%, respectively, while BV alone rates were 34% and 71%. Most pts had tx-emergent PN and had either complete resolution or some resolution/improvement. Nearly all ongoing PN was Grade 1/2; 1 pt had ongoing Grade 3 PN. **Conclusions:** BV alone and BV+DTIC appear to induce long-term remissions for a subset of elderly HL pts. The addition of DTIC appears to increase durability of response and survival although not statistically assessed. PN resolution/improvement was observed for the majority of pts. These durable responses suggest that BV+DTIC may be an induction option for frail, elderly pts ineligible for standard tx. Clinical trial information: NCT01716806.

	BV (N = 27)	BV+DTIC (N = 22)
Median observation time from first dose[a], mos (range)	42.6 (4.6, 56.3)	37.8 (14.8, 44.8)
Median PFS[a], mos (range)	10.5 (2.6+, 52.2+)	NR (4.2+, 39.6+)
3-yr PFS rate[a] (95% CI)	34% (16%, 53%)	52% (26%, 73%)
Median OS, mos (range)	NR (4.6+, 56.3+)	NR (6.7+, 44.8+)
3-yr OS rate (95% CI)	71% (49%, 85%)	90% (65%, 97%)
Tx-emergent PN, n (%)	24 (89%)	19 (86%)
Complete resolution, n/N (%)	9/24 (38%)	5/19 (26%)
Some resolution/improvement[b], n/N (%)	9/24 (38%)	8/19 (42%)
Median time to resolution/improvement, weeks	12.6	4.9
Ongoing Grade 1/2, n/N (%)	14/15 (93%)	14/14 (100%)

7543 Poster Session (Board #180), Mon, 8:00 AM-11:30 AM

Survival by age in children and adolescents with Hodgkin lymphoma: A pooled analysis of Children's Oncology Group (COG) trials. *First Author: Justine M. Kahn, Columbia University Medical Center, New York, NY*

Background: The National Cancer Institute defines adolescent/young adult as 15-39y. Guidelines from ASCO and Friends of Cancer Research call for including children ≥12y on late phase trials spanning children and adults. We examined whether, in children and adolescents receiving response-based therapy for Hodgkin lymphoma (HL), age ≥12y would define a group with inferior outcomes compared to younger patients. **Methods:** This was a pooled analysis of individual patient-level data from three COG Phase 3 trials for intermediate, low, high-risk HL (AHOD0031, AHOD0431, AHOD0831). 5-yr event free survival (EFS) and overall survival (OS) by age were estimated via Kaplan Meier method. Cox regression models examined the influence of age on EFS and OS, adjusted for race/ethnicity, sex, insurance, histology, Ann Arbor stage, B symptoms, bulk, study, and radiation therapy (RT). **Results:** We included 2071 of 2155 patients, 1-21y enrolled from 2002 -2012. Mean age at diagnosis was 14.6y (±3.5) with 54% ≥15y (N = 1121) and 81% ≥12y (N = 1684). At median follow-up of 6.9 years, patients < 15y had statistically significantly better EFS (< 15y: 85% vs. ≥15y: 80%, p = 0.02). A difference in EFS was noted in those < 12y vs. ≥12y (87% vs. 81%, p = 0.0503). OS was significantly better in patients < 15y vs. ≥15y (98% vs. 95%, p = 0.006), but did not differ in < 12y vs. ≥12y (99% vs. 97%, p = 0.136). Cumulative incidence of second malignant neoplasm did not differ by age category. In multivariable models, older age was an independent predictor of treatment failure in both age categories (Table). **Conclusions:** With contemporary, response-based therapy on COG trials, adolescents ≥12 and ≥15y had worse EFS than younger groups. This suggests that children ≥12y may benefit from therapy escalation and inclusion in late phase trials of novel agents incorporating antibody drug conjugates or checkpoint inhibitors.

Multivariable cox model of 5-yr EFS and OS by age group.

	5-yr EFS			5-yr OS		
	HR	95% CI	p-value	HR	95% CI	p-value
< 12 years (R: ≥12)	0.71	(0.51, 0.98)	0.04	0.51	(0.2, 1.34)	0.17
< 15 years (R: ≥15)	0.74	(0.59, 0.93)	0.01	0.39	(0.2, 0.76)	0.006

HR: hazard ratio; 95%CI: 95% confidence interval; R: reference group

7544 Poster Session (Board #181), Mon, 8:00 AM-11:30 AM

Radiation therapy in primary testicular lymphoma (PTL): Does practice match the standard of care? *First Author: Thomas Ollila, The Warren Alpert Medical School of Brown University, Providence, RI*

Background: National guidelines recommend contralateral testicular radiation as part of therapy for primary testicular lymphoma (PTL) regardless of stage, yet adherence to this in clinical practice is uncertain. We examined factors associated with receipt of radiation and overall survival (OS) of patients with PTL treated with or without radiation. **Methods:** Using data from the National Cancer Data Base (2004-2014), which contains > 80% of lymphomas diagnosed in the United States (US), we evaluated patients with diffuse large B-cell PTL who were treated with multiagent chemotherapy. We examined factors associated with receipt of radiation using log-binomial regression for relative risk (RR) with 95% confidence intervals (CI). OS was analyzed in a multivariable extended Cox model, accounting for immortal time bias. **Results:** Out of 1,821 patients, only 49.7% received radiation therapy. In a multivariable model, significant factors associated with lower use of radiation included black race (RR 0.66, 95%CI, 0.44-0.99), age 71-80 (RR 0.83, 95%CI, 0.75-0.93) or > 80 (RR 0.52, 95%CI 0.42-0.65) relative to age 60-70, Ann Arbor stage 2 (RR 0.78, 95%CI, 0.68-0.89) or 3/4 (RR 0.74, 95%CI, 0.66-0.84) relative to stage 1, and presence of comorbidities (RR 0.84, 95%CI, 0.75-0.95). There were no significant differences by income, insurance status, distance to hospital, or type of hospital (community or academic). Among patients who received radiation therapy, OS was 86% (95%CI, 83-88%) at 3 years (y) and 79% (95%CI, 75-82%) at 5 y, whereas for those who did not it was 66% (95%CI, 63-70%) at 3 y and 57% (95%CI, 53-60%) at 5 y. Receipt of radiation was associated with lower mortality adjusting for other factors (hazard ratio 0.68, 95%CI, 0.56-0.82). **Conclusions:** Nearly half of PTL patients in this "real-world" analysis do not receive radiation therapy despite a benefit supported by prospective trials. Association with socio-demographic factors and with survival suggest that delivery of radiation therapy may be an indicator of expertise or overall quality of care in PTL. Further research should examine if other components of PTL therapy like central nervous system prophylaxis are also suboptimally delivered in the US.

7545 Poster Session (Board #182), Mon, 8:00 AM-11:30 AM

Overall survival (OS) and transplantation (ASCT) utilization in real-world patients with relapsed/refractory diffuse large B-cell lymphoma (RR-DLBCL). *First Author: Chadi Nabhan, Cardinal Health Specialty Solutions, Dublin, OH*

Background: Many patients (pts) with RR-DLBCL treated in the real-world are not offered ASCT despite its curative potential. Understanding the impact of ASCT on OS in the real world is critical to better position novel therapies as an alternative to ASCT. **Methods:** We retrospectively analyzed real-world pts with RR-DLBCL treated between 1/1/10-12/31/16 in 126 community-based hematology/oncology practices across the US. Pts treated with first line (1L) R-CHOP or DA-EPOCH-R were grouped into 2 categories: early relapse (progressive disease [PD] on treatment within 365 days from completing last cycle) and late relapse (any 2L treatment 366-730 days from last cycle of 1L). Pts were stratified whether ASCT was performed after 2L. Pts receiving rituximab monotherapy in 2L or later were excluded from analysis. A period of ≥6 months of clinical inactivity at end of follow-up served as a proxy for death. Median (95% CI) OS were estimated by Kaplan-Meier method, and adjusted hazard ratios (HR) were estimated by Cox proportional hazard models to adjust for differences in pt characteristics (sex, age at DLBCL diagnosis, time to relapse (2L), 1L R-CHOP, and comorbidities). **Results:** For the 430 pts, median age was 65 (range 18-84) years and 61% were male. Following 1L, over 86% (n = 371) had early relapse, and 14% (n = 59) had late relapse. Across all lines, 33% (n = 144) pts received a salvage regimen intended for transplant, with 38% (n = 55) of these pts proceeding to ASCT. For all pts at first relapse, median OS was 13.8 mo. from initiation of 2L. Median OS was significantly longer among those who underwent ASCT compared to those who did not (21.4 mo. vs 10.5 mo.; adjusted $P < 0.01$); HR = 0.51 (95% CI 0.32-0.81). Median OS shortened with each subsequent line of therapy—more so for non-ASCT group with a median OS at 2L of 10.5 mo., 3L of 9.4 mo., and 4L+ of 3.9 mo. for non-ASCT. **Conclusions:** Although 33% of real-world pts with RR-DLBCL received salvage regimens intended for ASCT, only 13% of all evaluable pts eventually underwent ASCT. The low utility of ASCT and the poor OS rates in non-ASCT pts in this real-world population demonstrate an unmet need for novel therapies in this setting.

7546 Poster Session (Board #183), Mon, 8:00 AM-11:30 AM

A basal gene expression signature to predict for synergy of combined EZH2 and HDAC inhibition in EZH2 dysregulated lymphomas. *First Author: Jennifer Kimberly Lue, Columbia University Medical Center, New York, NY*

Background: EZH2 is the catalytic subunit of PRC2, and induces methylation of H3K27. Activating mutations and overexpression of EZH2 are found in NHL. Inactivating mutations in histone acetyltransferases (HATs) are also common in germinal center (GC) B-cell lymphomas and together with EZH2 mutations enforce a condensed chromatin state. Given the dysregulation of EZH2 and HATs in GC-B cell lymphomas, we hypothesized that dual inhibition of EZH2 and HDAC would be synergistic. **Methods:** Lymphoma cell lines (n = 21) were exposed to the EZH2 inhibitor GSK126 (G) and HDAC inhibitor romidepsin (R). Cell viability was assessed via Celltiter-Glo assay. Synergy was assessed by Excess over Bliss (EOB), where EOB > 10 defines synergy. A cutoff of > 20 was used. Western blot, mass spec and Co-IP were performed after exposure to G+R. Mice xenografts were enrolled in: 1. Control; 2. G (100mg/kg); 3. R (2mg/kg); 4. G+R. GSEA and differential gene expression of synergistic vs. non-synergistic cell lines was performed. **Results:** EZH2 mutation is associated with increased sensitivity to G ($p = 0.02$). HAT mutations do not predict sensitivity to R ($p = 0.2$). G+R treatment was highly synergistic in cell lines with EZH2 dysfunction. G+R led to increase acetylation and decrease methylation of H3K27 as well as decreased protein expression of PRC2 members as compared to single agent. Exposure to R or G+R led to dissociation of EZH2 from other PRC2 members as well as HDAC2 and DNMT3L, which is secondary to RbAP46/48 acetylation. A selective HDAC1/2 inhibitor, ACY957, was combined with G and showed synergy. G+R led to significant tumor growth delay compared to single agents ($p < 0.05$), and led to improved OS (Median OS G = 16 d; R = 16 d; G+R = 24 d; $p < 0.001$). Synergistic cells lines share a common basal gene expression signature which was validated in DLBCL via the TCGA database. Synergistic cell lines are enriched in pathways involved in chromatin silencing and remodeling, including epigenetic pathways (FDR < 0.2). **Conclusions:** G+R is highly synergistic. Responses are predicted by the presence of EZH2 dysregulation and a shared basal gene expression signature. G+R may serve as a targeted approach for NHL dependent upon EZH2 dysfunction.

7547 Poster Session (Board #184), Mon, 8:00 AM-11:30 AM

Acalabrutinib monotherapy in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *First Author: Martin JS Dyer, The Ernest and Helen Scott Haematological Research Institute, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom*

Background: Acalabrutinib, a highly selective, potent, covalent BTK inhibitor, was assessed as monotherapy in pts with R/R de novo DLBCL. **Methods:** Eligible pts aged ≥18 y, with ECOG PS ≤2 and confirmed R/R non-germinal center (GCB) type DLBCL assessed by local IHC received oral acalabrutinib 100 mg bid until progressive disease (PD) or unacceptable toxicity. The primary endpoint was safety. Secondary endpoints included pharmacokinetics (PK), pharmacodynamics and investigator-assessed overall response rate (ORR; per Lugano criteria), duration of response (DOR) and progression-free survival (PFS). **Results:** 21 pts enrolled. To most recent prior therapy, 11 were relapsed (rel; partial response or better [≥PR], then PD), 10 were refractory (ref; no response/stable disease). Median age was 64 y (range 32-84); 86% had ECOG PS ≤1; 57% had extranodal disease; 81% had Ann Arbor stage III/IV; median no. of prior therapies was 3 (range 1-5). Median time on study was 3.9 mo (range 0.8-22.5); 1 pt continues therapy. Pts discontinued treatment primarily for PD (81%); 2 pts discontinued due to AEs (considered unrelated). PK was similar to prior studies, with rapid absorption and clearance; median steady-state BTK target occupancy was 97%-99% (n=5). ORR (≥PR) for all pts was 24% (5/21; 19% complete response [CR]). NanoString subtyping conducted on 15 pts revealed 5 GCB, 9 activated B-cell (ABC), and 1 unclassified DLBCL. The Table lists characteristics of the 5 responders. Common AEs (any grade) were diarrhea (43%), fatigue (43%), anemia (29%), cough (29%) and dizziness (29%); common Grade 3/4 AEs were anemia (24%), fatigue (10%) and abdominal pain (10%). Three pts had Grade 5 AEs (respiratory failure, meningeal progression, and sepsis); none were drug related. No atrial fibrillation, hypertension, TLS or Grade ≥3 bleeding AEs occurred. **Conclusions:** Acalabrutinib monotherapy was tolerable and had activity in difficult-to-treat DLBCL pts, including ref pts, supporting further studies in DLBCL. Clinical trial information: NCT02112526.

Pt	Subtype by Nanostring	Rel/ref	Prior therapies, #	Best response	DOR, mo	PFS, mo
1	ABC	Ref	3	CR	0.7+	2.6+
2	ABC	Rel	2	CR	13.7+	15.5+
3	ABC	Rel	2	PR	1.8	3.7
4 (ongoing)	GCB	Ref	3	CR	15.9+	20.3+
5	Missing	Rel	4	CR	1.9	3.8

+Censored.

7548 Poster Session (Board #185), Mon, 8:00 AM-11:30 AM

Results of real-time cell-of-origin subtype identification by gene expression profiling in patients with ABC-type diffuse large B-cell lymphoma in the phase III trial of lenalidomide plus R-CHOP vs placebo plus R-CHOP (ROBUST). *First Author: Grzegorz S. Nowakowski, Mayo Clinic, Rochester, MN*

Background: Gene expression profiling (GEP) is the gold standard in identification of activated B-cell-like (ABC) DLBCL, a subtype associated with inferior outcomes. The combination of lenalidomide + R-CHOP (R^2-CHOP) provided efficacy based on cell-of-origin (COO) in phase II DLBCL studies. ROBUST is a global, randomized, double blind, phase III study comparing R^2-CHOP vs placebo + R-CHOP in patients with previously untreated ABC-type CD20+ DLBCL (NCT02285062). **Methods:** ROBUST methods were previously described (Nowakowski, *Fut Oncol* 2016). Formalin-fixed paraffin-embedded excisional/surgical or core needle biopsy samples were analyzed by central pathology using the NanoString Lymphoma Subtyping Test (LST), based on the Lymph2Cx GEP assay (Scott, *Blood* 2014). Turnaround time was defined as number of days between central pathology sample receipt and results being provided to the study site. **Results:** From January 21, 2015 to August 3, 2017, 2093 patients were screened and 570 were enrolled in ROBUST. Three central pathology labs in China, USA and the UK received 2110 samples. Of 1798 successfully tested samples, COO was 788 (44%) ABC and 1010 (56%) non-ABC; 312 (15%) samples were non-processable for technical reasons (incorrect/insufficient slides or blocks, or low tissue RNA concentration and/or purity). According to geographic region of origin, the ABC-type DLBCL rate among successfully tested samples was 60% (241/404) from China/Japan/SK/Taiwan; 40% (441/1105) from Russia/Europe/Middle East; and 37% (106/289) from North America/Australia/New Zealand. Mean turnaround time was 2.4 days. **Conclusions:** Real-time COO assessment was feasible from multiple regions globally with a short turnaround time in the phase III ROBUST study, which minimizes the delay in receiving treatment. The percent of ABC-type DLBCL was similar to other reported studies of subtype analysis in the literature. Our findings impact the design and size estimation of future studies in newly diagnosed DLBCL utilizing COO as a biomarker, which provides a significant advance in precision medicine in DLBCL. Clinical trial information: NCT02285062.

7549 Poster Session (Board #186), Mon, 8:00 AM-11:30 AM

Acalabrutinib alone or in combination with rituximab (R) in follicular lymphoma (FL). *First Author: Nathan Hale Fowler, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Bruton tyrosine kinase (BTK) inhibition has shown clinical benefit in FL. Acalabrutinib is a highly selective, potent, covalent inhibitor of BTK. We evaluated acalabrutinib ± R in a Phase 1b study of patients (pts) with treatment-naive (TN) or relapsed/refractory (R/R) FL. **Methods:** Pts with R/R FL (≥1 prior treatment) were randomized to acalabrutinib (mono) or acalabrutinib + R (combo); TN pts received the combo. In 28-day cycles, R (375 mg/m^2 IV) was given weekly in Cycle 1 and on Day 1 of Cycles 2-6; acalabrutinib (100 mg PO bid [2 pts received 200 mg qd]) was given until progressive disease (PD) or intolerance. The primary endpoint was safety. Secondary endpoints included overall response rate (ORR), duration of response (DOR), pharmacokinetics (PK) and pharmacodynamics. **Results:** Thirteen TN and 27 R/R pts were treated. In all pts, the median age was 66 years (range 32-83), 98% of pts had ECOG PS ≤1, and 88% had stage III/IV disease. R/R pts received a median of 2 prior therapies (range 1-5). At a median follow-up of 22 and 7.6 months, 62% of TN and 26% of R/R pts, respectively, were still on treatment. Discontinuations were primarily due to PD (TN 15%; R/R 56%) and adverse events (AEs; TN 8%; R/R 11%). BTK occupancy and PK parameters were consistent with previous acalabrutinib studies. In all pts, common AEs (any grade) were fatigue (48%), headache (43%), diarrhea (40%), nausea (30%) and sinusitis (25%). Common Gr 3/4 AEs were hypertension (8%), increased alanine aminotransferase, increased aspartate aminotransferase, and cellulitis (all 5%), with no Gr 5 events. There were no cases of atrial fibrillation or Gr ≥3 hemorrhage. Efficacy outcomes are reported in the table. **Conclusions:** Acalabrutinib, alone and combined with R, was well-tolerated and yielded promising response rates in FL. These results support further evaluation of acalabrutinib in FL. Clinical trial information: NCT02180711.

	TN combo (n = 13)	R/R combo (n = 13)	R/R mono (n = 12)[a]
ORR[b] (≥ partial response), n (%)	12 (92)	5 (39)	4 (33)
95% CI	64, 100	14, 68	10, 65
Complete response	4 (31)	1 (8)	1 (8)
Median DOR, mo	NR	NR	NR
Range[c]	12.1 to 20.5+	10.8+ to 20.5+	0.03+ to 18.7+

NR: not reached. [a] Pts dosed at 200 mg qd not included (1 SD, 1 PD). [b] Investigator assessed using Cheson 2014 criteria. [c] "+" indicates ongoing response.

7550 Poster Session (Board #187), Mon, 8:00 AM-11:30 AM

90 yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: Updated results after a median follow-up of 8.5 years from the GOTEL trial. *First Author: Mariano Provencio-Pulla, Hospital Puerta de Hierro, Madrid, Spain*

Background: Relapse is the main cause of therapeutic failure in follicular lymphoma (FL). We report updated long-term efficacy and toxicity results of a multicenter phase II study (GOTEL-Provencio et al, Leuk Lymphoma 2014) to evaluate the role of consolidation with Yttrium-90 ibritumomab tiuxetan in patients with intermediate- and high-risk FL after 4 cycles of CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) and 2 cycles of CHOP, without Rituximab. **Methods:** Patients older than the age of 18 with biopsy-proven, untreated, two-dimensionally measurable bulky stage II, III or IV FL (grade 1, 2 or 3) expressing the CD20 antigen were eligible for this trial. Patients were treated with standard CHOP-R immunochemotherapy every 21 days for 4 cycles, and 2 cycles of CHOP without rituximab. All patients achieving at least an unconfirmed partial response after four cycles of CHOP-R chemotherapy received treatment with two cycles of CHOP, without R. Consolidation treatment was with Yttrium-90 ibritumomab tiuxetan in a single dose. **Results:** Thirty patients were included. The overall response rate after consolidation therapy was 93%. The complete clinical response rate was 76.6%. With a median follow-up of 102 months (> 8-y). Twenty-three patients (77%) are alive without disease. 6 patients died (2 progressions, 1 AML, 3 others cause). The means for progression-free survival (PFS) and overall survival (OS) were not reached. OS at 5-year was 90% (IC 95%; 72-96%); PFS at 5-years was 70% (IC 95%, 50-83%). **Conclusions:** Our data support consolidation with Yttrium-90 ibritumomab tiuxetan as an effective treatment, which provides long progression-free and overall survival, in first line after a response to induction treatment in patients with intermediate- and high-risk FL. Updates on the long-term follow-up of these studies are needed because of the natural history of FL.

7551 Poster Session (Board #188), Mon, 8:00 AM-11:30 AM

Multi-center retrospective study evaluating outcomes of grade 3A follicular lymphoma (FL). *First Author: Kyle Greene, University of Utah Huntsman Cancer Institute, Salt Lake City, UT*

Background: Pathologic grading of FL (1, 2, 3A, 3B; based on increasing number of centroblasts) is prognostic and predictive. FL 3B is treated similarly to aggressive lymphomas with rituximab and anthracycline based chemo (RA). For FL 1-2, bendamustine and rituximab (BR) treatments are non-inferior to RA and better tolerated. Unfortunately, FL 3A was largely excluded from prospective trials and treatment with BR is extrapolated. We aimed to study pretreatment characteristics and the effect of treatment for FL 3A. **Methods:** We compiled disease characteristics of 178 patients (pts) with grade 3A FL from 1992-2017 from 6 academic institutions with sufficient follow-up. Those who were observed (n=15) were excluded. Data evaluated include: FLIPI Score (age, # involved sites, hemoglobin, stage) and gender. The outcomes were compared by treatment groups of: RA, BR, Rituximab only (RO) and other treatments (TX). Kaplan-Meier survival estimates were used to assess overall survival (OS) and progression free survival (PFS). Cox regression analysis was applied to remaining patient information. **Results:** We identified 163 treated pts (RA n=108, BR n=23, RO n=12, TX n=20.) Mean age was 59.8 (range 18-88) with 56% >60. Median OS and PFS were not reached, with the exception of PFS of 1.95 years for RO (p=0.03.) RO also had higher risk baseline features. No differences were observed between BR vs RA. Interestingly, age>60 trended towards better outcomes, but did not reach statistical significance (p=0.17.) Median follow-up was 3.5 years (range 21 days-27 years). Comparing 3-year PFS and OS of BR to RA (table 1), showed HR ~1 with high p-value suggesting similar efficacy. **Conclusions:** Controversy regarding optimal management of FL 3A continues. Age > 60 was protective and definitive therapy should be offered to all age groups when appropriate. Although limited by low pt numbers, our data suggest non-inferiority of BR to RA in FL 3A pts. Future prospective studies must include FL 3A pts so optimal treatments can be established.

Survival comparison with pts who received RA.

	HR	p-value	95% CI
3-Year PFS			
BR	1.09	0.881	0.49-2.85
TX	1.7	0.34	0391-4.83
RO	3.25	0.036	1.21-4.83
3 year OS			
BR	1.17	0.71	0.38-3.80
TX	2.1	0.081	0.57-5.14
RO	2.95	0.017	1.08-9.84

7552 Poster Session (Board #189), Mon, 8:00 AM-11:30 AM

A proposal for a new staging system for extranodal natural killer T-cell lymphoma, nasal type, to predict the treatment strategy: A multicentre study from the Chinese Southwest Oncology Group and Asia Lymphoma Study Group. *First Author: Tongyu Lin, Cancer Center Sun Yat Sen University, Guangzhou, China*

Background: The survival of patients with extranodal natural killer T-cell lymphoma (ENKTL), a rare and highly aggressive malignancy, is not accurately predicted by the routine lymphoma Ann Arbor staging system (AASS). Therefore, an optimal staging system for ENKTL is warranted. **Methods:** A training cohort of patients with newly diagnosed ENKTL from 19 Chinese centres was assessed to develop a new staging system for ENKTL. The results were validated in an independent cohort including patients from Korea, Singapore and China. The new staging system was named the Chinese Southwest Oncology Group and Asia Lymphoma Study Group staging (CA) system. **Results:** Based on analyses of the 1168-patient training cohort, the CA system used the following classification scheme: stage I, lesions confined to the nasal cavity or nasopharynx without local invasiveness; stage II, non-nasal-type disease or lesions confined to the nasal cavity or nasopharynx with local invasiveness and without lymph node involvement; stage III, lesions with regional lymph node involvement; and stage IV, involvement of lymph nodes on both sides of the diaphragm or disseminated disease. The 5-year OS rates for stages I through IV were 60.7%, 42.9%, 17.5%, and 32.1% for the AASS and 70.8%, 53.1%, 38.6%, and 29.9% for the CA ($P < 0.001$). Patient distribution was more balanced with CA than with the AASS. The 985-patient validation cohort produced similar survival and distribution results to those of the training cohort. CA exhibited better prognostic value than the AASS for all 2153 patients (ROC, 0.69; 95% CI, 0.64-0.74 vs 0.62; 95% CI, 0.68-0.56; P = 0·01) and predicted that the best treatment choice based on non- anthracycline treatment was radiotherapy alone for stage I; chemotherapy combined with radiotherapy, regardless of the treatment sequence, for stage II; induction chemotherapy followed by radiotherapy for stage III; and intensive chemotherapy for stage IV patients. **Conclusions:** The CA system outperformed the AASS in staging ENKTL patients and could be useful for treatment strategy prediction and future clinical trial design.

7553 Poster Session (Board #190), Mon, 8:00 AM-11:30 AM

Lenalidomide with R-IMED (rituximab, ifosfamide, methotrexate, etoposide and dexamethasone) in refractory or relapsed non-GCB diffuse large B-cell lymphoma: A phase II clinical trial. *First Author: Tongyu Lin, Cancer Center Sun Yat Sen University, Guangzhou, China*

Background: The prognosis of refractory or relapsed(R/R) non-germinal center B cell (non-GCB) subtype diffuse large B cell lymphoma (DLBCL) is dismal without established standard salvage chemotherapy regimen. We designed a phase II trial to prospectively evaluate the efficacy and safety of the combination of lenalidomide and rituximab with the IMED (ifosfamide, methotrexate, etoposide and dexamethasone) regimen(L-R-IMED) in refractory or relapsed non-GCB DLBCL. **Methods:** Eligible participants were adults with non-GCB subtype, CD20 positive DLBCL who were refractory to or had relapsed after R-CHOP-based regimens. Patients received lenalidomide 10 mg orally per day on days 1 through 14 with R-IMED every 21 days for four to six cycles. The response was evaluated using PET-CT scan after every 2 cycles. The primary endpoint was objective response rate (ORR) and progression-free survival (PFS). **Results:** Between January 2014 and November 2017, 40 patients with non-GCB subtype, CD20 positive, R/R DLBCL were enrolled, and 40 were evaluable for response. The median age was 51 years (range 20–85 years) and 60% (24 of 40) were men and 40% (16 of 40) were women. 50% of the patient (n = 20) had refractory disease and 50% (n = 20) had relapsed disease. The ORR was 70% (28 of 40) with 55% (22 of 40) achieving a complete response. The median follow-up time was 14.8 months. The median PFS was 10.9 months (95% CI: 7.9-13.9 months) and the median PFS of patients had a complete response was 28.6 months (95%CI:8.6-48.5months). The median overall survival was not reached. The most common hematologic adverse event was neutropenia. The most common nonhematologic adverse event was fatigue. There was no treatment-associated death. None of our patients discontinued treatment due to significant hematological toxicities. **Conclusions:** Among patients with R/R non-GCB DLBCL, L-R-IMED showed promising efficacy and tolerability profile. The regimen needs to be further verified by phase III study.

7554 Poster Session (Board #191), Mon, 8:00 AM-11:30 AM

Breast Implant Associated-Anaplastic Large Cell Lymphoma (BIA-ALCL): The French Lymphoma Study Association (LYSA) registry data. *First Author: Corinne Haioun, CHU Henri Mondor, Créteil, France*

Background: BIA-ALCL is recognized as a distinct entity. In the French *Lymphopath* network with 59,356 lymphomas registered since 2010, 55 peripheral T-cell lymphomas (PTCL) out of 526 breast lymphomas were reviewed, that included 46 cases of BIA-ALCL. **Methods:** since 2016, a WebEx national multidisciplinary meeting has been implemented by the French Cancer Agency in order to define therapeutic strategies for newly diagnosed cases. BIA-ALCL registry funded by LYSA is collecting patient clinical data including reasons for breast implantation (breast augmentation, reconstruction), implant manufacturer, treatments and outcome. **Results:** 29 BIA-ALCLs have been analyzed so far. Median age was 62 y (29-77). In 15 out of 29 patients (pts) the first implant followed a mastectomy for breast cancer. Ten pts were implanted twice and 6 pts 3 times or more. Most implants were silicone-filled and textured. The median time between the first and last implant surgery and BIA-ALCL diagnosis were 10y [4-37] and 4y [0.2-8] respectively. The two clinical presentations i.e. effusion (n = 22) and breast tumor mass (n = 7) correlated with the 2 distinct histological subtypes (in situ or infiltrative). The majority of pts (84%) were stage IE (n = 21) or II (n = 1), whereas 7 pts were stage IV. Implant removal with capsulectomy was performed in 26 out of 29 patients with additional treatment based mostly on CHOP or CHOP-like chemotherapy regimens in 12 pts. After 2 years of median follow-up, 25 pts are alive and free of disease. Four pts with tumor mass presentation have died, either from lymphoma progression alone (n = 3) or with concomitant active breast cancer (n = 1). **Conclusions:** In situ BIA-ALCLs have an indolent clinical course and remain in complete remission mainly after implant removal. Infiltrative BIA-ALCLs have a more aggressive clinical course. Multiple implants and/or a past history of breast cancer could favor the occurrence of BIA-ALCL. New insights into the biology of BIA-ALCL might translate into more targeted and effective therapies.

7555 Poster Session (Board #192), Mon, 8:00 AM-11:30 AM

Primary testicular lymphoma: Treatment patterns and survival of 1740 men from the National Cancer Database. *First Author: Fernando Caumont, Virginia Mason Medical Center, Seattle, WA*

Background: The standard of care (SOC) for primary testicular lymphoma (PTL) is orchiectomy, chemotherapy (CHT) and radiation (RT) of the contralateral testis regardless of stage. PTL is rare and usually presents in elderly men; we hypothesized that men may not receive SOC and may have worse outcomes. To assess this, we queried the National Cancer Database (NCDB) which includes 70% of newly diagnosed US cancers, to analyze treatment patterns and survival of men with PTL in the rituximab era. **Methods:** Using NCDB data (2006 to 2013), we searched for men diagnosed with extra nodal lymphoma (N = 109210), primary site testis (N = 1865). Patients were analyzed in 2 treatment groups: 1) CHT + RT (SOC group); and 2) CHT alone, RT alone and orchiectomy alone, grouped as no-SOC. Kaplan-Meier (KM) survival plots were used to investigate 5-year overall survival (OS). Log rank test was used to estimate survival differences between treatments. **Results:** 1740 men with PTL underwent orchiectomy. Median age was 69. 794 (45.6%) were Stage 1, 217 (12.5%) were Stage 2, 88 (5.1%) were Stage 3, 274 (15.7%) were Stage 4. 367 men (21.1%) had no staging information available and were not included in the survival analysis. 619 (35.5%) received SOC, 692 (39.8%) had CHT alone, 54 (3.1%) had RT alone, and 375 (21.6%) received no further treatment. KM analysis by stage (Table 1) showed 5-year OS was significantly higher in the SOC group vs.non-SOC for Stage 1 (83.8% vs. 66.1%, $p < 0.001$), Stage 2 (78.2% vs. 58.7%, $p = 0.003$) and Stage 4 (64.3% vs. 54.5%, $p = 0.001$). Stage 3 patients receiving SOC had a non-significant trend toward survival advantage (74.1% vs 60.7%, $p = 0.07$). **Conclusions:** This study represents the largest PTL cohort reported to date and is reflective of current treatments. These data show that most US PTL patients do not receive guideline-recommended SOC, and OS is significantly worse across stages for those that do not receive SOC, highlighting the need for improved management of PTL

5-year OS analysis by stage.

	SOC*			No-SOC*			
Stage	Survival (%)	Alive (N)	Dead (N)	Survival (%)	Alive (N)	Dead (N)	P-values
I	83.9	260	50	66.1	320	164	< 0.001
II	78.3	54	15	58.8	87	61	0.003
III	74.1	20	7	60.7	37	24	0.07
IV	64.4	56	31	54.6	102	85	0.001

*SOC: Standard of Care

7556 Poster Session (Board #193), Mon, 8:00 AM-11:30 AM

Safety and efficacy of GVD and anti-PD-1 (SHR-1210) regimen with or without low-dose decitabine priming for refractory bulky and aggressive primary mediastinal large B-cell lymphoma. *First Author: Wenying Zhang, Bio-therapeutic Ward,Chinese PLA General Hospital, Beijing, China*

Background: Relapsed/refractory PMBCL (rrPMBCL) generally has limited treatment options and dismal prognosis. Recently, monotherapy of anti-PD-1 was reported to induce an effective and durable clinical response in nearly half PMBCL patients. However, the use of anti-PD-1 alone is notably unpractical for those with bulky aggressive lesions or life-threatening tumor mass given that anti-PD-1 alone always induce delayed tumor degradation. This ongoing, phase I/II study was aimed to evaluate the safety and efficacy of GVD chemo-regimen plus anti-PD-1 (SHR-1210) with or without low-dose decitabine priming in rrPMBCL patients with bulky aggressive lesions. **Methods:** This trial is enrolling patients with rrPMBCL who have bulky disease (minimum measurement must be > 75 mm in the longest diameter) with aggressive phenotype, rapid progression and fatal prediction. Enrolled patients were randomizedly assigned into 2 salvage treatment cohorts: GVD (Gemcitabine 0.8 g/m^2,Vinorelbine 30 mg/d, Doxorubicin 20 mg/m^2 , day 1, per 3 weeks) plus SHR-1210 (4 mg/kg, day 2, per 3 weeks) with (cohort 1) or without (cohort 2) low-dose decitabine priming (10mg/d, day -1 to -5, per 3 weeks). Safety was assessed by CTCAEv4.0, and clinical response by International Working Group (IWG) Response Criteria. **Results:** The prominent adverse event is ≤Grade 3 hematotoxicity in cohort 1. All enrolled 18 heavily-pretreated PMBCL patients had an effective control of disease progression after 1-cycle treatment and no death incident occurred so far. 11 patients had completed 4- to 8-cycle treatment, among them, 7 from cohort 1 were 2 CR, 4 PR, and 1 SD; 4 from cohort 2 were 3 CR and 1 PR. 6 patients who finished 8-cycle treatment had a 6- to 10-month ongoing progression-free survival so far. **Conclusions:** Both 2 regimens had comparably life-saving and durable clinical efficacy. Although all observed adverse events were tolerable in both groups, patients enrolled in the future will by treated by regimen without decitabine in view of the relatively lower treatment-associated toxicities. Clinical trial information: NCT03346642.

7557 Poster Session (Board #194), Mon, 8:00 AM-11:30 AM

Relationship between MRD and PET responses and PFS in previously untreated follicular lymphoma in the GALLIUM trial. *First Author: Judith Trotman, Concord Repatriation General Hospital, University of Sydney, Sydney, Australia*

Background: In GALLIUM (NCT01332968; 1202 follicular lymphoma pts), investigator-assessed progression-free survival (PFS) was significantly prolonged by first-line obinutuzumab (G)- vs rituximab (R)-based immunochemotherapy. Lymphoma activity by ^{18}F-FDG PET-CT (PET; Lugano 2014 criteria) showed complete metabolic response (CMR) at end of induction (EOI) to be prognostic for prolonged PFS and overall survival. Minimal residual disease (MRD) negativity in peripheral blood (PB) and/or bone marrow (BM) at EOI was prognostic for prolonged PFS. MRD is a sensitive measure of disease in PB and/or BM, and may add to the prognostic information provided by PET. **Methods:** Induction with G or R plus bendamustine, CHOP or CVP was followed by maintenance in responders. PET scans at baseline and EOI were assessed by an independent review committee. CMR was defined as a score of 1–3 on a 5-point scale. Baseline PB and BM were screened for MRD by consensus PCR for clonal t(14;18) translocation and/or Ig variable domain rearrangement. MRD at EOI was positive if allele- or translocation-specific real-time quantitative or nested PCR were positive in PB or BM. **Results:** Median follow-up was 44 months. At baseline, 595/609 pts with PET scans had detectable lesions and 815/1101 with MRD evaluable samples had a suitable MRD marker; 298 were evaluable for both at EOI. CMR was seen in 266 pts; 250 of these were MRD-negative (**Table**). For these pts, 2.5-year PFS from EOI was 85% (95% CI: 80–89). This group had the best PFS: Cox proportional hazard ratio (HR)=0.39 (95% CI: 0.17–0.93; p=0.03) vs CMR + MRD-positive; and HR=0.39 (95% CI: 0.19–0.81; p=0.01) vs non-CMR + MRD-negative. There were too few non-CMR + MRD-positive pts for analysis. **Conclusions:** Most evaluable pts achieved CMR and MRD-negativity, with a minority progressing despite a favorable prognosis. Risk of progression or death in pts achieving only CMR or MRD-negativity was 2.5-fold greater than in pts who achieved both, suggesting that EOI PET and MRD responses could provide complementary information. Clinical trial information: NCT01332968.

	MRD Status		
PET Response	**Negative (%)**	**Positive (%)**	**All (%)**
CMR	250/298 (84)	16/298 (5)	266/298 (89)
Non-CMR	24/298 (8)	8/298 (3)	32/298 (11)
All	274/298 (92)	24/298 (8)	298/298 (100)

7558 Poster Session (Board #195), Mon, 8:00 AM-11:30 AM

Outcomes in newly diagnosed diffuse large B cell lymphoma presenting with hepatic and/ or renal dysfunction. *First Author: Srinivasa Reddy Sanikommu, Levine Cancer Institute, Charlotte, NC*

Background: In DLBCL, hepatic and/or renal dysfunction may occur due to tissue infiltration with lymphoma, bulky lymphadenopathy leading to obstruction or tumor lysis leading to renal dysfunction. These patients are often excluded from clinical trials and there is paucity of data in this population. Recently, ASCO and Friends of Cancer Research joint statement emphasized to broaden the clinical trial eligibility criteria to make the results more representative. Therefore, we performed a retrospective study in this population. **Methods:** We obtained baseline characteristics, and assessed outcomes in patients with previously untreated DLBCL who presented with hepatic and/or renal dysfunction which led to ineligibility for prospective clinical trials at Levine Cancer Institute. Patients were treated with R-CHOP or R-EPOCH. Doxorubicin and vincristine were dose reduced for $\geq$ grade 3 hepatic dysfunction. Etoposide was dose reduced for either $>$ grade 3 hepatic dysfunction or CrCl $<$ 40ml/min. There were no dose reductions in cyclophosphamide or rituximab. **Results:** Of 146 contiguous patients screened, 20 met criteria for hepatic and/or renal dysfunction. Median follow up was 19.1 mo. Hepatic dysfunction, renal dysfunction or both were seen in 7 (35%), 9 (45%) and 4 (20%) patients respectively. Median time from consultation to starting treatment was 3 days. Cycle 1 was given as an inpatient in 18 (90%) patients. During cycle 1, dose reductions due to organ dysfunction were performed in 5 (25%) patients. Median time to reversal of impaired organ function was 12 days. By cycle 2, 18 (90%) patients received full dose chemotherapy. CR was obtained in 17 (85%) patients. The estimated 2-year OS was 80% (95% CI 62.5–97.5%). No deaths were due to organ dysfunction or drug toxicity. The results are comparable with chemoimmunotherapy in patients with DLBCL who present with normal hepatic and renal function. **Conclusions:** Rapid initiation of standard chemoimmunotherapy with dose adjustments based on degree of hepatic and/or renal dysfunction can lead to excellent outcomes in patients with DLBCL who present with organ dysfunction. Organ dysfunction related to lymphoma can reverse rapidly with chemoimmunotherapy.

7559 Poster Session (Board #196), Mon, 8:00 AM-11:30 AM

Outcomes in patients with marginal zone lymphomas undergoing transformation to high-grade lymphomas. *First Author: Juan Pablo Alderuccio, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL*

Background: Marginal zone lymphomas (MZLs) are characterized by a long overall survival (OS). High-grade transformation (HGT) to aggressive lymphoma negatively impacts OS. Thus, identifying patients predisposed to HGT is of utmost clinical importance. Given the paucity of data on HGT in MZL patients, we undertook a retrospective study of the largest cohort to date of MZL patients to identify risk factors for HGT and death, thought analyses of transformation-free survival (TFS) and OS. **Methods:** In the Florida Cancer Registry, we identified 564 biopsy proven MZL patients seen at our institution between 1/1990-12/2016. In 453 patients, diagnostic biopsies were reviewed and MZL diagnosis confirmed based on the WHO Lymphoma classification and these were studied. **Results:** Median follow-up of our cohort was 4.8 years (range 0.02-22.1yrs). The cases were classified as MALT (85.9%), splenic (7.7%) and nodal (6.4%) MZLs. 34 (7.5%) patients had biopsy proven HGT to diffuse large B cell lymphoma (DLBCL). The percentages of HGT was 17.2% in nodal, 11.4% in splenic, and 6.4% in MALT (p= 0.05). Among 34 HGT cases, the median time to HGT was 21 months (range: 0-135 months); HGT was present at the time of initial MZL diagnosis in 7(21%) patients. On multivariate analysis of TFS, patients with elevated LDH (HR 4.09,95%CI:1.91-8.76) and failure to achieve CR to initial therapy (HR 3.91,95%CI:1.80-8.48) had significantly higher risk for HGT. In separated models, IPI $>$ 2 (HR = 2.19,95%CI:1.01-4.74), and FLIPI $>$ 2 (HR = 2.52,95%CI:1.12-5.65) were significant predictors of higher risk for HGT. In the 34 patients with HGT, median OS from diagnosis was 129.6 months (95%LL = 55.2) and from HGT 87.6 months (95%LL = 14.4). Patients presenting with HGT within 12 months from MZL diagnosis had shorter OS compared to patients with late HGT [5-year OS rate 0.50 (95%CI:0.19-0.75) vs. 0.75 (95%CI:0.49-0.89), HR = 3.36, (p= 0.0192)]. **Conclusions:** In this largest single-institution study, HGT occurred in 7.5% of patients with higher proportion in nodal MZL (17.2%). Elevated LDH, FLIPI/IPI $>$ 2 and failure to achieve CR to initial therapy were identified as major risk factors for HGT. Patients transforming within 12 months from MZL diagnosis had worst survival.

7560 Poster Session (Board #197), Mon, 8:00 AM-11:30 AM

Randomized, open-label, phase II trial of everolimus versus thalidomide in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. *First Author: He Huang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Patients with diffuse large B-cell lymphoma (DLBCL) with a high International Prognostic Index (IPI) are at higher risk for relapse after a complete response (CR) to first-line rituximab-based chemotherapy. This study aimed to compare the efficacy and safety of everolimus (EVE) *v* thalidomide (THA) as maintenance therapy in patients with DLBCL in complete remission and with a high risk of relapse after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). **Methods:** This was a single-center, phase II, randomized, open-label trial. Patients with stage II bulky or stage III to IV DLBCL, IPI $\geq$2, and a positron emission tomography/computed tomography-confirmed CR to first-line R-CHOP were randomized to receive EVE 5 mg/day for 1 year or THA 100 to 300 mg/day for 2 years or until disease relapse, unacceptable toxicity, or death. Eligible patients who refused any maintenance therapy were included as control group. Primary end point was disease-free survival (DFS). **Results:** A total of 102 patients were randomized to EVE (n = 50) or THA (n = 52). After a median follow-up of 34.2 months, 2-year DFS were 84.9% with EVE *v* 84.2% with THA (HR, 0.958; 95% CI, 0.370 to 2.484). 2-year overall survival (OS) were 93.4% with EVE *v* 91.4% with THA (HR, 0.711; 95% CI, 0.169 to 2.998). The control group included 137 patients, for whom 2-year DFS and OS was 62.4% and 81.6%, respectively. Both EVE and THA arms had a superior DFS (EVE *v* control, HR, 0.345; 95% CI, 0.165 to 0.722; THA *v* control, HR, 0.350; 95% CI, 0.174 to 0.706) and OS (EVE *v* control, HR, 0.216; 95% CI, 0.067 to 0.701; THA *v* control, HR, 0.335; 95% CI, 0.132 to 0.852) compared to control group. Grade 3 or 4 adverse events with EVE *v* THA were mucositis (8%), leukopenia (8%), thrombocytopenia (4%), infection (2%), and leukopenia (6%), thrombocytopenia (4%), infection (2%), respectively. **Conclusions:** The efficacy of everolimus and thalidomide as maintenance therapy was similar, both of which significantly improved DFS and OS in patients with high-risk DLBCL after achieving CR to R-CHOP. Everolimus administered 5 mg/day and thalidomide administered 100 to 300 mg/day were tolerated well.

7561 Poster Session (Board #198), Mon, 8:00 AM-11:30 AM

Dose-adjusted (DA)-EPOCH-R with high-dose methotrexate (HD-MTX) for newly diagnosed stage II-IV CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL): Primary analysis of PEARL5 study. *First Author: Kana Miyazaki, Mie University Graduate School of Medicine, Tsu, Japan*

Background: CD5+ DLBCL comprises 5-10% of DLBCL and is characterized by various aggressive clinical features and frequent CNS relapse. Our previous retrospective study (Miyazaki et al. Ann Oncol 2011) revealed that the 2-year (yr) PFS and CNS relapse rates in patients (pts) with newly diagnosed stage II-IV CD5+ DLBCL were 51% and 15%, respectively. An interim analysis of our multicenter phase II study for newly diagnosed stage II-IV CD5+ DLBCL (PEARL5 study) revealed that DA-EPOCH-R/HD-MTX provided a high CR rate (91%) with manageable toxicity (Miyazaki et al. ASH 2016). **Methods:** Pts with newly diagnosed stage II-IV CD5+ DLBCL between 20-75 yrs old and ECOG PS of 0-3 were eligible. Four cycles of DA-EPOCH-R followed by 2 cycles of HD-MTX (3.5 g/m^2) and additional 4 cycles of DA-EPOCH-R were planned as the protocol treatment. Cell-of-origin of DLBCL was determined by means of NanoString analysis system. The primary endpoint was 2-yr PFS. **Results:** From Aug 2012 to Nov 2015, 47 pts were enrolled in the study. All the pts were eligible and exhibited the following features: age, 37-74 yrs (median 62); M:F = 18:29; ECOG PS $>$ 1, 4%; stage III/IV, 53%; IPI HI/H, 47%; and ABC/GCB/unclassified, 39/4/3 (n = 46). With a median follow-up of 3.1 yrs (range, 2.0-4.9), the 2-yr PFS rate was 79% (95% CI, 64-88%). This compared favorably with the historical control of conventional R-chemotherapy (51%). The 2-yr OS rate was 89%. One pt in CR died in a traffic accident 0.8 yr after enrollment. The 2-yr CNS relapse rate was 9% (95% CI, 3-21%; n = 4). Among the 4 pts, 1 pt had primary testicular DLBCL. The remaining 3 pts experienced CNS relapse before HD-MTX. Two of these pts had high-grade B-cell lymphoma, NOS (WHO 2016) with *MYC* rearrangement, and the other pt discontinued the protocol treatment after the 1st rituximab due to grade 4 tumor lysis syndrome. The 2-yr PFS and OS rates in CD5+ ABC DLBCL (n = 39) were 77% and 87%, respectively. **Conclusions:** DA-EPOCH-R/HD-MTX is an effective treatment for newly diagnosed stage II-IV CD5+ DLBCL. Long-term efficacy and toxicity will be evaluated in a 5-yr follow-up in Nov 2021. Clinical trial information: UMIN000008507.

7562 Poster Session (Board #199), Mon, 8:00 AM-11:30 AM

Long term follow-up (FU) of lenalidomide plus R-CHOP therapy in patients with newly diagnosed diffuse large b-cell lymphoma (DLBCL): Combined analysis from two phase 2 trials. *First Author: Alessia Castellino, Department of Hematology, Mayo Clinic, Rochester, MN*

Background: The combination of lenalidomide (Len) with Rituximab-CHOP (R2CHOP21) has been shown to be safe and effective. These early results [Nowakowski et al. JCO 2014, Vitolo et al. Lancet Oncol 2014] led to two randomized trials. However, durability of response and safety have not been reported. Here, we present the long-term FU in de novo DLBCL patients (pts) who received R2CHOP21 in two independent phase 2 studies. **Methods:** We included newly diagnosed DLBCL pts enrolled in two R2CHOP21 phase 2 trials, conducted by Mayo Clinic (MC) and Italian Lymphoma Foundation (FIL). All pts received R-CHOP21 plus Len at 25 mg/d for 10 days/cycle and 15 mg/d for 14 days/cycle in MC and FIL trial respectively. We analyzed the long term FU outcome in terms of progression-free survival (PFS), time to progression (TTP), overall survival (OS) and the cumulative incidence of late toxicities and second tumors. **Results:** 108 DLBCL pts (59 MC, 49 FIL) were included. Main characteristics were: median age 69 years (y) (25 (23%) $\geq$ 75 y), stage 3-4 in 94 (87.0%) and International Prognostic Index (IPI) $\geq$ 3 in 60 (55.6%). At a median FU of 5.1 y, 5y PFS was 65.4%, 5y TTP 69.9% and 5y OS 77.4%. In total, 31 pts have relapsed, with only 4 cases occurring beyond 3y and only 2 CNS relapses. 5y PFS in germinal center (GCB) lymphomas vs non-GCB was 55.8% vs 65.7%, 5y TTP 62.3 vs 68.0 and 5y OS 71.7% vs 75.3% respectively. Only 4 pts had grade (gr) 4-5 late toxicities (1 gr 5 sepsis and 3 gr 4 neutropenia). Milder toxicities were infections (N 5 (4.6%), only 1 gr 3), thrombosis (N 1, gr 2) and persistent neuropathy (N 3, gr 1-2). Second neoplasia were 8 (6.4%): 1 acute myeloid leukemia, 2 second lymphoma (T-cell) and 5 other solid tumors. **Conclusions:** Long term FU shows that R2CHOP21 efficacy was maintained with high rate of PFS, TTP and OS, considering high risk features of patients included. The addition of len to RCHOP appears to mitigate the negative prognostic impact of non-GCB phenotype. The incidence of second tumors was low and no new worrisome safety signals were seen. This long -term analysis will aid interpretation of early results from randomized clinical trials, expected to be reported in near future.

7563 Poster Session (Board #200), Mon, 8:00 AM-11:30 AM

DEVEC metronomic schedule for aggressive B and T-cell lymphomas. *First Author: Maria Christina COX, Hematology Unit, Sant'Andrea Hospital, Roma, Italy*

Background: Metronomic chemotherapy (MC) is an emerging approach in solid tumours. Since MC has been poorly investigated in aggressive lymphomas in 2011, we formulated a new oral MC regimen termed DEVEC (Deltacortene, Etoposide, Navelbine, Cyclophosphamide). **Methods:** The DEVEC foresees an induction and a deescalated maintenance phase both consisting in 6 cycles. Rituximab is administered in CD20+ cases. Patients with aggressive B and T cell lymphomas, unsuitable for standard-chemotherapies, were enrolled in 6 Italian institutions. HIV+ and CNS involvement were excluded. Data were retrieved as of 31th January 2018 (EC approval n° 4640). **Results:** 58 patients started DEVEC between October 2011 and October 2017: the median follow-up time is 23 months. Median age was 79 years (26–93): 22 (37.9%) were refractory and 20 (34.5%) relapsed after previous treatments; 16 (27.62%) were treatment-naïve. Histology: DLBCL = 41(70.7%); PTCL = 15 (25.9%) and MCL = 2 (3.4%). By comprehensive geriatric assessment, patients scored as FIT = 7 (12%), UNFIT = 16 (27.6%), FRAIL = 23 (39.6%); Super-Frail (SF) = 10 (17.2%). In 53 evaluable cases the overall hematologic toxicity was mild and manageable with growth factors. Extra-hematologic toxicity of grade $\geq$3 was reported in 12/53 patients (22.6%) and were all classified as SAE: 6/12 cases occurred in SF. 5/12 patients discontinued DEVEC and died respectively 0, 1, 4, 4 and 5 months after treatment stop. In 50/53 patients, evaluable for outcome, the ORR was 68% and CR rate 44%. In the Naïve subset (n = 14) ORR = 92.8% and CR+CRu = 64%; in the Relapsed subset (n = 16): ORR = 93.7%; CR = 62.5%; in the Refractory subset (n = 20) ORR = 30%; CR = 10%. The estimated median OS and PFS were 15 (95%CI = 9.17-20.83) and 13 (CI 95% = 2.07-23.93) months, respectively. No significant differences in OS and PFS were observed in DLBCL vs PTCL. The direct cost of drugs of the oral DEVEC schedule was estimated 930 and 817 Euro (year 2016) for a single induction and maintenance cycle, respectively. **Conclusions:** To our knowledge this is the largest series of aggressive lymphoma treated with MC. DEVEC induced sustained CR in a substantial proportion of patients with very poor outlook and deserves further studies in aggressive lymphomas.

7564 Poster Session (Board #201), Mon, 8:00 AM-11:30 AM

A phase II trial of bevacizumab-GemAOD regimen for newly diagnosed extranodal NK/T cell lymphoma. *First Author: Zhiming Li, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Efficacy of L-asparaginase-based regimens has been confirmed for patients with extranodal natural killer/T-cell lymphoma (ENKTL). However, targeted therapy and optimal chemotherapy regimens for ENKTL remain to be determined. As high levels of vascular endothelial growth factor A (VEGF) is associated with a poor prognosis in ENKTL, we evaluated the efficacy and safety for bevacizumab (BEV) in the combination with gemcitabine, PEG-asparaginase, oxaliplatin and dexamethasone (BEV-GemAOD) regimen in untreated ENKTL in the Phase II Study (NCT 01921790). **Methods:** Patients with newly diagnosed ENKTL in stageI-IV from 18 to 80 years were eligible for enrollment. BEV-GemAOD regimen (bevacizumab 7.5 mg/kg d1; gemcitabine 1000 mg/m^2 d1, d8; PEG-aspargase 2500 U/m^2 d1; oxaliplatin 130 mg/ m^2 d1; dexamethasone 20 mg, d1-3; q3w) was planned as the protocol treatment. Patients with stage I/II received sandwich chemoradiation (BEV-GemAOD$\times$3 cycles followed by RT 50.4 Gy followed by BEV-GemAOD$\times$3 cycles). For stage III/IV, BEV-GemAOD regimen was repeated for six cycles. The primary endpoint was overall response rate (ORR) after six cycles of BEV-GemAOD. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. **Results:** 56 patients were enrolled from Oct 2013 to Feb 2018. 43 patients were evaluable for response: the median age, 37 years (range: 18-65 years); female, 25.6%; ECOG PS $>$ 1, 20.9%; stageIV, 37.2%; elevated LDH, 39.5%; elevated EBV DNA, 60.5%. After 2 cycles of BEV-GemAOD, ORR were 100%. CR rate (CRR) in stage I/II and III/IV were 88.9% (24/27) and 25% (4/16), respectively. After 6 cycles ORR were still 100%. CRR increased to 100% (27/27) and 87.5% (14/16), respectively. At median follow-up of 25.3 months, 2-year PFS and OS were 83.3% and 78.8%. The most common hematologic adverse event of grade 3/4 was neutropenia (32.6%). No patient died of treatment related toxicity. **Conclusions:** These results demonstrate that BEV-GemAOD regimen is feasible and provides high ORR, CRR and survival for either early- or late-stage patients with newly diagnosed ENKTL. Clinical trial information: NCT01921790.

7565 Poster Session (Board #202), Mon, 8:00 AM-11:30 AM

DLBCL outcomes in Malawi: Effect of HIV and derivation of a simplified prognostic score. *First Author: Matthew Painschab, Lineberger Comprehensive Cancer Center; University of North Carolina, Chapel Hill, NC*

Background: Prognostic factors for diffuse large B-cell lymphoma (DLBCL) in sub-Saharan Africa (SSA) are unknown. We report mature data from one of the first prospective DLBCL cohorts treated under real-world conditions in SSA. **Methods:** Patients ≥18 years with newly diagnosed DLBCL were enrolled in Malawi from 2013 to 2017. Participants were treated with CHOP chemotherapy, and concurrent antiretroviral therapy (ART) if HIV+. **Results:** 86 participants were enrolled with mean age 47 (SD 13). 54 (63%) were male, and 51 (59%) were HIV+, of whom 34 (67%) were on ART at DLBCL diagnosis. Median CD4 count was 113 cells/mL (IQR 62-227) and 25 (49%) had an HIV viral load < 400 copies/mL. HIV+ participants were younger and more urban, but otherwise similar to HIV-. 10 (12%) participants died before chemotherapy. Participants received a median 6 CHOP cycles (IQR 4-6). 28% of cycles were delayed or reduced for toxicity, more commonly in the HIV+ group, typically for neutropenia. No patients were lost to follow-up with median follow up 24 months (IQR 16-40) for patients still alive at administrative censoring. 2-yr overall survival (OS) was 38% (95% CI 28-49), and 42% (95% CI 30-53) for patients surviving to CHOP initiation. For those receiving CHOP, 13/43 (30%) deaths were treatment-related, and occurred primarily in patients with adverse baseline DLBCL characteristics. In multivariate analyses, only ECOG performance status (PS) ≥2 and lactate dehydrogenase (LDH) > 2x upper limit of normal (ULN) were associated with mortality. HIV was not associated with OS, but for HIV+ patients, being on ART prior to lymphoma diagnosis was associated with mortality. A simplified prognostic model of LDH > 2x ULN and PS≥2 outperformed the traditional age-adjusted IPI. **Conclusions:** DLBCL can be successfully treated in SSA and outcomes were not different for HIV+ and HIV- patients, although OS was worse than resource-rich settings. For HIV+ participants, those developing DLBCL on ART had worse OS, suggesting possible effects of the immunologic environment on tumor biology. A simplified prognostic model utilizing only PS and LDH may be optimal in resource-limited settings, where staging is imprecise, but requires additional validation.

7566 Poster Session (Board #203), Mon, 8:00 AM-11:30 AM

***Pd-l1* gene alterations to identify a subset of diffuse large B cell lymphoma that harbor a T cell inflamed phenotype.** *First Author: James K. Godfrey, University of Chicago, Chicago, IL*

Background: Programmed death – ligand 1 (PD-L1) expression on malignant cells is a dominant immune escape mechanism in cancer, and classically occurs as an adaptive response to the presence of activated T cells and interferon gamma in the tumor environment. Interestingly, a unique genetic mechanism underlying PD-L1 up-regulation has been described in a variety of lymphomas, in which the 9p24.1 chromosomal region encoding the PD-1 ligands is highly amplified. We sought to determine the incidence and immune landscape of *pd-l1* gene copy number alterations (CNA) in diffuse large B cell lymphoma (DLBCL). **Methods:** We utilized fluorescent in situ hybridization (FISH) to identify DLBCLs harboring *pd-l1* CNA, thereby enabling a characterization of the immunogenomic landscape of these lymphomas compared to those lacking *pd-l1* CNA. **Results:** Among 95 DLBCLs analyzed, 26% harbored *pd-l1* CNA (17 copy gain, 7 amplified, 1 translocation). *Pd-l1* CNA were highly enriched among DLBCLs with an activated B cell phenotype (75%). PD-L1 cell surface expression was strikingly enhanced in DLBCLs with *pd-l1* CNA versus those without, as assessed by PD-L1 H score. Furthermore, *pd-l1* CNA DLBCLs were associated with a pronounced infiltration by T cells with a restricted T cell receptor – beta repertoire, suggesting that lymphoma antigen-specific T cells had expanded in these samples. RNA-sequencing of *pd-l1* gene-altered versus non-altered DLBCLs revealed differential expression of *pd-l1*, as well as genes involved in T cell and cytokine signaling in the former, indicating that *pd-l1* CNA DLBCLs have been subjected to host immune surveillance. Lastly, whole exome sequencing of *pd-l1* gene altered versus non-altered DLBCLs is ongoing to identify potential differences in mutational loads and profiles. **Conclusions:** Our results indicate that *pd-l1* CNA identify a unique biological subset of DLBCL that has activated an endogenous anti-lymphoma immune response, and that may be more likely to respond to checkpoint blockade therapy with anti-PD-1 antibodies. We propose that a straightforward FISH analysis for *pd-l1* gene amplification may be useful as a predictive biomarker for immunotherapy responsiveness in DLBCL.

7567 Poster Session (Board #204), Mon, 8:00 AM-11:30 AM

Factors associated with duration of response after CD19-specific CAR-T cell therapy for refractory/relapsed B-cell non-Hodgkin lymphoma. *First Author: Jordan Gauthier, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: CD19-specific chimeric antigen receptor-modified T (CD19 CAR-T) cells achieve high complete remission (CR) rates in relapsed/refractory B-cell non-Hodgkin lymphoma (NHL), yet factors governing duration of response are unknown. **Methods:** We studied outcomes of 57 adults treated on a clinical trial (NCT01865617) with cyclophosphamide and fludarabine followed by 2 x 10^6 CD19 CAR-T cells/kg administered in a defined 1:1 ratio of CD4+/CD8+ CAR-T cells, and identified factors impacting progression-free survival (PFS) and overall survival (OS). **Results:** The median age was 56.5 years (range: 27 - 71) and the median number of prior therapies was 4 (range: 1 - 11). 25 patients (pts; 44%) had prior transplant, 47 (82%) had aggressive histology, and 46 (81%) had an IPI ≥ 2 at enrollment. The median lymph node burden (SPD) was 3343 mm^2 (range: 124 - 16765); 8 pts (14%) had bulky disease (diameter ≥ 10 cm). The median follow-up was 15.7 months. The best overall response and CR rates were 60% and 47%, respectively. Higher peak blood CAR-T cell counts (Cmax) and area under the curve (AUC) from day 0 - 28 after infusion by qPCR were associated with longer PFS (Cmax, HR = 0.48, P < 0.001; AUC, HR = 0.45, P < 0.001) and OS (Cmax, HR = 0.63, P = 0.03; AUC, HR = 0.61, P = 0.02). Higher CD8+, but not CD4+, CAR-T cell counts by flow cytometry correlated with longer PFS (Cmax, HR = 0.55, P < 0.001; AUC, HR = 0.53, P < 0.001) and OS (Cmax, HR = 0.62, P = 0.01; AUC, HR = 0.61, P = 0.01). SPD < median was associated with longer PFS (P = 0.004) and OS (P = 0.01). In multivariate analysis, low IPI (0-1 vs 3-4, HR = 0.11, P = 0.005) and indolent histology (HR = 0.05, P = 0.009) were associated with longer PFS; low IPI was associated with longer OS (0-1 vs 3-4, HR = 0.06, P = 0.007). In pts achieving CR after CAR-T cells, the probabilities of 1-year OS and PFS were 92% and 69%, respectively. In this subgroup, the median OS and PFS were not reached (median follow-up, 15 months). Multivariate analysis after adjusting for histology showed that the IPI and SPD adversely impacted PFS (IPI, P = 0.002; SPD, P = 0.007) and OS (IPI, P = 0.01; SPD, P = 0.02). **Conclusions:** Histology, IPI and CAR-T cell kinetics govern duration of response in NHL pts receiving CD19 CAR-T cells. Clinical trial information: NCT01865617.

7568 Poster Session (Board #205), Mon, 8:00 AM-11:30 AM

Phase II study of the PD1-inhibitor pembrolizumab for the treatment of relapsed or refractory mature t-cell lymphoma. *First Author: Stefan K. Barta, Fox Chase Cancer Center, Philadelphia, PA*

Background: PDL-1 is often expressed on tumor cells or in the microenvironment of T-cell NHL (Wilcox RA. Blood 2009) making inhibition of the PD1/PDL-1 axis a rational treatment target for T-cell NHL. **Methods:** We evaluated monotherapy with the PD1-inhibitor pembrolizumab (200mg flat dose q3weeks) for pts aged ≤18 with relapsed or refractory mature T-cell NHL in a multicenter prospective phase II trial. Primary endpoint was median progression-free survival (mPFS) defined as time from enrollment to either death or progression. The study was powered to demonstrate an improvement in mPFS from 3 to 6 months. **Results:** 18 pts were enrolled and included in the safety analysis. 17 pts were included in the survival analysis as 1 pt was found ineligible after central path review (n = 7 PTCL-NOS; n = 3 follicular T-cell lymphoma; n = 3 transformed MF; n = 1 MEITL, HSTCL, and AITL each; n = 1 ineligible histology). 2 pts came off study prior to response assessment for toxicities leaving 15 pts evaluable for response. Median age was 71 (18-88); 47% were male; median number of prior therapies was 2 (1-9); 76% were refractory to their last treatment. Response rate was 27% (4/15 pts; 95%CI 5-49%). All 4 responders (ALCL, MF, PTCL-NOS, FTCL) achieved a CR and were pts who had received ≤2 prior therapies. PDL1-expression was higher in responders, though not significantly (H-score 115 vs 68; p = 0.68). Median response duration was not reached with 2 of 4 responses ongoing > 9 months; 2 pts came off study in CR (n = 1 at 6 wks for toxicity; n = 1 at 6 mo for transplant). Median PFS and OS were 3.2 (95%CI 1.2-3.7) and 10.6 months (95%CI 3.2-100) respectively, with a median follow up of 5.9 months. 88% discontinued treatment early for PD (44%), toxicity (22%), pt choice, investigator choice, or transplant (6% each). Rash was the most common treatment attributable adverse event (AE) in 17% (n = 3). Most common AE ≥G3 were pneumonitis and rash (11% each). Treatment attributed SAE occurred in 11% (pneumonitis: n = 1; vasculitis: n = 1). Immune-related AE ≥G3 occurred in 5 pts (pneumonitis, rash: n = 2 each; vasculitis: n = 1). **Conclusions:** Pembrolizumab has moderate activity in T-cell NHL with acceptable toxicities. Combination therapies are being actively explored. Clinical trial information: NCT02535247.

7570 Poster Session (Board #207), Mon, 8:00 AM-11:30 AM

Copanlisib treatment in patients with relapsed or refractory indolent B-cell lymphoma: Subgroup analyses of diabetic patients from the phase II CHRONOS-1 study. *First Author: Martin H. Dreyling, Klinikum der Universität München LMU, Medizinische Klinik und Poliklinik III, Munich, Germany*

Background: Copanlisib is a pan-Class I phosphatidylinositol 3-kinase (PI3K) inhibitor with predominant PI3K-α and PI3K-δ activity recently approved in the US for treatment of relapsed follicular lymphoma. In the CHRONOS-1 trial, treatment of patients with relapsed or refractory indolent lymphoma resulted in an objective response rate of 59% (*JCO* 35:2169-2178, 2017). The most prominent adverse event following intravenous administration of copanlisib is transient hyperglycemia, thought to be due to impaired glucose uptake associated with PI3K-α isoform inhibition. We focus here on the diabetic mellitus (DM) patients enrolled in the phase II study. **Methods:** Indolent B-cell lymphoma patients with well-controlled DM were eligible and required to have fasting glucose < 160 mg/dL prior to each infusion. Patients received copanlisib 60 mg as a 1-hour infusion on days 1, 8, and 15 of a 28-day cycle. On C1D1, glucose was measured at pre-dose, and 3, 5, 6 and 8 hours after infusion. DM patients were instructed to check blood glucose at home 3x per day for 72 hrs after infusion until fasting glucose was < 160 mg/dL or non-fasting glucose was < 200 mg/dL. **Results:** Twenty patients with DM out of a total of 142 patients were enrolled; 17 patients with a history of DM, 1 with history of impaired glucose tolerance, and 2 diagnosed at screening. Comparing non-DM patients (n = 122) to DM patients, all-grade (G) hyperglycemia was 43% vs 85%, G3 31% vs 40%, and G4 2% vs 35%. In routine laboratory glucose assessments, G3 events were reported in 39% vs 70% and G4 in 2% vs 30%, non-DM vs DM respectively. Objective responses were observed in 9 of 20 patients (45%; 2 non-evaluable), including one complete response and stable disease in 8 patients (40%). Of note, 6 responders were on treatment > 300 days (or > 30 infusions), with 5 of these patients remaining on treatment at data cut-off. **Conclusions:** These results strongly suggest that the transient hyperglycemia seen with IV administration of copanlisib is also manageable in indolent lymphoma patients with DM as a comorbidity and should thus not preclude treatment of such patients. Clinical trial information: NCT01660451.

7571 Poster Session (Board #208), Mon, 8:00 AM-11:30 AM

Predictors of disease progression in smoldering Waldenström macroglobulinemia. *First Author: Saurabh Zanwar, Mayo Clinic, Rochester, MN*

Background: There are limited data on predictors of disease progression in patients (pts) with smoldering Waldenström Macroglobulinemia (SWM). We aim to address this issue in a large cohort of SWM with a long follow-up. **Methods:** Pts with Waldenström Macroglobulinemia (WM) seen at Mayo Clinic, Rochester from 1996-2013 were included. Time-to-progression (TTP) was defined as interval from diagnosis of SWM to initiation of WM-directed therapy per 2002 Consensus criteria or development of light chain amyloidosis (AL) or transformation. Cumulative incidence of progression (CIP) was calculated by competing risk analysis. Median values were chosen as cutoff for dichotomization of continuous variables for univariate analysis (UVA) and multivariate analysis (MVA). Kaplan Meier method was used for time-to-event-analyses. **Results:** Of 823 WM pts, 143 (17%) had SWM. After a median follow-up of 9.5 years (yrs) [95% CI 8-11.5 yrs], 110 (77 %) pts progressed (107 required therapy for WM, 3 developed AL). CIP was 11%, 37% and 52% at 1, 3 and 5 yrs, respectively. On UVA **(Table 1)**, hemoglobin (Hgb) ≤12.3 g/dL (p = 0.01) and beta-2 microglobulin (β2M) ≥2.7 ug/mL (p = 0.02) were significant predictors of TTP. On MVA, Hgb ≤12.3 g/dL [Risk ratio (RR) 1.9 (95% CI 1.1-3.5); p = 0.02] and β2M ≥2.7 ug/mL [RR 1.95 (95 % CI 1.1-3.6); p = 0.03] remained independent predictors of TTP. A score of 1 was assigned to both, giving a minimum score of 0 and maximum score of 2. The TTP was 9.3 yrs (95% CI 5.6-22.5 yrs), 4.1 yrs (95% CI 2.1-6 yrs) and 2.3 yrs (95% CI 1.5-4.5 yrs) for scores of 0, 1 and 2, respectively (p = 0.004). **Conclusions:** One-half of pts with SWM progress within five years from diagnosis. Pts with Hgb ≤12.3 g/dL and β2M ≥2.7 ug/mL at diagnosis have the shortest TTP.

Impact of baseline characteristics on TTP.

Parameter	Median (interquartile range)	P value (univariate)
Age (yrs)	64.3 (59-71.1)	0.76
MYD88^{L265P} mutated (%)	78	0.14
IgM (mg/dL)	2450 (1610-3590)	0.30
Marrow lymphoplasmacytic infiltrate (%)	30 (20-50)	0.88
LDH (U/L)	135 (106-157)	0.71
IgA (mg/dL)	64 (30-125)	0.56
IgG (mg/dL)	664 (486-997)	0.79
Involved/uninvolved serum free light chain ratio	9 (3.4-18.9)	0.07
Hemoglobin (g/dL)	12.3 (11.2-13.3)	**0.01**
Platelets (10^9/L)	264 (201-338)	0.52
β2M (ug/mL)	2.7 (2-3.7)	**0.02**

7572 Poster Session (Board #209), Mon, 8:00 AM-11:30 AM

Early detection of post-transplant lymphoproliferative disorder using circulating tumor DNA. *First Author: Joanne Soo, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Diffuse large B cell (DLBCL)-like post-transplant lymphoproliferative disorder (PTLD) affects 2-5% of transplant recipients. Although 50% of PTLDs can be related to Epstein-Barr virus (EBV) infection (Luskin et al., 2015) and high or increasing EBV viral load may precede EBV+ PTLD (Tsai et al., 2008), preemptive monitoring of EBV titers does not reliably predict development of PTLD (Dierickx et al., 2018). We aimed to assess the utility of circulating tumor DNA (ctDNA) for early detection of PTLD. **Methods:** We applied CAPP-Seq (Newman et al., 2014) to diagnostic tumor and plasma samples and matched germline in a cohort of 9 transplant recipients who developed PTLD to identify somatic alterations. We compared mutational patterns in PTLD to 149 de novo DLBCL cases sequenced by the same method as well 1112 published whole exome sequences (Pasqualucci et al, 2011; Reddy et al, 2017). We additionally sequenced serial post-transplant plasma samples preceding diagnosis in 5 patients and during or after treatment in 8 patients to determine the dynamics of ctDNA and compared these patterns to clinical outcome and EBV titers. **Results:** There was no significant difference in mutational burden between patients with PTLD and de novo DLBCL (median PTLD variants: 216, IQR = 79 – 321; median de novo DLBCL variants: 143.5, IQR = 45 – 243.8; p = 0.35), though there was a trend toward greater variant count in EBV- compared to EBV+ PTLD (p = 0.064). The prevalence of alterations in known driver genes including CREBBP, CARD11, MYD88, and EZH2 was similar between PTLD and de novo DLBCL. Prediagnostic plasma samples were available for 5 cases, including two EBV- PTLD, and we detected ctDNA in all patients prior to clinical diagnosis (mean lead time = 114 days). In the 3 EBV+ cases, EBV titers were concordant with ctDNA levels in EBV+ cases at all time points. In addition, ctDNA levels during and after treatment were concordant with clinical response in all patients. **Conclusions:** PTLD patients have detectable ctDNA prior to clinical diagnosis. Development of screening tools utilizing both ctDNA and EBV titers could facilitate early detection of PTLD in the transplant population.

7573 Poster Session (Board #210), Mon, 8:00 AM-11:30 AM

AMC075: A randomized phase II trial of vorinostat with R-EPOCH in aggressive HIV-related NHL. *First Author: Juan Carlos Ramos, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: HIV+ individuals are at increased risk for developing aggressive NHL that are often EBV+ or HHV-8+. We recently reported a phase I study using the HDAC inhibitor vorinostat (V) with R-DA-EPOCH for untreated high-risk HIV-NHL. We hypothesized that V would enhance the anti-tumor effects of R-EPOCH, and transiently activate latent EBV, HHV-8, and HIV, thus targeting virus-infected reservoirs. The recommended phase II dose of V administered on days 1-5 with R-EPOCH was 300 mg. In 12 evaluable patients (pts), the complete response (CR) rate was 83% with a 1-yr event-free survival (EFS) of 83%. **Methods:** *Eligibility*: HIV+ pts with untreated high-risk non-Burkitt NHL (aa-IPI 2-3, or Ki-67 ≥ 80%, or DLBCL-ABC subtype, or other aggressive non-DLBCL NHLs) with CD4 count ≥ 50 cells/mm^3. *Randomized phase II (45 pts on each arm)*: The primary objectives were to determine safety and efficacy of R-DA-EPOCH +/- V using CR rate as the primary endpoint. Correlative studies compared treatment effects on HIV viral loads, T-cell subsets, and immunoglobulin (Ig) levels. Latent HIV reservoir was investigated longitudinally using quantitative viral outgrowth assay. **Results:** A total of 90 pts (93% male, median age = 48, median CD4 = 190 cells/mm^3) were treated; the most common NHLs were DLBCL (n = 31, 69%), plasmablastic lymphoma (PBL) (n = 8, 18%), primary effusion lymphoma (PEL) (n = 5, 11%) under VR-EPOCH arm vs. 35 (78%) DLBCL, 7 (16%) PBL, and 2 (4%) PEL under R-EPOCH. Grade 4 neutropenia and thrombocytopenia wer more common with VR-EPOCH (44% and 27%, respectively), vs R-EPOCH (16% and 2%, respectively). There were 2 treatment-related deaths (1 for each arm), and similar rates of febrile neutropenia (18% vs. 16%, respectively). CR rates were 65% for VR-EPOCH vs. 77% for R-EPOCH (1-sided P = 0.895). The 1-yr EFS rates (±standard errors) in evaluable pts for V-R-EPOCH (n = 43) vs. R-EPOCH (n = 45) were 75.6% (±6.4%) vs. 82.2% (±5.7%), with 1-yr overall survival of 77.6% (±6.3%) vs. 86.7% (±5.1%), respectively. V had no significant impact on HIV viral loads, latent reservoir, T-cell subsets, or Ig levels. **Conclusions:** This study demonstrated no clinical benefit of adding an HDAC inhibitor to concurrent curative chemotherapy in aggressive HIV-NHL upfront. Clinical trial information: NCT01193842.

7574 Poster Session (Board #211), Mon, 8:00 AM-11:30 AM

Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA. *First Author: Michael Pfreundschuh, University Saarland Medical Schooly, Homburg Saar, Germany*

Background: The role of RT to B and E for young patients with good-prognosis DLBCL is ill-defined. **Methods:** 18-60 year-old patients (aaIPI = 0 with B [≥7.5 cm], aaIPI 1) qualifying for radiotherapy to B or E were randomized to 6xR-CHOP-14 or 6x-R-CHOP-21 followed by RT (39.6 Gy) to B and E sites or observation in a 2x2 factorial design. Primary endpoint was event-free survival. **Results:** A planned interim analysis of the first 285 patients had revealed a significantly better EFS of patients assigned to RT (p = 0.004) resulting in the pre-defined closing of the non-RT arms. 305 pts (R-CHOP-21: 155; R-CHOP-14: 150) assigned to RT and 162 (R-CHOP-21: 81, R-CHOP-14: 81) assigned to observation were evaluable for this final analysis. There were no relevant differences in protocol adherence and toxicity between the two chemotherapy regimens. EFS, PFS and OS after R-CHOP-14 and R-CHOP-21 were not different. After 66 months median observation 3-year EFS was worse in pts not assigned to RT (68% vs. 84%; p = 0.001), due to a higher rate of PR (11% vs. 2%) triggering additional treatment (mostly RT) as an EFS event. 3-year PFS of pts assigned to RT was not significantly better (89% vs. 81%; p = 0.221) and 3-year OS (93% vs. 93%, p = 0.506) was not different, which was confirmed in a multivariate analysis adjusting for elevated LDH, stage III/IV, B and E involvement (HR_{EFS}= 0.5 [95%CI: 0.4-0.8], p = 0.001; HR_{PFS}= 0.7 [0.5-11], p = 0.174; HR_{OS}= 1.2 [0.6-2.2], p = 0.674). Results were not different when the analysis was restricted to patients with bulky disease only. **Conclusions:** There were no differences in outcome between R-CHOP-14 and R-CHOP-21. Patients assigned to observation had a worse EFS because of more events largely due to a higher PR rate triggering additional treatment with no differences in PFS and OS. These results highlight the difficulties in interpreting residual masses in DLBCL without a PET which has been shown to identify (elderly) patients with B who can be spared from radiotherapy without compromising their outcome [Pfreundschuh et al., ASCO 2017, #7506]. S*upported by Deutsche Krebshilfe, Amgen and Roche* Clinical trial information: NCT00278408.

7575 Poster Session (Board #212), Mon, 8:00 AM-11:30 AM

R-CHOP preceded by blood-brain barrier permeabilization (BBBp) by NGR-tumor necrosis factor (NGR-hTNF) in patients with relapsed or refractory primary CNS lymphoma (rrPCNSL): First results of the "INGRID" phase II trial. *First Author: Andres J. Ferreri, IRCCS San Raffaele Scientific Institute, Milano, Italy*

Background: PCNSL pts are treated with HDMTX-based chemo, which requires hospitalization and extensive expertise to manage toxicity. R-CHOP could overcome these troubles, but CNS access of related drugs is poor. TNF induces BBBp and improves CNS access of anticancer drugs. The addition of NGR peptide enhances biological properties of TNF without major toxicity. The hypothesis that NGR-hTNF can improve CNS availability and activity of R-CHOP in pts with rrPCNSL is being evaluated in a phase II trial. Herein, we report results of a per-protocol exploratory analysis. **Methods:** HIV-neg pts (age 18-80 y; PS ≤3) with PCNSL failed after HDMTX-based chemo were enrolled. Pts received 6 cycles of R-CHOP, preceded by NGR-hTNF 0.8 μg/m² in 1-hr inf in cycles 2-6. Response, microvasculature and vessel permeability were assessed by DCE- and DSC-MRI. Permeability was assessed in enhanced lesions and perilesional areas; results were expressed as Ktrans values normalized using contralateral white matter. R-CHOP drugs levels were assessed on matched CSF and serum/plasma samples. **Results:** The first 10 registered pts (median age 61 yo, range 41-68; 7 males) were analyzed. Pts were heavily pretreated: 7 had received ASCT, WBRT or both; 6 had refractory disease. Response to NGR-hTNF R-CHOP was complete in 5 pts and partial in 2; 3 pts experienced PD. All responding pts received consolidation (WBRT or ASCT); DoR was > 6 months in 6 pts, only one responding pt died. Treatment was well tolerated; no cases of g≥3 non-hematol toxicity, dose reduction or interruption were recorded. Neutropenia (54% of courses) and thrombocytopenia (15%) were the only g4 toxicities. NGR-hTNF delivery increased permeability as median (range) Ktrans of enhanced and perilesional areas raised from baseline values of 23.5 (6.8-98.8) and 2.5 (0.4-3.9) to 35.3 (23.9-887.7; p = 0.39) and 4.7 (2.2-37.7; p = 0.01), respectively. PK and perfusion data will be presented at the meeting. **Conclusions:** This exploratory study suggests that NGR-hTNF increases vascular permeability in pts with rrPCNSL. R-CHOP preceded by NGR-hTNF is safe and active in these pts. Clinical trial information: 201400153211.

7576 Poster Session (Board #213), Mon, 8:00 AM-11:30 AM

Circulating tumor DNA to predict timing of relapse in mantle cell lymphoma. *First Author: Mark J. Roschewski, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Mantle cell lymphoma is clinically heterogeneous. MRD- after frontline therapy improves PFS, but virtually all pts relapse. Surveillance after induction is not uniform and clinical decisions are empirical. Detection of ctDNA in the blood throughout therapy is promising. We used AdaptiveÕs next-generation sequencing assay to detect and quantify ctDNA in blood throughout therapy for MCL. **Methods:** Untreated MCL pts received bortezomib (BZ) + DA-EPOCH-R x 6 then randomized to obs vs. BZ maint x 18m. Pt serum collected pre-Tx, w/each cycle, and w/each surveillance visit paired w/CT scans at regular intervals for 5y. FFPE was analyzed for tumor-specific clonotypes. Tumor DNA was amplified using locus-specific primer sets for the Ig heavy-chain and light-chain loci, BCL1, and BCL2 translocations. Amplified products were sequenced, and pts w/o a high-frequency tumor clonotype excluded. Baseline ctDNA levels were compared to tumor burden and proliferation. Levels of ctDNA at EOI and during surveillance were analyzed for the ability to predict progression. **Results:** 53 MCL pts were treated between 1996 and 2013. After median f/u of 9.6y, 5-yr OS is 80.1% and median PFS is 30.7m. With FFPE available, 50 of 52 (96%) had an tumor-specific clonotype, and 46 of 48 pts (96%) had detectable ctDNA in serum prior to therapy. ctDNA was successfully tracked in 625 of 647 (97%) serum samples. Pre-treatment ctDNA levels more strongly correlated with total metabolic tumor volume (r_s= 0.74) than Ki-67 (r_s= 0.55) or serum LDH (r_s= 0.49). Overall, 47 pts responded to induction (44 CR; 3PR), and median TTP after EOI was 26m (range 0-131). 40 of 50 pts (80%) achieved MRD- at EOI, which was assoc with superior median PFS (45m vs. 25m, p = 0.001) and OS (NR vs. 40m, p = 0.01) vs. MRD+ pts. In 31 of 41 (76%) progressors, ctDNA was present prior to clinical progression with a median lead-time of 9m (range 0-38). Of 9 non-progressors, 8 remained ctDNA negative. BZ maint had no impact on PFS or OS. **Conclusions:** Nearly all pts with MCL have detectable baseline ctDNA. Achieving MRD- at EOI was associated with improved PFS and OS compared to MRD+ pts. ctDNA was detected a median 9m before progression. Clinical trial information: NCT00114738.

7577 Poster Session (Board #214), Mon, 8:00 AM-11:30 AM

Quality of life in cutaneous T-cell lymphoma subjects treated with anti-CCR4 monoclonal antibody mogamulizumab versus vorinostat: Results from the phase 3 MAVORIC trial. *First Author: Pierluigi Porcu, Thomas Jefferson University, Philadelphia, PA*

Background: Cutaneous T-cell lymphomas (CTCL) are rare non-Hodgkin's lymphomas that cause significant morbidity and adversely affect quality of life (QoL), most severely in Sezary syndrome (SS) patients (pts). **Methods:** A multicenter Phase 3 trial compared mogamulizumab (MOGA) vs vorinostat (VOR) in pts with Stage IB-IV CTCL who had failed ≥ 1 systemic therapy. Progression free survival was the primary endpoint. Validated QoL measurements included the Skindex-29 (SDX-29), Functional Assessment of Cancer Therapy-General (FACT-G) and EuroQol-5D. SDX-29 and FACT-G are reported here. Longitudinal modeling of symptoms, function, and QoL subdomains were evaluated using longitudinal mixed models on prespecified covariates. Meaningful change threshold (MCT) was evaluated and categorical change analyzed by group over time. Time to clinically meaningful worsening was defined using distribution-based minimally important difference thresholds. **Results:** 372 pts were randomized (186 in each arm). MOGA resulted in symptomatic and functional improvement with differences in SDX-29 Symptoms (Cycle, C3, C5, and C7; p < 0.05) and Functional (C3 and 5; p < 0.05) scales. The proportion of pts who improved by at least the MCT from baseline was significantly greater for MOGA vs VOR on SDX-29 Symptoms at C3 (61.1% vs 45.3%), C5 (64.5% vs 42.4%), C7 (67.1% vs 47.5%), and C11 (84.1% vs 50.0%) and SDX-29 Functioning domain at C5 (54.3% vs 28.8%). Significant difference in the FACT-G Physical Well-Being scale (C1, C3, and C5; p < 0.05) were observed in favor of MOGA and a greater proportion of pts declined by at least the MCT in favor of MOGA vs VOR at C1 (19.3% vs 34.7%), C3 (17.4% vs 42.9%), C5 (13.1% vs 43.3%), and C7 (15.9% vs 37.5%). The median time to worsening of symptoms on SDX-29 was 27.4 m for MOGA vs 6.6 m for Vor. In SS pts, the median time to worsening varied in favor of MOGA (p < 0.005) on all SDX-29 domains. In mycosis fungoides pts, time to worsening did not vary between arms. **Conclusions:** Symptoms, function, and overall QoL of CTCL pts favored MOGA over VOR across study time points. Pts with highest symptom burden and functional impairment derived the most QOL benefit from MOGA. Clinical trial information: NCT01728805.

7578 Poster Session (Board #215), Mon, 8:00 AM-11:30 AM

Efficacy of up-front hematopoietic cell transplantation in peripheral t-cell lymphoma, not otherwise specified (PTCL-NOS): A National Cancer Database analysis. *First Author: Bhagirathbhai R. Dholaria, Moffitt Cancer Center, Tampa, FL*

Background: Peripheral T cell lymphoma-not otherwise specified (PTCL NOS) is the most common subtype of mature T cell lymphoma in the Western World with inferior survival compared to the B-cell lymphomas. Herein, we studied the impact of up-front hematopoietic cell transplantation (HCT) on PTCL-NOS survival outcomes. **Methods:** The National Cancer Database (NCDB) with PTCL-NOS incident cases from 2004-2015 was used. We compared the outcomes of patients receiving chemotherapy only versus chemotherapy coupled with a consolidative autologous (auto) or an allogeneic (allo) HCT. Those without any form of chemotherapy treatment (n = 1823) were excluded from the analysis. **Results:** A total of 5252 PTCL-NOS patients were identified; 4812 received chemotherapy only and 440 received chemotherapy and a HCT (auto-HCT = 410; allo-HCT = 30). HCT recipients were more likely to be younger (median age, 55 vs. 63 years), had lower Charlson/Deyo co-morbidity score, of the white race, had a higher median household income, be treated at an academic facility and had private insurance. IPI and Ann-Arbor stage distribution were not significantly different between the groups. The median overall survival (OS) for all patients, chemotherapy alone and chemotherapy + HCT was 17.2 months, 14.7 months and not reached, respectively.($p< 0.001$) The 10-year OS was 15% and 52% for chemotherapy alone and chemotherapy + HCT group, respectively ($p< 0.001$). There was no significant difference in OS between auto-HCT and allo-HCT patients (p =0.93). After adjusting for baseline characteristics in Cox-regression model, HCT (Hazard ratio (HR) = 0.36, 95% confidence interval (CI): 0.20-0.65, p =0.001) was associated with improved OS. IPI-intermediate (HR = 1.9, 95% CI: 1.2-2.9, p =0.008) or IPI-high (HR = 3.5, 95% CI: 2.1-5.8, $p< 0.001$) were associated with poor OS. **Conclusions:** In this large US-based analysis, up-front HCT was an independent prognostic factor associated with improved OS of PTCL-NOS. Efforts to ensure early referral to transplant centers and education on the role of HCT to both our patients and hematologists to optimize the access to HCT are urgently needed.

7579 Poster Session (Board #216), Mon, 8:00 AM-11:30 AM

The effect of duvelisib, a dual inhibitor of PI3K-δ,γ, on components of the tumor microenvironment in previously untreated follicular lymphoma. *First Author: Carla Casulo, University of Rochester, Wilmot Cancer Institute, Rochester, NY*

Background: Duvelisib (DUV), an oral dual inhibitor of PI3K-d,g, is clinically active in hematologic malignancies, including follicular lymphoma (FL), CLL, and T cell lymphoma (Flinn, 2017). PI3K-δ inhibition directly targets malignant cells and PI3K-γ inhibition disrupts the supportive tumor microenvironment. In the CONTEMPO trial (NCT02391545), previously untreated FL patients (pts) treated with DUV+rituxumab had an ORR of 93% (36% CRR) and pts treated with DUV+obinutuzumab had an ORR of 89% (41% CRR). In both treatment arms chemokines reflective of the tumor microenvironment were inhibited (Casulo, 2016). **Methods:** *Ex vivo* whole blood assays were conducted from healthy volunteers and 32 FL pts enrolled in CONTEMPO [pre-and post-DUV]. *Ex vivo* and *in vitro* PI3K-γ assays [(fMLP-stim monocyte and CXCL12-stim human T cell pAKT(S473), murine bone marrow monocyte migration, and macrophage polarization quantified by ARG1 expression] and PI3K-δ assays [LPS-stimulated monocyte pAKT (S473)] with PI3K-δ-selective [idelalisib (IDELA), TGR-1202, IPI-3063] and PI3K-γ-selective [IPI-549] inhibitors were compared. **Results:** DUV (IC_{50} 0.4 ±0.1 mM) and IDELA (IC_{50} 1.0±0.2 mM) potently inhibited LPS-induced human monocytes via PI3K-δ compared with the PI3K-γ selective IPI-549 (IC_{50} 12±0.5 mM). For TGR-1202, the IC_{50} (25±8 mM) was below the RP2D clinical exposure. DUV (IC_{50} 0.5±0.2 mM) and IPI-549 (IC_{50} 1.6 ±0.2 mM) potently inhibited PI3K-γ dependent fMLP-stimulated human monocytes compared to IDELA (IC_{50} 9.4±2.3) and TGR-1202 (IC_{50} 55±16 mM). In FL pts treated with DUV, these PI3K-γ and PI3K-δ selective assays were inhibited 1-4 hours post treatment. Consistent with a PI3K-γ mechanism, both DUV and IPI-549 inhibited macrophage polarization to M2, reduced CXCL12-induced macrophage migration (DUV IC_{50} 51 nM; IPI-549 IC_{50} 85 nM), and blocked CXCL12-induced T cell migration (DUV EC_{50} 128±39 nM; IPI-549 EC_{50} 17±17nM), which was not observed with PI3K-δ inhibitor IPI-3063 (IC_{50} 630±71nM). **Conclusions:** The disruption of PI3K-d,g function in FL pts treated with DUV supports its inhibition of the tumor microenvironment through cancer-supportive macrophages and T cells. Clinical trial information: NCT02391545.

7580 Poster Session (Board #217), Mon, 8:00 AM-11:30 AM

Safety and efficacy of anti-CD20 immunotoxin MT-3724 in relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL) in a phase I study. *First Author: Michelle A. Fanale, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MT-3724 is a novel recombinant fusion protein consisting of a CD20 binding variable fragment (scFv) fused to Shiga-like toxin-I A1. The SLT-I A1 forces MT-3724 internalization and irreversibly inactivates ribosomes triggering cell death. We present interim results from a Phase I study in patients (pts) with B-cell NHL who relapsed after prior response to anti-CD20 Mab and chemotherapy (NCT02361346). **Methods:** 24 pts were treated by 13FEB2018: 21 pts (12 DLBCL) at 5-100 μg/kg/dose in 6 dose escalation cohorts and 3 pts (all DLBCL) at 75 μg/kg/dose in MTD expansion cohort. MT-3724 was given as six 2-hr IV infusions on Days 1-12 of each cycle (C) for up to 5 cycles. Investigator assessed tumor response after C2, C4 and C5 using Cheson criteria. **Results:** Demographics in 24 evaluable pts were: 54% female, mean age 66 yrs (range 34-78); ≥4 prior NHL therapies in 67%; ECOG status 0 in 42%, 1 in 46%, 2 in 4% and unknown in 8%. All pts had ≥1 AE (59 G≥3; 13 related), and 15 pts (63%) had 33 SAEs (23 G≥3; 4 related). The most common AEs were peripheral edema (67%), fatigue (43%), diarrhea (38%), myalgia (38%) and cough (33%). MT-3724 was not tolerated at 100 μg/kg/dose (2 pts had 1 DLT each: G2 pneumonia and G2 ileus). In dose escalation, no pts had DLT at doses ≤MTD of 75 μg/kg/dose. In the MTD expansion, 2 of 3 pts had G2 capillary leak syndrome (CLS) leading to dose delay and reduction. The CLS events occurred in obese pts (96 and 154 kg = high total of 7208 and 11572 μg/dose) and were reversible, but MTD was reduced to 50 μg/kg/dose and capped at 6000 μg/dose. Five pts (all DLBCL) had clinical benefit at 5-75 μg/kg/dose [1 CR and 2 PR (ORR 12.5%)' 2 SD with large tumor reduction (48% and 49%; DCR 21%)]. All pts with benefit had undetectable serum rituximab (RTX) level at screening. No pts with detectable screening RTX level had benefit, likely due to competitive inhibition of CD20 binding by prior RTX. **Conclusions:** MT-3724 showed clinical anti-tumor activity in heavily pre-treated pts with R/R B-cell NHL. Consistent with mechanism of action, MT-3724 had the best activity in rapidly growing DLBCL. Safety and efficacy assessment is ongoing at the adjusted MTD of 50 μg/kg/dose in DLBCL pts with undetectable screening RTX level. Clinical trial information: NCT02361346.

TPS7581 Poster Session (Board #218a), Mon, 8:00 AM-11:30 AM

Phase 3 zanubrutinib (BGB-3111) vs bendamustine + rituximab (BR) in patients (pts) with treatment-naïve (TN) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). *First Author: Peter Hillmen, St. James's University Hospital, Leeds, United Kingdom*

Background: Inhibition of Bruton's tyrosine kinase (BTK) has emerged as a strategy for targeting B-cell malignancies including CLL/SLL. Zanubrutinib has been shown to be a novel 2nd-generation, potent, and specific BTK inhibitor in clinical studies to date. Early clinical data suggest that zanubrutinib treatment in pts with TN (n = 16) or relapsed/refractory (R/R; n = 50) CLL/SLL induced deep and sustained responses, with a 94% overall response rate (ORR) including 6% and 2% complete response rates in TN and R/R CLL/SLL, respectively (ICML 2017). We hypothesize that zanubrutinib monotherapy may have superior efficacy and potentially improved safety vs standard BR chemoimmunotherapy in pts with TN CLL/SLL. **Methods:** This ongoing Phase 3, randomized, open-label, global study (NCT03336333, BGB-3111-304) compares the efficacy and safety of zanubrutinib vs BR in adult pts with TN CLL/SLL considered unsuitable for treatment with FCR (fludarabine, cyclophosphamide, rituximab). In Cohort 1, pts lacking del (17p) (n ≈ 420) are randomized 1:1 to oral zanubrutinib 160 mg twice-daily or BR x 6 cycles. Randomization is stratified by age (< 65 vs ≥ 65 y), Binet stage (C vs A/B), geographic region (North America vs Europe vs Asia-Pacific) and *IGHV* mutational status (mutated vs unmutated). In Cohort 2, pts with del(17p) (n ≈ 47) are enrolled and all receive zanubrutinib as in Cohort 1. Key inclusion criteria include histologically confirmed CD20+ CLL/SLL requiring treatment per iwCLL criteria, ECOG PS 0-2, and adequate hematologic function. The primary endpoint is progression-free survival (PFS) of zanubrutinib as compared to BR in Cohort 1 by independent review committee (IRC) according to iwCLL guidelines with modification for treatment-related lymphocytosis. The analysis of PFS between the 2 arms in Cohort 1 will be based on a log-rank test stratified by the randomization stratification factors. Key secondary end points include ORR, duration of response, overall survival, and safety in Cohorts 1 & 2. In Cohort 1, next-line treatment with zanubrutinib after IRC-confirmed progression on BR is included in the study design. Recruitment is ongoing. Clinical trial information: NCT03336333.

TPS7582 **Poster Session (Board #218b), Mon, 8:00 AM-11:30 AM**

The GAIA (CLL13) trial: An international intergroup phase III study for frontline therapy in chronic lymphocytic leukemia (CLL). *First Author: Von Tresckow Julia, Department I of Internal Medicine and Center of Integrated Oncology Cologne-Bonn, German CLL Study Group, University of Cologne, Cologne, Germany*

Background: Chemoimmunotherapy (CIT) is still standard of care in first line treatment of fit CLL patients (pts) without del(17p) or TP53 mutation. However, CIT is often associated with side effects caused by the general cytotoxicity of chemotherapy. Testing of chemotherapy-free treatment regimens with increased efficacy and superior toxicity profiles including CD20-antibodies and targeted drugs such as venetoclax (Ve) and ibrutinib (I) head to head with CIT is therefore warranted in this pt group. **Methods:** The trial is an investigator initiated trial of the German CLL Study Group in cooperation with the Nordic CLL Study Group, HOVON, SAKK, Cancer Trials Ireland and the Israeli CLL Study Group. Sponsor of the trial is the University of Cologne. It is registered at www.clinicaltrials.gov as # NCT02950051. 920 pts with a cumulative illness rating scale score ≤ 6 and a creatinine clearance $\geq$70ml/min who are diagnosed with previously untreated CLL according to iwCLL guidelines without del(17p) or TP53 mutation will be included and 1:1:1:1 randomized into four treatment arms. In the standard arm, six cycles of CIT with fludarabine, cyclophosphamide plus rituximab for pts $\leq$ 65 years or bendamustine plus rituximab for pts $>$ 65 years are given. In the experimental arms 12 cycles of Ve containing regimes are tested: Ve plus rituximab (RVe), Ve plus obinutuzumab (GVe) and Ve plus ibrutinib and obinutuzumab (GIVe). Two co-primary endpoints were defined: minimal residual disease (MRD) negativity for the comparison of CIT versus GVe and progression free survival (PFS) for the comparison of CIT versus GIVe. Secondary endpoints include comparisons of MRD and PFS for the other treatment arms, overall survival, safety parameters and health-related quality of life. Recruitment started in December 2016 and is estimated to take 33 months (m). The final analysis of the MRD endpoint is expected to be performed 49 m after trial initiation together with the interim PFS analysis. The final analysis of the PFS endpoint is expected to take place after 73 m, which will also be the formal end of trial. After the second meeting of the data safety monitoring board in February 2018 the trial continues recruiting as planned. Clinical trial information: # NCT02950051.

TPS7583 **Poster Session (Board #219a), Mon, 8:00 AM-11:30 AM**

KEYNOTE-667: Phase 2, open-label study of pembrolizumab in children and young adults with newly diagnosed classical Hodgkin lymphoma (cHL) with slow early response (SER) to frontline chemotherapy. *First Author: Christine Mauz-Korholz, Justus-Liebig University of Giessen, Giessen, Germany*

Background: High risk for relapse is observed in cHL patients (pts) with SER to initial chemotherapy and the burden of late organ toxicities may be higher following dose intensification. **Methods:** The phase 2, open-label KEYNOTE-667 (NCT03407144) study will enroll 400 pts aged 3 to 17 (children) or 18 to 25 years (young adults) with newly diagnosed, confirmed stage IA, IB, or IIA cHL without bulky disease (Group 1 [low-risk]) or stage IIEB, IIIEA, IIIEB, IIIB, IVA, or IVB cHL (Group 2 [high-risk]); measurable disease; and performance status per Lansky Play-Performance Scale $\geq$50 (age $\leq$16 years) or Karnofsky score $\geq$50 (age $>$ 16 years). Pts will receive induction with doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD; Group 1) or vincristine, etoposide/etoposide phosphate, prednisone/prednisolone, doxorubicin (OEPA; Group 2) for 2 cycles, followed by early response assessment by PET/CT/MRI. Pts with rapid early response (Deauville score 1-3) will receive standard therapy. Pts with SER (Deauville score 4-5) will receive consolidation with pembrolizumab 2 mg/kg Q3W up to 200 mg (children) or 200 mg Q3W (young adults) plus 2 cycles AVD (Group 1) or 4 cycles cyclophosphamide, vincristine, prednisone/prednisolone, dacarbazine (COPDAC-28; Group 2). PET/CT for late response assessment (LRA) will be performed after consolidation. After LRA, Group 1 pts with SER will receive radiotherapy (RT); in Group 2, pts with Deauville score 4-5 will receive RT. All pts will receive maintenance with pembro Q3W concomitantly with RT. Pembro dosing will continue up to 17 administrations, with an option to stop after 24 weeks due to CR, or until progression, unacceptable toxicity, or withdrawal. The primary endpoint is objective response rate (ORR) per Cheson 2007 IWG criteria by group in SER pts. Secondary endpoints include SERs with PET negativity after consolidation, event-free survival (EFS), overall survival (OS), and radiotherapy frequency and details by group. ORR with 95% CI will be estimated using the Clopper-Pearson method. EFS and OS will be estimated by Kaplan-Meier methods. Safety will be assessed in all treated pts. Clinical trial information: NCT03407144.

TPS7584 **Poster Session (Board #219b), Mon, 8:00 AM-11:30 AM**

Phase I/II study to evaluate the safety and efficacy of tenalisib, a novel PI3K δ/γ dual inhibitor in combination with pembrolizumab in patients with relapsed/refractory classical Hodgkin lymphoma. *First Author: Rod Ramchandren, Barbara Ann Karmanos Cancer Institute, Detroit, MI*

Background: Despite impressive activity of PD-1/PD-L1 therapy in HL, proportions of patients do not respond and eventually progress. Growing evidence suggests that high infiltrations of immune-suppressive myeloid cells are responsible for anti-PD-1/PD-L1 therapy resistance. These observations suggest a need for an immunotherapeutic combination to overcome such resistance mechanisms. PI3K δ/γ isoforms are known to play a role in modulating the tumor microenvironment. Tenalisib demonstrated marked reduction of Tumor Associated Macrophages (TAMs) and angiogenesis and showed synergy with checkpoint inhibition in syngeneic mouse models. Tenalisib has demonstrated single agent activity in relapsed refractory heavily pre-treated cHL (ORR 29% CR 7% PR 21%). The proposed study hypothesizes that Tenalisib in combination with Pembrolizumab improve the depth and durability of responses to anti-PD1 therapy. **Methods:** The primary objective of this phase I/II, open label, 3+3 dose-escalation study is to evaluate the safety, tolerability, and identify the maximum tolerated dose of tenalisib in combination with Pembrolizumab in relapsed/refractory cHL. Patients will be enrolled in two escalating cohorts (Tenalisib 400/ 800 mg BID and Pembrolizumab 200 mg, IV) to determine MTD/ optimal dose. In Expansion part, two groups will be initiated. The first expansion group will enroll 18 patients who are naïve to anti-PD-1 therapy to explore the additive/synergistic effect of the combination by measuring efficacy parameters (ORR, DoR, PFS). The second group will enroll 27 patients who have received treatment with pembrolizumab for at least 6 months and have not demonstrated a complete response. The objective is to understand whether combination therapy will overcome PD-1 resistance by augmenting conversion rates (i.e., improvement from progressive disease to CR or from SD to PR) upon combination. Disease response assessments will be determined per the Lugano classification (Cheson 2014). Eligible subjects will receive Tenalisib BID orally and Pembrolizumab 200 mg, IV every three weeks in a 21-day cycle.

TPS7585 **Poster Session (Board #220a), Mon, 8:00 AM-11:30 AM**

ZUMA-7: A phase 3 randomized trial of axicabtagene ciloleucel (Axi-Cel) versus standard-of-care (SOC) therapy in patients with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL). *First Author: Olalekan O. Oluwole, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: For pts with DLBCL who fail 1st-line therapy, the only potentially curative treatment is salvage chemotherapy followed by autologous stem cell transplant (ASCT). Only »50% of pts receiving salvage chemotherapy proceed to ASCT and 3-y progression-free survival (PFS) is 53% after ASCT (Gisselbrecht et al. *JCO.* 2010). In ZUMA-1, the pivotal, single-arm study of axi-cel, an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, the objective response rate (ORR) was 82% (58% complete response [CR] rate) in pts with refractory large B cell lymphoma; 40% remained in CR with 15.4-mo median follow-up (Neelapu & Locke et al. *NEJM.* 2017). This trial was primarily in pts with $\geq$ 2 prior lines of therapy and supported US FDA approval of axi-cel for the treatment of adult pts with R/R DLBCL after $\geq$ 2 prior lines of systemic therapy. ZUMA-7 investigates axi-cel as 2nd-line therapy for pts with R/R DLBCL. **Methods:** ZUMA-7 (NCT03391466) is a randomized (1:1) Phase 3, open-label, multicenter study of axi-cel vs SOC 2nd-line treatment in pts with R/R DLBCL. Planned enrollment is 350 pts. Eligible pts must have R/R DLBCL after 1st-line therapy (including an anti-CD20 antibody and an anthracycline) and intend to proceed to ASCT if they respond to 2nd-line therapy. Exclusion criteria include prior SCT, prior CD19-targeted therapy, or active infection. Pts randomized to axi-cel will undergo leukapheresis, then lymphodepleting chemotherapy (fludarabine 30 mg/m^2/d and cyclophosphamide 500 mg/m^2/d for 3 d), followed by a single infusion of axi-cel at 2×10^6 CAR T cells/kg. Corticosteroid bridging therapy is allowed for pts with high disease burden at screening. Pts in the SOC arm will receive investigator's choice of 2nd-line salvage therapy (R-ICE, R-DHAP, R-ESHAP, or R-GDP); pts who respond after 2–3 cycles will receive high-dose therapy and ASCT. The primary endpoint is event-free survival defined as time from randomization to disease progression, start of new lymphoma therapy, or death. Secondary endpoints include ORR, overall survival, PFS, duration of response, safety, and pt-reported outcomes. Accrual is ongoing. Clinical trial information: NCT03391466.

TPS7586 **Poster Session (Board #220b), Mon, 8:00 AM-11:30 AM**

A phase 1 open-label, safety, pharmacokinetic, and preliminary efficacy study of STRO-001, an anti-CD74 antibody drug conjugate, in patients with advanced B-cell malignancies. *First Author: Amrita Y. Krishnan, City of Hope, Duarte, CA*

Background: Sutro's cell-free antibody production system was used to make STRO-001, a novel CD74 targeting antibody drug conjugate. CD74 is expressed on B cells throughout differentiation, and is an attractive target for treatment of B cell malignancies. STRO-001 demonstrates potent cytotoxicity in non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) cell lines and anti-tumor activity in xenograft models. Toxicology studies demonstrate dose-dependent B-cell depletion and reversible hematologic toxicity when STRO-001 is administered at up to 10 mg/kg. **Methods:** This study is a first-in-human Phase 1, open-label, multicenter, dose escalation (Part 1) study with dose expansion (Part 2) to identify the maximum tolerated dose (MTD), recommended phase 2 doses (RP2D) and to evaluate the safety, tolerability, and preliminary anti-tumor activity of STRO-001 in adults with B-cell malignancies (MM and NHL) who are refractory to, or intolerant of, all therapy known to provide clinical benefit. STRO-001 is given to all patients on study via intravenous infusion on Day 1 and Day 15 of each cycle until disease progression. Dose limiting toxicities will be assessed in the first cycle (Days 1-28) of dose escalation. In Part 1, 2 cohorts (1 for MM and 1 for NHL) will enroll 30 patients each to determine the MTD and RP2D for expansion while Part 2 will enroll 4 cohorts based on disease subtypes (MM, diffuse large B cell, mantle cell and follicular lymphomas). Efficacy will be evaluated per MM-specific or NHL-specific criteria. Key inclusion criteria include relapsed or relapsed/refractory disease, adequate bone marrow and renal function, and ability to comply with treatment, testing and pharmacokinetic (PK) schedules. NHL patients must have at least one measurable lesion. Key exclusion criteria include leukemic manifestations of lymphoma, need for ongoing anti-coagulants or immunotherapy including systemic corticosteroids and a history of CNS involvement. Samples will be collected to assess the PK and immunogenicity. No formal statistical hypothesis testing will be conducted in this study. This study is currently open for enrollment in the US. Clinical trial information: NCT03424603.

TPS7587 **Poster Session (Board #221a), Mon, 8:00 AM-11:30 AM**

ILyAD (Indolent Lymphoma and Vitamin D): A phase III double blind, prospective randomized trial to evaluate the supplemental effect of vitamin D on progression-free survival in patients with low tumor-burden indolent non-Hodgkin lymphoma treated with rituximab therapy. *First Author: Michael Brady, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Follicular lymphoma (FL) is the most prevalent lymphoma in the US. Though outcomes have improved substantially, this disease is characterized by an incurable clinical course requiring chronic, costly, often morbid therapy. Therefore, lower intensity and better-tolerated, cost-effective treatments are needed. In a recent study of newly diagnosed FL patients treated with standard chemotherapy plus anti-CD20 therapy, we reported a significant association between low vitamin D levels and clinical outcomes in two independent cohorts. The magnitude of this association is stronger than the individual clinical prognostic factors within the FL-IPI score and may be the strongest association reported to date of a pre-therapy prognostic factor in FL. These results strongly support a randomized trial to evaluate whether vitamin D supplementation can improve outcome in patients with indolent lymphoma treated with rituximab. **Methods:** This NIH-funded, multi-center, double-blind, randomized phase III study will enroll adult subjects with biopsy-proven indolent, low tumor burden FL, SLL, Marginal Zone or MALT histologies. Subjects will be randomized, 2:1, to vitamin D 2000IU daily or placebo daily for 3 years, or until disease progression, while receiving standard treatment with rituximab in 4 weekly doses. The primary endpoint is 3-year event free survival (EFS), secondary endpoints include response at week 13 and overall survival. Events are defined as lack of response at week 13, disease progression, initiation of new treatment or death. The study provides 81% power to detect HR of 0.55 at a 0.05 significance level, which corresponds to an increase in 3-year EFS from 40% to 60%. Correlative studies will identify if vitamin D levels can predict patients for whom supplementation is particularly effective and whole exome sequencing will determine whether key vitamin D related germline variations are critical determinants of outcome. The study is currently open and accruing with an enrollment goal of 210 subjects. Clinical trial information: NCT03078855.

TPS7588 **Poster Session (Board #221a), Mon, 8:00 AM-11:30 AM**

A phase 1, open-label, multicenter, non-randomized study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of AZD4573, a potent and selective CDK9 inhibitor, in subjects with relapsed or refractory hematological malignancies. *First Author: Simon Rule, Department of Haematology, Derriford Hospital, Plymouth, United Kingdom*

Background: Cyclin-dependent kinase 9 (CDK9) belongs to the group of transcription-regulating CDKs and promotes transcription elongation through phosphorylation of RNA Polymerase II at serine 2 (pSer2-RNAPII). Studies using multi-CDK inhibitors with CDK9 activity demonstrated that transient inhibition of CDK9 can modulate expression of oncogenes with short-lived transcripts and proteins (e.g. MCL1, MYC), providing an intriguing therapeutic rationale. Transient and selective inhibition of CDK9 is key to preferentially kill tumor cells dependent on survival proteins without causing broad toxicity due to prolonged transcription suppression. Multi-CDK inhibitors, e.g. Dinaciclib (Flynn et al., Leukemia 2015) have been progressed in early trials and shown to reduce levels of MCL1 and induced clinical responses attributed to CDK9 inhibition. However, a more potent and selective CDK9 inhibitor that has appropriate pharmacokinetics for tuneable target engagement and an optimal dose/schedule, leading to improved efficacy, is warranted. We developed a selective CDK9 inhibitor, AZD4573, with nanomolar potency that exhibits anticancer activity across a diverse set of hematological models. Pre-clinical experiments demonstrated a rapid, dose-dependent decrease in pSer2 RNAPII with concomitant depletion of MYC and MCL1 mRNA and protein leading to induction of cleaved caspase/PARP. AZD4573 induced significant antitumor activity in xenograft models when given as monotherapy or in combination (Cidado J et al, AACR 2018). These data suggest clinical progression of AZD4573 for treatment of hematological malignancies. **Methods:** This study is a multicenter, open-label, first in human phase 1 dose-escalation study including an intra-subject ramp-up. The purpose is to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary antitumor activity of AZD4573 in subjects with relapsed/refractory haematological malignancies. Study enrolment is ongoing. Clinical trial information: NCT03263637.

TPS7589 **Poster Session (Board #222a), Mon, 8:00 AM-11:30 AM**

A phase 3 study comparing polatuzumab vedotin plus R-CHP versus R-CHOP in patients with DLBCL (POLARIX). *First Author: Herve Tilly, Centre Henri Becquerel, University of Rouen, Rouen, France*

Background: R-CHOP remains the standard of care in patients (pts) with previously untreated diffuse large B-cell lymphoma (DLBCL). However, pts with high-risk disease have poorer outcomes with R-CHOP. Polatuzumab vedotin (pola) is an antibody-drug conjugate targeting CD79b; it delivers the antimitotic agent MMAE and is being evaluated as a replacement strategy for vincristine within the R-CHOP regimen. In a phase Ib/II study in higher risk DLBCL pts, pola + R-CHP produced promising efficacy across different subtypes of DLBCL and a safety profile similar to that observed in the R-CHOP arm of the GOYA study (Tilly H, et al. Hematol Oncol 2017; Vitolo U, et al. J Clin Oncol 2017). **Methods:** This is a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in pts with previously untreated DLBCL. Pts (planned N = 875) aged 18-80 years with CD20-positive DLBCL (including DLBCL not otherwise specified [NOS], germinal center B-cell like [GCB], and activated B-cell like [ABC] subtypes), ECOG performance status 0–2, and IPI score 2–5, will be randomized 1:1 to one of two treatment groups, stratified by IPI score (2 versus 3–5), bulky disease and geographical region. Arm A will receive pola 1.8 mg/kg on Day 1 plus R-CHP (standard dosing schedule) plus vincristine placebo for 6 cycles; Arm B will receive R-CHOP (standard dosing schedule) with pola placebo for 6 cycles. In both arms, R will be administered as monotherapy in cycles 7 and 8. The primary endpoint is progression-free survival, as assessed by the investigator, using the Lugano classification (Cheson B, et al. J Clin Oncol 2014). Secondary endpoints include PET-CT complete response rate at end of treatment assessed by an independent review committee, event-free survival due to efficacy reason, 2-year PFS rate, and overall survival. PET-CT and CT scans will be obtained at screening, after 4 cycles (planned interim assessment), and 6–8 weeks after end of study treatment. Patient follow-up will continue for 5 years after end of treatment. Enrolment began November 2017. Clinical trial information: study is funded by F. Hoffmann-La Roche Ltd; Clinical trial information: NCT03274492.

TPS7590 Poster Session (Board #222b), Mon, 8:00 AM-11:30 AM

The PRIMO study: A phase 2 study of duvelisib efficacy and safety in patients with relapsed or refractory peripheral t-cell lymphoma (PTCL). *First Author: Steven M. Horwitz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Duvelisib is an oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ being developed for the treatment of hematologic malignancies. In preclinical investigations, duvelisib potently killed TCL cell lines with constitutive phospho-AKT (S473) and reprogrammed tumor-associated macrophages from an immunosuppressive to immunostimulatory phenotype in PTCL mouse xenograft models (Horwitz, Blood 2017). In a Phase 1 study duvelisib monotherapy demonstrated encouraging clinical activity and an acceptable safety profile (Flinn, Blood 2017), with an overall response rate (ORR) of 50% (3 complete responses [CRs], 5 partial responses [PRs]) in patients (pts) with PTCL (n = 16). These results suggest duvelisib monotherapy may provide a meaningful benefit in relapsed/refractory (RR) PTCL, a population in need of new and effective therapies. **Methods:** This Phase 2, open-label, study of duvelisib monotherapy in adult pts PTCL employs a Dose Optimization Phase (DOP) and an Expansion Phase (EP) (NCT03372057). The primary objectives are to identify the optimal dose of duvelisib and examine the efficacy, safety, and tolerability of duvelisib at the optimal dose. The study will enroll up to 120 pts with histologically confirmed PTCL subtypes of PTCL-NOS, angioimmunoblastic TCL, anaplastic large cell lymphoma, and natural-killer TCL. Disease responses will be measured by ^{18}FDG-PET-CT scanning as assessed by an independent review committee per IWG criteria. The DOP, to be conducted at 4-6 centers in the U.S., will include 20 pts randomly assigned to 1 of 2 parallel cohorts. Cohort 1 will receive a starting dose of 25 mg duvelisib PO BID, with potential sequential escalation to 50 mg and then 75 mg based on responses and tolerance of therapy. Pts in Cohort 2 will receive 75 mg duvelisib PO BID. The EP, to be conducted globally at ~40 centers, will include pts treated at the optimal dose as determined from the DOP. The primary endpoint is ORR (CR + PR) in all pts receiving the optimal dose for at least 1 cycle in either phase. Secondary endpoints include AEs, duration of response, and PFS. This study is open for enrollment. Clinical trial information: NCT03372057.

8000 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Once-weekly vs twice-weekly carfilzomib (K) dosing plus dexamethasone (d) in patients with relapsed and refractory multiple myeloma (RRMM): Results of the randomized phase 3 study A.R.R.O.W. *First Author: Maria-Victoria Mateos, Hematology, Hospital Clinico Universitario de Salamanca-IBSAL, Salamanca, Spain*

Background: Twice-weekly K at 20/27 mg/m^2 is approved for the treatment of RRMM. To develop a more convenient K regimen, once-weekly K plus d was assessed in the phase 1/2 CHAMPION-1 study, establishing a maximum tolerated dose of K 20/70 mg/m^2 for RRMM pts. We present results from the pre-planned interim analysis of the phase 3 study A.R.R.O.W. comparing Kd once-weekly at 20/70 mg/m^2 (once-weekly group) vs twice-weekly at 20/27 mg/m^2 (twice-weekly group). **Methods:** Pts with 2–3 prior therapies and prior exposure to proteasome inhibitor and immunomodulatory agent were eligible. Pts were randomized 1:1 to receive either once- or twice-weekly K plus d. The once-weekly group received K (30-min IV) on days (D) 1, 8, and 15 of all cycles (20 mg/m^2 on D1 [cycle 1]; 70 mg/m^2 thereafter). The twice-weekly group received K (10-min IV) on D1, 2, 8, 9, 15, and 16 (20 mg/m^2 on D1 and 2 during cycle 1 and 27 mg/m^2 thereafter). All pts received d at 40 mg on D1, 8, 15 (all cycles), and 22 (cycle 1–9 only). Treatment was given in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall response rate (ORR), overall survival, safety, and pharmacokinetics. **Results:** Baseline characteristics were generally balanced. Median PFS (once- vs twice-weekly) was 11.2 mo vs 7.6 mo (hazard ratio = 0.69; 1-sided P= 0.0014). ORR (once- vs twice-weekly) was 62.9% vs 40.8% (P< 0.0001); 7.1% vs 1.7% had a complete response or better. Grade ≥3 adverse events (AEs) occurred in 67.6% (once-weekly) and 61.7% (twice-weekly). Treatment-related grade 5 AEs occurred in 5 pts (2.1%) (once-weekly) and 2 pts (0.9%) (twice-weekly). The incidence of grade ≥3 hypertension and cardiac failure (once- vs twice-weekly) was 5.9% vs 5.5% and 2.9% vs 4.3%, respectively. **Conclusions:** Once-weekly Kd at 20/70 mg/m^2 significantly improved PFS and ORR vs twice-weekly Kd at 20/27 mg/m^2. The incidence of AEs was comparable between groups. No new safety risks were found in the once-weekly group. Overall, once-weekly Kd showed favorable benefit-risk profile with a convenient dosing regimen vs twice-weekly Kd. Clinical trial information: NCT02412878.

8001 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Pomalidomide (POM), bortezomib, and low-dose dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients (pts) with relapsed or refractory multiple myeloma (RRMM): Phase 3 OPTIMISMM trial. *First Author: Paul G. Richardson, Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: POM, a standard-of-care treatment (Tx) in RRMM, has demonstrated synergistic anti-myeloma activity with dexamethasone (DEX) and proteasome inhibitors (PIs). POM + DEX is indicated for RRMM after ≥ 2 prior Txs including LEN and a PI, and is the only Tx to be investigated exclusively after LEN. As LEN becomes increasingly established in up-front Tx of MM, pts who have exhausted the benefit of LEN represent a clinically relevant unmet medical need. In preclinical studies, POM inhibited proliferation of LEN-resistant cells. Here we report final PFS and safety data from the first phase 3 POM triplet trial comparing PVd vs Vd in an entirely post-LEN treated population. **Methods:** Pts with RRMM, 1-3 prior Tx lines, and ≥ 2 cycles (c) of prior LEN were randomized 1:1 to receive PVd or Vd. In 21-d c, pts received POM 4 mg/d on d 1-14 (PVd arm only); BORT 1.3 mg/m² on d 1, 4, 8, and 11 of c 1-8 and on d 1 and 8 of c 9+; and DEX 20 mg/d (10 mg if aged > 75 yrs) on the days of and after BORT. The primary endpoint was PFS. **Results:** 559 pts were enrolled: 281 PVd and 278 Vd. Median age was 67 and 68 yrs, respectively. All pts had prior LEN (71% vs 69% LEN refractory), 72% vs 73% had prior BORT, and 70% vs 66% were refractory to last Tx. Median prior Tx lines was 2; 40% in PVd and 41% in Vd arm had 1 prior Tx line. After a median follow-up of 16 mos, PVd significantly reduced the risk of progression or death by 39% vs Vd (Table). OS data are not mature. Most common grade 3/4 treatment-emergent AEs were neutropenia (42% vs 9%), infections (31% vs 18%), and thrombocytopenia (27% vs 29%). **Conclusions:** To date, OPTIMISMM is the only phase 3 study in early RRMM to report a significant and clinically meaningful PFS improvement in pts who were entirely LEN exposed and 70% LEN refractory. Furthermore, the results showed improved benefit in pts with only 1 prior Tx line. POM safety remained manageable, consistent with its known profile. Clinical trial information: NCT01734928.

Efficacy.

	ITT		1 Prior Tx Line	
	PVd n = 281	Vd n = 278	PVd n = 111	Vd n = 115
PFS, mos				
Median	11.20	7.10	20.73	11.63
HR (95% CI)	0.61 (0.49-0.77)		0.54 (0.36-0.82)	
P	< .0001		.0027	
ORR (≥ PR), %	82.2	50.0	90.1	54.8
≥ VGPR, %	52.7	18.3	61.3	22.6

8002 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Daratumumab (DARA) in combination with carfilzomib and dexamethasone (D-Kd) in lenalidomide (Len)-refractory patients (Pts) with relapsed multiple myeloma (MM): Subgroup analysis of MMY1001. *First Author: Ajai Chari, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY*

Background: Len-refractory pts have poor outcomes, highlighting an unmet medical need. In the phase 1b MMY1001 study (NCT01998971), D-Kd induced deep responses and was well tolerated in pts with relapsed MM. We examined the safety and efficacy of D-Kd in len-refractory pts. **Methods:** In total, 85 carfilzomib (carf)-naïve pts with 1-3 prior lines of therapy were enrolled. Pts received carf (20 mg/m^2 on Cycle 1 Day 1 [C1D1] and 70 mg/m^2 on C1D8+) on days 1, 8, and 15 of 28-day cycles and dexamethasone 40 mg QW. DARA was given QW C1-C2, Q2W C3-C6, and Q4W thereafter; 10 pts received a standard first dose of DARA (16 mg/kg) on C1D1, and 75 pts received a split first dose of DARA (8 mg/kg on C1D1 and C1D2). Refractoriness was defined as progression ≤60 days of completion of last line of therapy. **Results:** Among len-refractory pts (n = 51) in the MMY1001 D-Kd arm, median age was 66 yrs (range 38-85 yrs). Pts had received a median of 2 (range 1-4) prior lines of therapy; 98% had received bortezomib (bort), 18% had received pomalidomide (pom), 43% were refractory to bort, and 18% were refractory to pom. In total, 20 pts (39%) discontinued due to progressive disease (26%), adverse events (AEs; 6%), pt withdrawal (6%), or physician decision (2%). The most common hematologic grade 3/4 treatment-emergent AEs (TEAEs; ≥10%) were thrombocytopenia (37%), anemia (29%), neutropenia (28%), and lymphopenia (26%). Infusion-related reactions were observed in 37% of pts (43% for standard first DARA dose; 36% for split first DARA dose); none were grade 3/4. With 8.3 months of median follow up, median PFS was 14.1 months (95% CI 9.4-not estimable); the 12-month PFS rate was 69% (95% CI 49-82). ORR and MRD-negative rates are summarized in the Table. Median time to MRD negativity (10^{-5}) was 5.1 months. **Conclusions:** The combination of DARA and weekly Kd was well tolerated and demonstrated promising efficacy in len-refractory pts. Updated data will be presented. Clinical trial information: NCT01998971.

%	Len refractory	All
Overall response rate (ORR)[a]	81	86
sCR	8	6
CR	4	14
VGPR	56	53
PR	13	14
MRD-negative rate		
10^{-4}	6	9
10^{-5}	2	5
10^{-6}	0	2

[a]Among response-evaluable pts who received > 2 cycles or discontinued treatment.

8003 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

Randomized phase 3 trial of ibrutinib/rituximab vs placebo/rituximab in Waldenström's macroglobulinemia. *First Author: Meletios A. Dimopoulos, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece*

Background: Single-agent ibrutinib (ibr) is highly active in relapsed Waldenström's Macroglobulinemia (WM) and is approved in the US and EU for WM. We report the results of a multinational, prospective, randomized trial of ibr/rituximab (IR) vs placebo/rituximab (R) in WM at a preplanned interim analysis. **Methods:** Pts with confirmed symptomatic WM were randomized to daily ibr (420 mg) or placebo, both with R (375 mg/m^2/wk IV for infusions at wks 1-4 and 17-20). Pts treated with a prior R-based regimen required a response (≥MR) to the last R therapy. The primary endpoint was PFS by IRC. We also report response rates, Hb improvement, TTnT, OS, and safety. **Results:** For 150 randomized pts, median age was 69 y; 38% had a high IPSSWM; 45% were treatment-naïve. MYD88^{L265P} and CXCR4^{WHIM} mutations were found in 85% and 36% of 136 pts with available data. At median follow-up of 26.5 mo, IR prolonged PFS compared with R (median PFS, not reached [NR] vs 20 mo; HR, 0.20; CI: 0.11-0.38, P < 0.0001); 30-mo PFS rates were 82% vs 28%. PFS improved in all relevant subgroups, including treatment-naïve (HR, 0.34; CI: 0.12-0.95), relapsed (HR, 0.17; CI: 0.08-0.36), MYD88^{L265P}/CXCR4^{WT} (HR, 0.17; CI: 0.06-0.49), MYD88^{L265P}/CXCR4^{WHIM} (HR, 0.24; CI: 0.09-0.66), and MYD88^{WT}/CXCR4^{WT} (HR, 0.21; CI: 0.04-1.1). Overall (≥MR) and major (≥PR) response rates by IRC were higher for IR vs R, 92% vs 47% and 72% vs 32% (both P < 0.0001). Improvements in Hb were seen in 73% vs 41% of IR and R patients (P < 0.0001). 75% of IR pts continued on treatment. Median TTnT was NR for IR and 18 mo for R (HR, 0.096; P < 0.0001). The 30-mo OS rates were 94% vs 92% in the 2 arms. With median time on treatment of 25.8 mo for IR, grade ≥3 treatment-emergent AEs occurred in 60% vs 61% of pts on each arm. Serious AEs occurred in 43% vs 33% of pts on IR vs R, whereas no fatal AEs occurred with IR and 3 with R. Meaningful reductions in any grade IgM flare (8% vs 47%) and grade ≥3 infusion reactions were observed (1% vs 16%) with IR. **Conclusions:** The IR combination demonstrated superior efficacy to R, producing significant improvements in PFS for all WM patients regardless of prognostic or genotypic factors with a predictable toxicity profile. IR should be considered a standard therapeutic option for patients with WM. Clinical trial information: NCT02165397.

8004 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase 2 study of venetoclax plus carfilzomib and dexamethasone in patients with relapsed/refractory multiple myeloma. *First Author: Luciano J. Costa, University of Alabama at Birmingham, Troy, AL*

Background: The BCL-2 inhibitor venetoclax (VEN) has demonstrated efficacy, as monotherapy and combined with PI bortezomib, in relapsed/refractory (R/R) multiple myeloma (MM). We report preliminary data for VEN combined with second generation PI carfilzomib and dexamethasone (VENKd) in R/R MM. **Methods:** In this ongoing phase 2, dose escalation study (NCT02899052), pts with R/R MM received VENKd on 28-d cycles: VEN 400 mg/day + K 27 mg/m^2 d1,2,8,9,15,16+ dex 40 mg d1,8,15,22 (Cohort 1), same regimen but with VEN 800 mg/day (Cohort 2), VEN 800 mg/day + K 70 mg/m^2 d1,8,15 + dex 40 mg d1,8,15, 22 (Cohort 3/expansion cohort), or VEN 800 mg + K 56 mg/m^2 d1,2,8,9,15,16 + dex 40 mg d1,2,8,9,15,16,22,23 (optional Cohort 4; no data available at cutoff). Treatment continued until progressive disease (PD) or unacceptable toxicity. **Results:** As of 01Dec2017, 26 pts were enrolled. Median age was 67.5 years (40 – 79), 68% had ISS II/III disease, and 23% had t(11;14). Pts received a median of 1 prior therapy (1 – 3); no pts had prior K exposure, 96% had received prior PI (54% refractory), 62% were IMiD refractory, and 35% double refractory. At data cut off, 23 pts were on therapy for 0.3 – 10 months and 3 pts discontinued the study for PD, physician decision, and death. 85% of pts had an AE, grade 3/4 AEs were neutropenia (15%), hypertension (12%), thrombocytopenia (8%), decreased white blood cells (8%), and nausea (4%). 7 serious AEs occurred, but no dose-limiting toxicities were reported. Maximum tolerated dose was not reached and Cohort 3 is being expanded. VEN pharmacokinetics with Kd were comparable to VEN plus bortezomib and dexamethasone. Of 17 pts evaluated after completing ≥2 cycles, 3 had complete response (CR), 2 very good partial response (VGPR), 3 partial response (PR), 3 stable disease, and 2 PD (awaiting response data for 4 pts). Median time to first response was 1 month. Of 5 evaluable pts with t(11;14) MM, 1 achieved CR, 1 VGPR, 3 PR. **Conclusions:** VENkd is well tolerated with promising preliminary efficacy that supports study in pts with R/R MM. Accrual continues with 34 pts enrolled to date. Updated safety and efficacy results will be available for presentation. Clinical trial information: NCT02899052.

8005 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

A phase 1 trial of ruxolitinib, lenalidomide, and methylprednisolone for relapsed/refractory multiple myeloma patients. *First Author: James R. Berenson, Institute for Myeloma & Bone Cancer Research, West Hollywood, CA*

Background: Preclinical studies from our laboratory have demonstrated that ruxolitinib (RUX) in combination with lenalidomide (LEN) and dexamethasone shows marked anti-myeloma effects both *in vitro* and *in vivo*. Furthermore, MUC1 is responsible for LEN resistance in MM cells, and RUX blocks its expression in MM cells. Thus, RUX may restore sensitivity to LEN. Therefore, a phase 1 trial was conducted to determine the safety and efficacy of RUX in combination with LEN and methylprednisolone (MP) for relapsed/refractory (RR)MM patients (pts) who had previously been treated with LEN/steroids and a PI and showed progressive disease at study entry. **Methods:** A traditional 3+3 dose escalation design was used to enroll subjects in four cohorts with planned total enrollment to be 28 pts. Subjects received RUX twice daily continuously, LEN daily on d1-21 of a 28-d cycle and MP orally every other day. In DL0, pts received RUX 5 mg, LEN 5 mg, and MP 40 mg. In DL+1 and +2, both doses of LEN and MP remained unchanged and RUX was escalated to 10 and 15 mg, respectively. DL+3 escalated LEN to 10 mg with MP unchanged and RUX at 15 mg. **Results:** As of February 1, 2018, 28 pts had been enrolled, and 21 were evaluable. The median age was 66 years (range, 63-81), and 29 (55%) were male. Pts received a median of 6 prior treatments (range, 2-11). No DLTs occurred, and DL+3 was expanded. Among evaluable pts, the CBR and ORR were 48% and 33%, respectively (1 CR, 6 PR and 3 MR), and 7 and 4 showed SD and PD. G3 AEs included transient thrombocytopenia (14.3%), anemia (9.5%) and gastrointestinal bleeding (9.5%). SAEs included a humeral fracture (4.8%), a cerebral vascular accident from a pt with atrial fibrillation who discontinued his anticoagulation (4.8%), renal insufficiency (4.8%), sepsis (4.8%), and neutropenic sepsis (4.8%). **Conclusions:** This Ph 1 trial demonstrates for the first time that a JAK inhibitor, RUX, can overcome refractoriness to LEN and steroids for RRMM pts. These promising results are leading to other clinical trials with immunomodulatory agents and steroids with RUX as well as expansion of the current clinical trial to 49 pts, and may represent a new therapeutic approach for treating MM. Clinical trial information: NCT03110822.

8006 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

Phase II study of ex vivo expanded cord blood natural killer cells for multiple myeloma. *First Author: Nina Shah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Multiple myeloma (MM) is an incurable disease with immune dysregulation and exhaustion. Remissions in some patients (pts) after allo-stem cell transplant (SCT) suggest a graft versus myeloma effect; however toxicity limits its widespread use. Allogeneic natural killer (NK) cells are safe and potentially active against various hematologic malignancies, including MM. We previously demonstrated safety of ex vivo expanded cord blood (CB) derived NK cells in doses up to 1 e8 cells/kg in the setting of high dose melphalan and auto-SCT (ASCT) (Shah et al, Br J Haematol 2017). Here we present results of the phase II portion of our study. **Methods:** Pts with symptomatic MM who were appropriate candidates for ASCT were eligible. CB units with at least 4/6 match at HLA-A, B and DR were chosen for each pt. When possible, CB units with potential NK alloreactivity (KIR-HLA mismatch) were prioritized. Due to pre-clinical data demonstrating synergy between lenalidomide and NK cells, patients received lenalidomide (10 mg daily) from days (-8) to day (-2). Melphalan 200 mg/ m^2 was given intravenously on day (-7). Freshly expanded CBNK cells were infused on day (-5). Autologous peripheral blood progenitor cells were infused on day (0). **Results:** 33 patients were enrolled. 24/33 (74%) pts had at least 1 of the following adverse features: high risk cytogenetics/FISH (del1p, amp1q, t(4;14), t(14;20), t(14;16), del (17p), cyotgenetic del (13)), history of progression/relapse or ISS III disease. Successful expansion to target dose (1 e8 cells/ kg) was achieved in all but 3 patients (who received 5 e7 cells/kg). There were no toxicities associated with the CB NK cell infusions. Responses at 3 months were CR:18/33 (55%); VGPR: 4/33 (12%); PR: 7/33 (21%). Best response was CR: 21/33 (65%); VGPR: 6/33 (18%); PR: 3/33 (9%). With a median follow-up time of 22 months, 10 pts have progressed and 3 have died. Median PFS has not been reached. By DNA microsatellite chimerism analysis, donor CB-NK cells were detected 1-13 days after infusion for 25/33 (76%) pts. **Conclusions:** In this relatively high risk MM population, CBNK cells in the setting of auto-SCT is a promising adjunct immunotherapy. Updated data and correlative analyses will be presented at the annual meeting. Clinical trial information: NCT01729091.

8007 **Oral Abstract Session, Fri, 2:45 PM-5:45 PM**

bb2121 anti-BCMA CAR T-cell therapy in patients with relapsed/refractory multiple myeloma: Updated results from a multicenter phase I study. *First Author: Noopur S. Raje, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: bb2121 is a second-generation chimeric antigen receptor (CAR) T cell therapy targeting B cell maturation antigen (BCMA) to redirect T cells to recognize and kill malignant myeloma cells. Initial data from the dose-escalation (DE) phase of CRB-401, a first-in-human study of bb2121 in relapsed/refractory multiple myeloma (RRMM), have shown promising efficacy and safety. We report updated safety and efficacy results on 43 patients (pts) enrolled in this ongoing study. **Methods:** CRB-401 (NCT02658929) is a 2-part, phase I study of bb2121 in pts with RRMM. DE pts had received ≥ 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent, or were double refractory, and had ≥ 50% BCMA expression on plasma cells. In the dose-expansion (Exp) phase, pts had to have received daratumumab and been refractory to last line of therapy; no BCMA expression was required. Following lymphodepletion with Flu (30 mg/m^2)/Cy (300 mg/m^2) given daily for 3 days, pts received 1 infusion of bb2121. **Results:** As of 02 Oct 2017, 21 pts had received bb2121 in the 4 DE cohorts (median follow-up, 35 weeks); no DLTs and no grade ≥ 3 neurotoxicities (NTX) were observed. Cytokine release syndrome (CRS), primarily grade 1-2, was reported in 15 of 21 (71%) pts; 2 pts had grade ≥ 3 CRS that resolved in 24 hours. There were 2 deaths on study; both pts had achieved complete response (CR) and had not progressed. Overall response rate in the 18 evaluable pts in DE cohorts ≥ 150 × 10^6 CAR T cells was 94%; 10 of 18 (56%) pts had CR or unconfirmed CR; 9 of 10 evaluable pts were MRD-negative. With a median follow-up of 40 weeks in ≥ 150 × 10^6 DE cohorts, median response duration and progression-free survival (PFS) had not been reached; PFS rates at 6 and 9 months were 81% and 71%, respectively. Doses of 150 to 300 × 10^6 CAR T cells were selected for the Exp phase. Results from an additional 5 months of follow-up and initial data from ~20 pts from the Exp cohort will be presented. **Conclusions:** bb2121 shows promising efficacy at dose levels ≥ 150 × 10^6 CAR T cells with deep and durable ongoing responses and manageable CRS and NTX. These data support the potential of bb2121 anti-BCMA CAR T cell therapy as a new treatment paradigm for RRMM. Clinical trial information: NCT02658929.

8008 Oral Abstract Session, Fri, 2:45 PM-5:45 PM

FDA analysis of pembrolizumab trials in multiple myeloma: Immune related adverse events (irAEs) and response. *First Author: Aviva C Krauss, US Food and Drug Administration, Silver Spring, MD*

Background: Development of irAEs with checkpoint inhibition may be associated with response in some disease settings. **Methods:** We evaluated overall survival (OS), safety and objective response rates (ORR) among patients who developed irAEs and those who did not in two trials of pembro in MM. KEYNOTE 183 (KN183) evaluated pomalidomide and dexamethasone (PomDex) with or without pembro in patients with relapsed/refractory (RR) MM, and KEYNOTE 185 (KN185) evaluated lenalidomide and dexamethasone (LenDex) with or without pembro in patients with newly diagnosed (ND) MM ineligible for autologous stem cell transplant. FDA placed both trials on clinical hold in July 2017 due to worse OS in the pembro-containing arms. **Results:** Using a June 2, 2017 data cut-off: median follow-up on KN183 was 8.1 months, 249 patients were randomized. There were 29 deaths in the pembro arm and 21 in the control arm, for an OS hazard ratio (HR) of 1.61 (95% CI: 0.91, 2.85). ORR was 34% in the pembro arm and 40% in the control arm. Median follow-up on KN185 was 6.6 months, 301 patients were randomized. There were 19 deaths in the pembro arm and 9 in the control arm, for an OS HR of 2.06 (95% CI: 0.93, 4.55). ORR was 64% in the pembro arm and 62% in the control arm. Neither trial showed a difference in time-to-progression between arms. In KN183, 58% of patients on the pembro arm developed an irAE, with an ORR of 37%, not significantly different than the 31% in those without an irAE. A trend was noted for improved ORR (49%) in those on the control arm (PomDex) with an irAE, compared to 33% in those without an irAE. In contrast, ORR in patients with NDMM in KN185 who developed an irAE were higher than in those who did not. **Conclusions:** The utility of immunotherapy in patients unable to mount adequate immune responses merits further study, as does the worse OS observed in both trials.

	KN183		KN185	
	Pembro+PomDex	PomDex	Pembro+LenDex	LenDex
ITT pop, N	**125**	**124**	**151**	**150**
Deaths	23%	17%	13%	6%
ORR	34%	40%	64%	62%
Safety Pop, N	**120**	**121**	**149**	**145**
Pts with irAE	58%	45%	68%	44%
G≥3 irAE	18%	13%	36%	8%
ORR in pts with				
No irAE	31%	33%	45%	53%
irAE	37%	49%	73%	73%
G≥3 irAE	29%	50%	70%	67%

8009 Poster Discussion Session; Displayed in Poster Session (Board #18), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Updated efficacy data and MRD analysis according to risk status in newly diagnosed myeloma patients treated with carfilzomib + lenalidomide or cyclophosphamide (FORTE trial). *First Author: Francesca Maria Gay, Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy*

Background: Carf plus Len-Dex (KRd) or Cyclo-Dex (KCd) is effective in NDMM. Treatment of high-risk pts is an unmet medical need. **Methods:** NDMM pts ≤65 yrs were randomized (1:1:1; stratification ISS and age) to ARM A: 4 28-day induction cycles with KCd (Carf: 20/36 mg/m^2 IV days 1,2,8,9,15,16; Cyclo: 300 mg/m^2 days 1,8,15; Dex: 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and consolidation with 4 KCd; ARM B: 4 28-day cycles with KRd (Carf: 20/36 mg/m^2 IV days 1,2,8,9,15,16; Len: 25 mg days 1-21; Dex: 20 mg days 1,2,8,9,15,16) followed by MEL200-ASCT and 4 KRd; ARM C: 12 KRd cycles. Primary endpoint was VGPR rate with KRd vs KCd induction. For this analysis, the 2 KRd arms were pooled (2:1), as treatment was the same until that point. Enrollment was completed in March, 2017; data cut-off was November 30, 2017. **Results:** 474 pts were randomized (KRd, n = 315; KCd, n = 159). Pts characteristics were well balanced: 49% of KRd pts vs 49% of KCd pts had ISS Stage 2-3 at baseline, 31% vs 35% had high-risk chromosomal abnormalities [del17 and/or t(4;14) and/or t(14;16) by FISH], 68% vs 74% had Revised ISS Stage 2-3. Rates of sCR/CR (14% vs 3%; P = 0.0004), ≥nCR (33% vs 21%; P = 0.0106) and ≥VGPR (75% vs 60%; P = 0.0017) were significantly higher with KRd vs KCd. The advantage of KRd was consistent in all subgroups; ≥VGPR, ≥nCR in high-risk pts treated with KRd were comparable to the overall population. MRD evaluation (8 color second generation flow cytometry, sensitivity 10^{-5}) was available in a subset of pts: 144 KRd and 56 KCd. Rate of MRD negativity in evaluable pts was 56% with KRd vs 29% with KCd (P = 0.008). MRD negativity in high-risk pts treated with KRd was comparable to the overall population (Table). Treatment was well tolerated, as previously shown (Gay F ASCO 2017). **Conclusions:** KRd induction significantly improved sCR/CR, ≥ nCR, ≥VGPR rates and MRD negativity vs KCd with similar efficacy in high-risk pts. Clinical trial information: NCT02203643.

	All pts		HIGH RISK by FISH		ISS 2-3		Revised ISS 2-3	
	KCd	KRd	KCd	KRd	KCd	KRd	KCd	KRd
Response	**N = 159**	**N = 315**	**N = 43**	**N = 79**	**N = 69**	**N = 143**	**N = 91**	**N = 173**
≥nCR	21%	33%	12%	30%	16%	31%	13%	29%
≥VGPR	60%	75%	63%	71%	58%	78%	59%	76%
MRD	**N = 56**	**N = 144**	N = 14	N = 38	**N = 36**	N = 73	N = 39	N = 88
MRD negative	29%	56%	36%	61%	31%	58%	26%	56%

8010 Poster Discussion Session; Displayed in Poster Session (Board #19), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase 3 randomized study of pembrolizumab (pembro) plus lenalidomide (len) and low-dose dexamethasone (Rd) versus Rd for newly diagnosed and treatment-naive multiple myeloma (MM): KEYNOTE-185. *First Author: Saad Zafar Usmani, Levine Cancer Institute, Charlotte, NC*

Background: KEYNOTE-185 (NCT02579863) evaluated Rd ± pembro in patients (pts) with newly diagnosed, ASCT-ineligible MM. **Methods:** Pts were randomized 1:1 to pembro (200 mg Q3W) + Rd (len 25 mg [days (d) 1-21] + 40 mg dex [weekly] every 28d) vs Rd until progression (PD), unacceptable toxicity, or withdrawal. Randomization stratified by age (< 75 vs ≥75 y), and disease stage (ISS I or II vs III). Primary end point was PFS per 2011 IMWG; secondary end points included OS and safety. On July 3, 2017, based on interim data presented to the DMC, the FDA halted KEYNOTE-185. **Results:** 301/640 pts enrolled (151, pembro-Rd; 150, Rd), with median (range) age: 74 y (53-89) vs 74 y (57-91); 24 (16%) pts in pembro-Rd am vs 10 (7%) pts in Rd arm had high-risk cytogenetics. Median (range) drug exposure was 131.0 d (1-485) in pembro-Rd arm vs 162 d (1-467) in Rd arm; median 6.0 cycles. AEs with ≥5% difference between arms: constipation, pyrexia, rash, vomiting, decreased appetite, pneumonia, oral candidiasis, pruritus, hypo-/hyperthyroidism. No SAEs with ≥5% difference between arms. In pembro + Rd arm, immune-mediated AEs (≥2%): hypothyroidism (7%), hyperthyroidism (6%), colitis (2%), and skin reactions (13%). 19 (13%) pts died in the pembro-Rd arm (6 from PD, 13 from AEs); 5/19 deaths were high risk. 9 (6%) pts died in the Rd arm (1 from PD, 8 from AE); 0/9 were high-risk. 6 (4%) treatment related deaths occurred; 4 (3%) [1 cardiac arrest, 1 pneumonia; 1 myocarditis, 1 cardiac failure]) were related to pembro. Median duration of follow-up was 6.4 mo vs 6.9 mo. Median TTP was not reached in either arm. Median PFS was not reached in either arm; HR, 1.22 (95% CI, 0.67-2.22); *P*= 0.75. Median OS was not reached in either arm; HR, 2.06 (95% CI, 0.93-4.55); *P*= 0.97. A retrospective random forest analysis and a subsequent multivariable Cox regression analysis led to no conclusive results due to the small number of death events (< 10%) at time of analysis. **Conclusions:** Benefit-risk profile for combination of pembro-Rd is unfavorable for newly diagnosed MM. Evaluation of T-cell subsets and cytokines along with long-term safety and survival follow-up is ongoing. Clinical trial information: NCT02579863.

8011 Poster Discussion Session; Displayed in Poster Session (Board #20), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Subcutaneous daratumumab (DARA SC) plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) in patients (Pts) with newly diagnosed amyloid light chain (AL) amyloidosis: Safety run-in results of andromeda. *First Author: Ray Comenzo, Division of Hematology/Oncology, John C. Davis Myeloma and Amyloid Program, Tufts Medical Center, Boston, MA*

Background: Systemic AL amyloidosis is characterized by disposition of insoluble amyloid fibrils into tissues and organs via clonal expansion of CD38$^+$ plasma cells. The safety run-in of DARA SC + CyBorD in ANDROMEDA (NCT03201965) is presented. **Methods:** Eligible pts had ≥1 involved organs, ECOG score ≤2, absolute neutrophil count ≥1.0 × 10^9/L; hemoglobin ≥8.0 g/dL; platelet count ≥50 × 10^9/L; estimated glomerular filtration rate ≥20 mL/min/1.73m^2, and NT-ProBNP ≤8,500 ng/L. In the safety run-in, pts received a concentrated co-formulation of DARA (1,800 mg in 15 mL) and recombinant human hyaluronidase enzyme (rHuPH20; 30,000 U) in a single, pre-mixed vial, given by manual SC injection qw in Cycles 1-2, q2w in Cycles 3-6, and q4w thereafter ≤2 y. Cy 300 mg/m^2 PO or IV and Bor 1.3 mg/m^2 SC were given on Days 1, 8, 15, 22 of each 28-day cycle for ≤6 cycles and D 40 mg was given qw. Dosing was staggered ≥48 hours between pts to assess infusion related reactions (IRRs). Safety was evaluated after ≥10 pts received ≥1 treatment cycle. **Results:** Pts (n = 15) had a median (range) age of 63 (35-77) y and a median of 58 (15-157) d from diagnosis. Pts had a median of 1 (1-3) involved organ, with kidney involvement affecting 67% of pts and 40% of pts with ≥2 organs involved. At baseline, 73% and 27% of pts were grouped into New York Heart Association class I and II, respectively, and 93% of pts had an ECOG score of ≤1. Pts received a median of 2 (1-4) treatment cycles and a median of 5 (1-10) DARA injections. Most common (> 2 pts) treatment emergent adverse events (TEAEs) were nausea (47%), diarrhea (33%), fatigue (33%), injection site erythema (20%), anemia (20%), and rash (20%). Dyspnea and peripheral edema were reported in 1 (7%) pt each. One grade 3/4 TEAE (hypertension; unrelated to treatment) and no serious TEAEs occurred. IRRs occurred in 2 (13.3%) pts (all grade 1). Additional data will be presented. **Conclusions:** DARA-CyBorD is tolerable in pts with AL amyloidosis with a low IRR rate and no new safety signals. The limited incidence of dyspnea and peripheral edema indicate a low risk for volume overload. Randomization into ANDROMEDA has begun. Clinical trial information: NCT03201965.

8012 Poster Discussion Session; Displayed in Poster Session (Board #21), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

A phase II study of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma. *First Author: Andrew Jenho Yee, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Elotuzumab is an approved monoclonal antibody targeting SLAMF7 on NK cells and plasma cells that enhances the activity of lenalidomide and bortezomib in multiple myeloma (MM). We studied elotuzumab with pomalidomide, bortezomib, and dexamethasone (elo-PVD) in relapsed and refractory MM. **Methods:** The primary objective was to determine the overall response rate (ORR). Patients with refractory disease and ≥1 prior lines of treatment (including lenalidomide and a proteasome inhibitor) were eligible to participate. Elotuzumab was weekly for the first 2 cycles and then every other week. Pomalidomide was on days 1-21; bortezomib was on days 1, 8, 15; and dexamethasone was weekly. Each cycle was 28 days. **Results:** At time of data cutoff, 33 patients (pts) who started treatment were evaluable. The median age was 64 (range 52-79), and the median number of prior regimens was 3 (range 1-9); 27% had high risk FISH. All pts had prior lenalidomide and proteasome inhibitors (bortezomib 94%, 76% carfilzomib) and were refractory to their last line of therapy. Prior therapies also included: auto SCT (45%), pomalidomide (36%), daratumumab (21%), and isatuximab (3%). 31 pts were assessable for response (2 patients did not complete cycle 1 due to rapid disease progression or stroke and were not evaluable). The median length of follow up was 3.3 months (range 0.5-18.2): 23 pts continue on study; 7 pts discontinued for progressive disease and 3 pts discontinued for adverse events (AEs) (sepsis, pneumonia, or stroke). Best ORR was 52% (PR = 11, VGPR = 4, CR = 1); ORR for pts with prior anti-CD38 antibody, 43%; carfilzomib, 43%; pomalidomide, 40%. Median PFS was 9.7 months (95% CI 7.5-Inf). Grade 3-4 hematologic AEs included anemia (7%), neutropenia (34%), and thrombocytopenia (17%). Common non-hematologic AEs all grades included fatigue (38%), upper respiratory infection (38%), constipation (38%), hyperglycemia (38%), and neuropathy (38%, Gr 1-2 only), with 2 possibly related deaths (sepsis, pneumonia). **Conclusions:** Elo-PVD shows encouraging responses in patients with refractory MM. Treatment was well-tolerated with manageable toxicity and attention to infectious AEs. Clinical trial information: NCT02718833.

8013 Poster Discussion Session; Displayed in Poster Session (Board #22), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Subcutaneous daratumumab (DARA) in patients (Pts) with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open-label, multicenter, dose escalation phase 1b study (PAVO). *First Author: Ajai Chari, Tisch Cancer Institute, Mount Sinai School of Medicine, New York, NY*

Background: Intravenous (IV) administration of DARA 16 mg/kg is approved as monotherapy and in combination with standard of care regimens for RRMM. The phase 1b PAVO study (NCT02519452) demonstrated that delivery of DARA with recombinant human hyaluronidase enzyme (rHuPH20) by subcutaneous (SC) infusion through a syringe pump (Part 1) or by manual SC injection (Part 2) was well tolerated with an efficacy profile consistent with IV DARA (Chari A, et al. ASH 2017; abstract 838). We present updated data from Part 2. **Methods:** Eligible pts received ≥2 prior lines of therapy (LOTs) including a proteasome inhibitor and an immunomodulatory drug. In Part 2, pts received a concentrated co-formulation of DARA (DARA SC; 1,800 mg in 15 mL) and rHuPH20 (30,000 U) dose in a single, pre-mixed vial, which was administered in 3 to 5 minutes by manual SC injection. Primary endpoints were C_{trough} of DARA at the end of weekly dosing on Cycle 3 Day 1 (C3D1) and safety. Secondary endpoints included overall response rate (ORR), rate of complete response, time to response, and duration of response. **Results:** Pts in Part 2 (n = 25) had a median age of 68 years and received a median of 3 prior LOTs. At a median follow-up of 4.6 months, none discontinued due to treatment-emergent adverse events (TEAEs). Pharmacokinetic analyses indicated that DARA SC had a T_{max} of approximately 72 h and achieved similar or greater C_{trough} on C3D1 compared to what has been observed with DARA IV. Most common Grade 3/4 TEAEs (> 1 pt) were lymphopenia (16%), thrombocytopenia (8%), and neutropenia (8%). IRRs were reported in 3 (12%) pts, all occurring ≤6 h of the first injection. No grade 4 IRRs or discontinuations due to IRRs occurred. DARA SC injections in the periumbilical area were well tolerated with reversible erythema observed in 20% of pts. DARA SC achieved an ORR of 44%, including 28% ≥very good partial response. **Conclusions:** DARA SC, which enables dosing in 3-5 minutes, was well tolerated with low IRR rates, had an acceptable PK profile, and demonstrated clinical response rates similar to DARA-IV. Updated data based on longer follow-up will be presented at the meeting. Clinical trial information: NCT02519452.

8014 Poster Discussion Session; Displayed in Poster Session (Board #23), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Phase I-b study of isatuximab + carfilzomib in relapsed and refractory multiple myeloma (RRMM). *First Author: Ajai Chari, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Isatuximab (ISA) is an anti-CD38 mAb with potent anti-myeloma effects as monotherapy or together with lenalidomide (Len) + dexamethasone (d) in RRMM. Carfilzomib (K) is a proteasome inhibitor approved for use in RRMM as a single agent or in combination (Kd or LenKd). Objectives: The primary objective was to assess the maximum tolerated dose (MTD) of ISA + K in RRMM. Secondary objectives were assessment of safety, PK, immunogenicity, and efficacy (IMWG response criteria (ORR)). (NCT02332850) **Methods:** Eligible patients (pts) had disease progression after 2 prior lines, an ECOG < 3, and adequate organ function. A 3+3 dose escalation (DE) design was utilized. 3 dosing levels (DL) were tested: ISA 10 mg/kg Q2W, ISA 10 mg/kg QW x 4 then Q2W and ISA 20 mg/kg QW x 4 then Q2W in combination with K standard dose (27 mg/m2) and schedule. An expansion cohort (EC) of 18 pts was enrolled at DL2. **Results:** 15 pts were treated in DE and 18 in the EC. The median age (n = 33) was 61 yrs (range 39-79). Pts received a median of 3 (2-8) prior lines. All pts were IMid and PI exposed: 26/29 Len refractory (Refr), 21/29 Vel Refr, 13/29 Pom Refr and 8/11 K Refr. Median follow-up is 6.5m (0.5 – 24m). 29 pts are evaluable for response. ORR = 66% (1 sCR, 7 VGPR, 11 PR) and CBR is 86%. The median progression free survival has not been reached. Disposition: 15 pts have progressed (4 deaths from PD), 1 pt withdrew after 27 cycles and 17 remain on therapy. The median # of cycles given is 3 (range 1-27). No DLT or severe toxicity has been observed. Common adverse events (AEs-all grades, incidence ≥ 15%), were thrombocytopenia (66%), pain (60%), upper respiratory infection (56%), diarrhea (40%), fatigue (40%), anemia (33%), cough (33%), elevated creatinine (30%), nausea (30%), neutropenia (27%), headache (27%), dyspnea (16.7%) and fever (16.7%). Serious AEs occurred in 9pts and < 5% of AEs were Gr 3/4. Infusion reactions (IRs) were the most common ISA-related AE: 17 IRs in 16/32 pts (50%: Gr 1 (9) + Gr 2 (8)). **Conclusions:** Combining ISA and K appears safe; toxicity is c/w the AEs of the individual agents with few G3/4 AEs. Encouraging anti-MM activity (ORR 66%) was seen at all DLs. ISA 10 mg/Kg QW x 4 then Q2W dosing was selected for an ongoing Phase III trial of ISA + Kd versus Kd (IKEMA: NCT03275285). Clinical trial information: NCT-02332850.

8015 Poster Discussion Session; Displayed in Poster Session (Board #24), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Low vs high dose carfilzomib (Cfz) with dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): Results of SWOG S1304. *First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL*

Background: Cfz has > 1 FDA approved doses in RRMM. Dose-response correlation is assumed without prospective data to compare efficacy of low-dose (27 mg/m^2; LDC) vs high-dose Cfz (56 mg/m^2; HDC). **Methods:** S1304 (NCT01903811), a randomized phase 2 trial compared LDC + dex vs HDC + dex, in Cfz nave RRMM pts with ²6 prior lines of treatment (Tt). Cycle 1 was 20 mg/m^2 with total planned Tt 1 year on each arm. Those progressing on LDC could cross to HDC. **Results:** 143 pts were enrolled, with 121 eligible + evaluable (LDC: 64, HDC: 57). Median follow up was 32 months (mo). There were no significant differences in pt characteristics or ORR between study arms (Table). Median PFS on HDC was 8 mo vs 6 mo on LDC (intent to treat); not statistically significant (HR 0.996 95% CI 0.785, 1.265). OS on 2 arms was also not significantly different (HR 1.069 95% CI 0.797, 1.434). PFS or OS were not significantly different between 2 arms in 1-3 vs 4-6 prior lines of Tt, bortezomib (btz) refractoriness or among pts who received ³2 or 12 cycles (2- and 12-month landmarks). There was a trend that HDC benefitted pts with any number of prior lines and not btz refractory, while LDC benefitted more 1-3 prior lines. Significantly different grade 3-5 AEs on the 2 arms are shown (Table). Cardiac AEs were not significantly different. **Conclusions:** In this only randomized comparison of different Cfz doses we did not find a PFS or OS benefit with HDC despite improved VGPR rates. Certain AEs were significantly higher with HDC. Ongoing weekly Cfz trials will further help define its utilization in RRMM.Clinical trial information: NCT01903811.

Selected patient characteristics, responses and grade 3-5 AEs at least possibly attributable to study treatment.

Characteristic	HDC (n = 57)	LDC (n = 64)	P-value
Age ³65	56%	48%	0.467
B2M ³3.5 mg/L	54%	56%	0.857
Cr ³2 mg/dL	0%	2%	1.000
Hb < 10 g/dL	11%	23%	0.091
4-6 Prior lines	26%	22%	0.671
Bortezomib refractory	49%	50%	1.000
Response Category	(n = 53)	(n = 59)	
VGPR	26%	8%	0.113
PR	21%	31%	
SD	40%	41%	
Increasing Disease	13%	20%	
AE Category	(n = 57)	(n = 64)	
General (most common: fatigue)	19%	3%	0.006
Nervous system (most common: peripheral neuropathy)	7%	0%	0.047
Investigations (most common: thrombocytopenia)	35%	16%	0.020
Cardiac	5%	8%	0.721
Maximum grade any AE	65%	39%	0.006

8016 Poster Discussion Session; Displayed in Poster Session (Board #25), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Maintenance therapy (MT) with 25 versus 5 mg lenalidomide (Len) after prolonged Len consolidation therapy (CT) in newly-diagnosed, transplant-eligible patients (pts) with multiple myeloma (MM). *First Author: Roland Fenk, University Hospital Duesseldorf, Dept. of Hematology, Oncology and clinical Immunology, Duesseldorf, Germany*

Background: While Len MT after high-dose therapy (HDT) and autologous blood stem cell transplantation (aBSCT) is standard of care in pts with MM, optimal dosage has not been established. **Methods:** In this prospective, randomized, open label, multicenter phase III trial 188 pts (ITT population) were included 3 months after first-line HDT and aBSCT and were equally randomized to receive either 25 (n = 94, arm A) or 5 mg (n = 94, arm B) Len (21 of 28 days cycle) MT until disease progression following a uniform 6 months 25mg Len CT. **Results:** Patients characteristics were equally distributed with a median age of 58 years (range: 30-72). Len CT could be completed in 86 % pts and Len MT was applied for one year in 72 % and 61 % pts in arm A and B (2 years: 44 % vs. 34 %; 3 years: 27 % vs. 15 %). In arm A 51 %, 22 %, 10 % and 3 % pts continued 25 mg Len without dose reductions / discontinuations after CT, 1, 2 and 3 years MT. Dose reductions were mainly due to hematologic AEs (68 %), especially grade 3 neutropenia (56 %). Overall toxicity was higher in the 25 mg arm and infections (≥ grade 2) were the major AE during MT (1st year: 62 % vs. 42 %, 2nd year: 44 % vs. 36 %, 3rd year: 44 % vs. 28 %). The incidence of second primary malignancies was similar in both arms. Response rates improved during CT with an increase of sCR from 8 % to 21 % (p = 0.0001). During MT, 36 % and 23 % of pts. in arm A and B achieved sCR as best response (p = 0.08). After a median follow-up of 46.7 months the primary endpoint event-free survival (EFS) from randomization was significantly different with a median EFS of 44.8 and 33.0 months for arm A and B (HR 0.65, range: 0.44-0.97; p = 0.032). This was confirmed by Landmark analysis including only patients who entered MT (HR 0.63; p = 0.042). Overall survival (OS) was not different with a median 4-year-OS of 79 % and 67 % for arm A and B (p = 0.16). **Conclusions:** Low-dose Len is associated with significantly shorter EFS compared to the concept of upholding high-dose Len. Still, the rate of toxicity observed and the need for dose reductions in most patients requires reconsideration of the high-dose schedule and awaiting of long-term OS. Support: Celgene. Clinical trial information: NCT 00891384.

8017 Poster Discussion Session; Displayed in Poster Session (Board #26), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Carfilzomib weekly 20/56mg/m², lenalidomide and dexamethasone for early relapsed refractory multiple myeloma. *First Author: Valentine Richez, Nice Sophia Antipolis University, Nice, France*

Background: Triplet-based lenalidomide plus dexamethasone (Rd) combinations have become the new standard of care for early relapse and refractory multiple myeloma (RRMM), including carfilzomib plus lenalidomide/dexamethasone (KRd) based on ASPIRE phase 3 data. In ASPIRE, K is given twice a week at 20/27mg/m² on days 1, 2, 8, 9, 15, 16 of a 28 days based cycle. In ENDEAVOR, a second Kd phase 3 study validated that K 20/56mg/m² twice weekly was safe in early RRMM. We hypothesized that KRd on a weekly basis was far less inconvenient to patients (pts). The aim of this study was to evaluate efficacy and toxicity of KRd weekly regimen in pts treated for early RRMM. **Methods:** 28 pts received KRd in 28-day cycles until disease progression or until occurrence of unacceptable toxic effects. K was administered as a 30-minute infusion on days 1,8,15 (starting dose, 20mg/m^2 on day 1 of cycle 1; target dose, 56mg/m^2). R (25mg) was given on days 1 to 21. D (40mg) was administered weekly. **Results:** The median age was 64 years (45 - 80) with 14% older than 70 years, sex ratio M/F 1.3 and ISS disease stage 2 or 3 in 39%. Pts had received a median of 1 (1 - 3) previous lines of therapy including proteasome inhibitors (100%) and immunomodulatory drugs (43%). With a median follow up of 8 months, 3 pts (11%) relapsed, and one patient died. The median number of KRd cycles administered was 6.5 (1 – 12). Overall response rate was 93%, with 89% ≥VGPR and 61% ≥CR. The mean time to a response was 1.6 months. The median TTP and OS at 12 months were 89% and 95%, respectively. 29% of pts have discontinued treatment, with solely 50% due to adverse events (AEs). Hematologic AEs ≥ grade 3 were reported in 57% and non hematologic AEs ≥ grade 3 in 36%. No pts died related to AEs. Overall AEs ≥ grade 3 seen in ≥10% of pts was neutropenia, thrombocytopenia, vomiting and pyrexia. No pts experienced any severe cardiovascular AEs, including cardiac failure or any severe cardiac issues or thromboembolic events. **Conclusions:** KRd weekly at 20/56mg/m^2 is effective and safe to early RRMM pts. Further studies are warranted to confirm this data on a larger MM population. Furthermore, analysis of long-term outcome is needed on our studied population.

8018 Poster Discussion Session; Displayed in Poster Session (Board #27), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Overall survival (OS) results of randomized phase III study (ADMYRE trial) of plitidepsin and dexamethasone (DXM) vs. DXM alone in patients with relapsed/refractory multiple myeloma (RRMM): Evaluation of the crossover impact. *First Author: Javier Gomez, PharmaMar, Madrid, Spain*

Background: Plitidepsin is a synthetic cyclic depsipeptide isolated from the marine tunicate *Aplidium albicans* targeting the proto-oncogene eEF1A2, which is over-expressed in multiple myeloma cells. In ADMYRE trial, Plitidepsin plus dexamethasone (DXM) (Arm A) met the primary endpoint (progression-free survival) and showed a survival improvement *versus* DXM alone (Arm B) (ASH 2017). **Methods:** RRMM patients with at least three but not more than six prior regimens, including at least bortezomib and lenalidomide/thalidomide, were randomized at 2:1 ratio to receive plitidepsin 5 mg/m^2 D1 and 15 plus DXM 40 mg D1,8,15 and 22 (Arm A), or DXM 40 mg D1,8,15 and 22 (Arm B) every four weeks. The rank preserving structural failure time (RPSFT) and the two-stage methods were used to present overall survival (OS) results after mitigating the crossover effect. **Results:** Two-hundred fifty-five patients were enrolled: (Arm A: 171/Arm B: 84). Thirty-seven patients in Arm B (44%) switched to Arm A after progression. Intention-to-treat (ITT) analysis not discounting the crossover effect showed a 20.3% risk reduction in favor of Arm A (median OS: A 11.6 mo. B: 8.9 mo.; HR = 0.797; log-rank p = 0.1261). Risk reduction improved to 32.4% with the RPSFT method (median OS: A 11.6 mo. B: 7.2 mo.; HR = 0.676; log-rank p = 0.0103) and to 37.8% with the two-stage method (median OS: A 11.6 mo. B: 6.4 mo.; HR = 0.622; log-rank p = 0.0015). Although assumptions for RPFST and two-stage analyses were plausibly met, statistically significant risk reductions were still maintained when severe penalizations were applied, with median OS differences around four months. **Conclusions:** Plitidepsin in combination with DXM demonstrated a clinically significant benefit in terms of overall survival in heavily pretreated RRMM, a disease where new therapeutic alternatives are still needed. Clinical trial information: NCT01102426.

8019 Poster Discussion Session; Displayed in Poster Session (Board #28), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Carfilzomib, bendamustine, and dexamethasone (KBd) in advanced multiple myeloma: The EMN09-trial. *First Author: Martin Gramatzki, Division of Stem Cell Transplantation and Immunotherapy, University of Kiel, Kiel, Germany*

Background: Various new agents have been introduced recently to treat relapsed/refractory multiple myeloma (RRMM), yet the chronification of the disease requires additional options for patients (pts) in advanced stages. Here, effectiveness and tolerability are important. Many advanced pts have received little chemotherapy but may suffer from peripheral neuropathy (PN). Carfilzomib (K) is a potent novel proteasome inhibitor not inducing significant PN. K was combined with bendamustine (B) to achieve synergistic effects. KB with low-dose dexamethasone (d) was tested in RRMM pts in a phase 1/2 trial (NCT02056756). **Methods:** 63 RRMM pts with ≥2 lines of prior therapy received KBd. Therapy consisted of 8 28-day courses of B at 70 mg/m^2 day 1,8; K at 27 mg/m^2 (initially 20 mg/m^2) day 1,2,8,9,15,16; d at 20 mg on every treatment day plus day 22,23. Responding pts received Kd maintenance every 14 days until PD. In the phase 1, a dose escalation in 6 pts to K at 36 mg/m^2 was attempted but led to 2 dose limiting toxicities. Thus, the phase 2 was conducted with K at 27 mg/m^2. **Results:** Pts had a median age of 66 years (range 37-79) and presented with RRMM in a median of 5.2 years after diagnosis. They were extensively pretreated, with a median of 4 prior lines (range 2-9) and 75% had previously received autologous stem cell transplantation, 87% bortezomib and 86% immunomodulatory drugs. At least VGPR rate was 32%, including 18% CR/sCR/nCR; 19% of pts achieved PR, 41% SD, 8% PD. Median PFS was 11.6 months, median OS 24.0 months. 1-year PFS was 72% in standard-risk and 35% in high-risk cytogenetics pts. Infections, particularly pneumonia, cardiac and thromboembolic adverse events (AEs) were the most frequent non-hematological AEs of grade ≥3; 51% of pts experienced ≥1 severe AE. Also the hematological toxicity was manageable. **Conclusions:** KBd was effective and well-tolerated in advanced RRMM pts requiring treatment rather late in the course of their disease. This cost-effective combination therapy with K at the 20/27 mg/m^2 and B at 70 mg/m^2 can be applied in an outpatient setting, with no significant nausea, hair loss or PN. Yet, cardiopulmonary and vascular signs need attention and infection prophylaxis is mandatory in these immunosuppressed pts. Clinical trial information: NCT02056756.

8020 Poster Discussion Session; Displayed in Poster Session (Board #29), Mon, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Mon, 3:00 PM-4:15 PM

Remission observed from a phase 1 clinical study of CAR-T therapy with safety switch targeting BCMA for patients with relapsed/refractory multiple myeloma. *First Author: Yarong Liu, HRAIN Biotechnology, Shanghai, China*

Background: Encouraging results are seen from several early phase clinical trials on the cellular immunotherapy based on chimeric antigen receptor (CAR)-engineered T (CAR-T) targeting B cell maturation antigen (BCMA) for the treatment of relapsed/refractory (RR) multiple myeloma (MM). We developed an anti-BCMA CAR-T cell product manufactured via gamma-retrovirus-mediated transduction of activated T cells to express a second-generation CAR with the 4-1BB costimulatory domain along with a truncated epidermal growth factor receptor (tEGFR) as a safety switch. The preclinical study confirmed its high reactivity against MM cells. **Methods:** A phase 1 clinical trial (NCT03093168) has been launched to evaluate the safety and feasibility of this BCMA CAR-T cell product for treating RRMM. The enrolled RRMM patients had received at least 3 prior treatment regimens, including a proteasome inhibitor and an immunomodulatory agent, or are double-refractory, and have over 20% BCMA expression on plasma cells. Patients were subjected to a lymphodepleting regimen with Cy once (300 mg/m^2, d-3) and Flu daily for 3 days (25 mg/m^2, d-5 to d-3) prior to the CAR-T infusion (d0) at a dose of 9×10^5 CAR$^+$ cells/kg. The efficacy was assessed by the International Uniform Response Criteria for Multiple Myeloma, and the toxicity iss graded by CTCAE 4.02. **Results:** As of December 31, 2017, 10 patients had been infused with this intended dose of the autologous BCMA CAR-T cells, and 7 patients had reached at least 1 month of follow-up. As of this data cut-off, no greater than Grade 1 neurotoxicities or cytokine release syndrome (CRS) had been observed. The overall response rate (ORR) for the 7 evaluable patients was 86%, including 2 sCRs and 2 MRD-negative responses (2 VGPR). The CAR-T cell expansion and persistence were consistently observed throughout these patients. **Conclusions:** Our result demonstrates the promising efficacy with the infused dose, including 2 sCRs and ongoing clinical responses for more than 12 months, with only mild and manageable CRS to date. These initial data provide strong evidence to support the further development of this anti-myeloma cellular immunotherapy. Clinical trial information: NCT03093168.

8021 Poster Session (Board #30), Mon, 8:00 AM-11:30 AM

A phase 3 randomized study of pembrolizumab (Pembro) plus pomalidomide (Pom) and dexamethasone (Dex) for relapsed/refractory multiple myeloma (RRMM): KEYNOTE-183. *First Author: Maria-Victoria Mateos, University of Salamanca Hospital, Salamanca, Spain*

Background: KEYNOTE-183 (NCT02576977) evaluated pom + low-dose dex (SOC) ± pembro in patients (pts) with RRMM. **Methods:** Pts were randomized 1:1 to pembro (200 mg Q3W) + SOC (4 mg pom [d 1-21] + 40 mg dex [d 1, 8, 15, 22]) every 28 d vs SOC until progression (PD), unacceptable toxicity, withdrawal. Coprimary endpoints: PFS (2011 IMWG criteria), OS; secondary endpoints: safety, ORR. On July 3, 2017 based on interim data presented to the DMC, the FDA halted KEYNOTE-183. **Results:** 249/300 pts enrolled (125, pembro + SOC; 124, SOC) with median (range) age: 65 y (45-94) vs 67 y (22-90); 28 (22%) vs 17 (14%) pts had high-risk cytogenetics. Median (range) drug exposure was 123.5 d (2-477) vs 127 d (2-463); median 4.4 cycles. AEs with ≥5% difference between arms: neutropenia (38% vs 27%), nausea (17% vs 12%), pneumonia (23% vs 15%), ALT increase (10% vs 3%), headache (13% vs 4%). No SAEs had ≥5% difference between arms. In pembro + SOC arm, 21 (18%) pts had immune-mediated AEs: skin reaction (5%), pneumonitis (4%), hyperthyroidism (3%), infusion reaction (2%), myopathy (2%), myocarditis, iridocyclitis, hepatitis, Steven-Johnson syndrome (SJS; 1% each). 29 (23%) pts vs 21 (17%) died (16 from PD, 13 from AEs vs 18 from PD, 3 from AEs). 4 (3%) treatment related deaths occurred; 2 (1.5% [1 myocarditis, 1 SJS]) related to pembro. Median follow-up was 7.8 mo vs 8.6 mo. Median PFS: 5.6 mo vs 8.4 mo; HR, 1.53 (95% CI, 1.05-2.22); P= 0.98. Median TTP: 8.1 vs 8.7 mo. Median OS: not reached vs 15.2 mo; HR, 1.61 (95% CI, 0.91-2.85); P= 0.95. In a retrospective random forest analysis age, ECOG PS, disease stage, presence of plasmacytoma, double refractory status were more relevant contributors to death than treatment. A subsequent multivariable COX regression analysis showed age, ECOG, presence of plasmacytoma significantly contributed to risk of death. Age and presence of plasmacytoma were prognostic, while ECOG was prognostic and predictive of outcome with OS HR = 0.85 (ECOG 0) and OS HR = 2.3 (ECOG 1). **Conclusions:** The benefit-risk profile for combination of pembro, pom and dex is unfavorable for RRMM. Evaluation of T-cell subsets and cytokines along with long-term safety and survival follow-up is ongoing. Clinical trial information: NCT02576977.

8022 Poster Session (Board #31), Mon, 8:00 AM-11:30 AM

Weekly carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed or refractory multiple myeloma (RRMM): A phase 1b study. *First Author: Noa Biran, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ*

Background: KRd is approved for treatment of RRMM patients (pts). Under the approved KRd regimen, carfilzomib is given twice weekly (20/27 mg/m^2; 10-min IV infusion). Here we present updated results from a dose-finding study assessing weekly KRd. **Methods:** This study consisted of a dose-evaluation component and a dose-expansion component in both RRMM and newly diagnosed MM. Results for RRMM pts are presented here. Two dose levels were evaluated: carfilzomib 56 mg/m^2 and carfilzomib 70 mg/m^2. All pts received carfilzomib (30-min IV infusion on days [D] 1, 8, and 15; 20 mg/m^2 on C1D1), lenalidomide 25 mg (D1–21), and dexamethasone 40 mg (D1, 8, 15, and 22) on a 28-day cycle (dexamethasone was not given on D22 for cycles 9+). Pts in the expansion arm received the selected KRd regimen on the same schedule used for dose evaluation. Response was assessed by investigators. **Results:** Twenty-two RRMM pts were enrolled in the dose-evaluation part and received study drug (56 mg/m^2, n = 10; 70 mg/m^2, n = 12). The maximum tolerated dose of carfilzomib was not reached; the 70 mg/m^2 dose was selected for dose expansion and 34 additional RRMM pts received this dose. Results are presented for pts who received carfilzomib 56 mg/m^2 during dose evaluation (n = 10; median 2 prior regimens [range 1-3]) and for pts who received carfilzomib 70 mg/m^2 during dose evaluation or expansion (n = 46; median 1 prior regimen [range 1-5]). Median (mean) average carfilzomib dose was 53.2 (52.8) mg/m^2 in the 56 mg/m^2 group and 62.4 (61.3) mg/m^2 in the 70 mg/m^2 group. Pt incidence of grade ≥3 adverse events was 70.0% (56 mg/m^2) and 71.7% (70 mg/m^2). Pt incidence of carfilzomib discontinuation due to adverse events was 20.0% (56 mg/m^2) and 17.4% (70 mg/m^2). There were three total deaths in the 70 mg/m^2 group (one each due to cardiac arrest, cardiac disorder, and progressive disease). Overall response rates were 90.0% (56 mg/m^2) and 89.1% (70 mg/m^2); 20.0% (56 mg/m^2) and 30.4% (70 mg/m^2) of pts achieved a complete response (CR) or stringent CR. **Conclusions:** Once weekly KRd was effective and had manageable toxicity in pts with RRMM. As a weekly carfilzomib dosing regimen could offer pts greater convenience, these results support further clinical evaluation. Clinical trial information: NCT02335983.

8023 Poster Session (Board #32), Mon, 8:00 AM-11:30 AM

Utility and prognostic value of ^{18}F-FDG PET/CT scan in patients with newly diagnosed multiple myeloma. *First Author: Mohammed A. Aljama, Mayo Clinic, Division of hematology, Rochester, MN*

Background: Positron emission tomography–Computed tomography (PET/CT) can identify bony lesions, assess disease burden and detect extra-medullary disease in patients with newly diagnosed multiple myeloma (MM). **Methods:** We conducted a retrospective review of patients who had a PET/CT performed within sixty days of diagnosis and prior to commencement of therapy to identify the nature and prognostic impact of PET/CT abnormalities in newly diagnosed MM. **Results:** Between April 2005 and June 2017, 314 patients were identified and included in the analysis. 235 (75%) patients had focal lesions (FL), 183 (58%) had ≥3 FL, 38 (12%) had extra medullary disease (EMD) and 194 (62%) had documented lytic lesions. Median maximum standardized uptake value (SUVmax) in the entire cohort was 5.9 (range 0-48.3). Presence of ≥3 FL and EMD predicted overall survival (OS); median OS of 58 months for ≥3 FL vs 89 months for < 3 FL (P= 0.009) and median OS 45 months for EMD present vs 71 months for EMD absent (P= 0.025). Compared to those with SUVmax of less than 8.5, those with SUVmax of more than 8.5 had a shorter overall survival, 89.6 versus 57.8 months, respectively (P= 0.022). **Conclusions:** PET/CT is a valuable tool in assessing disease burden and provides prognostic information in patients with newly diagnosed MM treated with novel agents.

Variable	Cohort N = 314	< 3 Lesions N = 131	≥ 3 Lesions N = 183	P value	Non-EMD N = 276	EMD N = 38	P value
Age years, median (IQR)	65 (58-72)	66 (57-73)	64 (58-71)	0.6	65 (57-71)	66 (61-78)	0.2
Male, %	197 (63)	85 (65)	112 (61)	0.6	173 (63)	23 (64)	1
Median Hemoglobin	12.0 (10.3-13.3)	12.2 (10.7-13.4)	11.8 (9.9-13.2)	0.1	12.0 (10.3-13.3)	11.4 (9.3-13.6)	0.4
Median Calcium	9.6 (9.1-10.2)	9.5 (9.0-10.0)	9.6 (9.1-10.3)	0.1	9.6 (9.1-10.2)	9.5 (9.1-9.9)	0.3
Median Creatinine	1 (0.8-1.2)	1 (0.9-1.3)	1.2 (0.8-1.2)	0.5	1.0 (0.8-1.2)	1.0 (0.9-1.2)	0.5
Median LDH	166 (135-195)	155 (129-184)	170 (137-212)	0.03	161 (134-191)	194 (161-262)	
Bone marrow plasma cell count	40 (20-61)	40 (20-60)	46 (23-66)	0.2	41 (20-62)	40 (20-60)	0.9
ISS, n (%)*				0.01			0.9
I	56 (32)	30 (45)	26 (24)		50 (32)	6 (29)	
II	63 (36)	18 (27)	45 (41)		55 (36)	8 (38)	
III	57 (32)	19 (28)	38 (35)		50 (32)	7 (33)	
Missing	138						

* With available testing

8024 Poster Session (Board #33), Mon, 8:00 AM-11:30 AM

Early MRD negativity to predict deepening myeloma response in relapsed/refractory multiple myeloma (RRMM) patients treated with bb2121 anti-BCMA CAR T cells. *First Author: Nikhil C. Munshi, Dana-Farber Cancer Institute, Boston, MA*

Background: A high frequency of rapid minimal residual disease-negative (MRD-neg) responses has been seen in CRB-401, a phase I trial of bb2121 CAR T cell therapy for RRMM (Kochenderfer, ASH 2017). We report IMWG responses in MRD-neg patients (pts) and associated factors. **Methods:** Pts treated with $\geq 150 \times 10^6$ BCMA CAR+ T cells in the dose-escalation phase of CRB-401 and evaluable for MRD by Adaptive NGS-based MRD Assay (Adaptive Biotechnologies) were included in this analysis (n = 10 as of 02 Oct 2017; median follow-up: 34 wks; min, max: 7, 67). **Results:** Nine of 10 evaluable pts were MRD-neg with a sensitivity of 1 in 10^{-4} nucleated cells (1 pt), 1 in 10^{-5} (6 pts), and 1 in 10^{-6} (2 pts). Achievement of MRD negativity was independent of depth of response at first MRD-neg assessment; 2 pts had stable disease, 3 had PR, 2 had VGPR, and 2 had CR / stringent CR. Of 8 evaluable MRD-neg pts, all showed $\geq$ 85% and $\geq$ 97% decline in serum BCMA and involved free light-chain levels, respectively, at month (M) 1. Two of 9 MRD-evaluable pts were in CR at MRD-neg assessment and the remaining 7 achieved deeper response over time, 4 with CR or stringent CR, 2 with VGPR and 1 with PR between M1 and M15. One MRD-neg pt became MRD-positive at M12, and 1 MRD-neg pt had progressed as of data cut-off. Achievement of MRD negativity was independent of occurrence of cytokine release syndrome. MRD-neg was observed across all active bb2121 doses (150 [n = 3], 450 [n = 5], and 800 x 10^6 [n = 1] CAR+ T cells). Of 9 MRD-neg pts, 7 had at least 6M follow-up and 1 had IMWG progression (at M6); 3 had at least 12M follow-up, 1 had become MRD-positive and none had IMWG progression. Attainment of MRD-neg was independent of peak CAR T expansion (vector copy min, max: 93,744, 1,457,070 copies/μg gDNA; n = 9) and was observed in high ($>$ 50%) bone marrow plasma cells (BMPC; n = 6) and low BMPC (n = 3) tumor burden pts. Eight of 9 MRD-neg pts had cytogenetic abnormalities including del(17), del(13), amp(1q21), or t(11;14). **Conclusions:** bb2121 induced a high frequency of rapid MRD-neg response, independent of IMWG MM responses. These early MRD-neg responses starting at M1 offer insights into bb2121 kinetics and may portend achievement of deeper responses over time. Clinical trial information: NCT02658929.

8025 Poster Session (Board #34), Mon, 8:00 AM-11:30 AM

Autologous stem cell transplantation in multiple myeloma patients over age 75. *First Author: Ning Dong, Rutgers NJMS, Newark, NJ*

Background: Autologous stem cell transplantation (ASCT) has improved the outcome of patients with Multiple Myeloma (MM) substantially and is now the standard of care. Patients over the age of 75 years are often denied this procedure due to toxicity concern. Since 35% of patients with MM fall into this age category, the safety and effectiveness of ASCT in this patient population needs to be studied. **Methods:** 604 patients with MM who received an ASCT at John Theurer Cancer Center of HUMC between 2005-2014 were evaluated. A total of 44 patients $\geq$ 75 years of age (range 75-84) and 560 patients younger than 75 at time of ASCT were included. The Kaplan–Meier method was used to compare survival between those two age groups. **Results:** Features of patients older than 75 were summarized in table 1. Melphalan 200mg/ m^2 was our primary conditioning regiment (75% of all patients). MM patients who received ASCT at age 75 or older had similar PFS and OS when compared with younger patients; the 3-year PFS was 52% and 46%, respectively; median PFS was 36.1 months vs 33.7 months, respectively, p = 0.76; the 3-year OS was 84% vs 82%, respectively; median OS was 93.3 months vs 127.8 months, respectively, p = 0.27. Two patients died within 100 days after ASCT. One died from subdural hematoma on day +11 and the other from Staphylococcus aureus sepsis on day +25. **Conclusions:** MM patients over the age of 75 can have similar outcomes from ASCT compared to the younger population. Elderly patients with MM should not be denied ASCT merely based on age.

Patient features of MM patients who received ASCT at age 75 or older.

	N = 44
Age, mean (range)	76.8 (75-84)
Female	14 (32%)
Mobilization	
Cyclophosphamide-based regiment	30 (68%)
GCSF	14 (32%)
Received plerixafor	8 (18%)
CD34 cells collected (x 10e6/kg), mean (range)	12.7 (3.1-27.9)
Days of CD34 collection, mean (range)	3.7 (2-9)
Disease Status at HSCT	
CR	1 (2%)
VGPR	12 (27%)
PR	21 (48%)
SD	6 (14%)
PD	2 (5%)
Unknown	2 (5%)
Conditioning regiment	
Melphalan 200mg/ m^2	33 (75%)
Melphalan 140mg/m^2	9 (20%)
Other	2 (5%)
Best Response post ASCT	
Stringent CR	9 (20%)
CR	9 (20%)
VGPR	11 (25%)
PR	7 (16%)
SD	2 (5%)
PD	1 (2%)
Unknown	5 (11%)

8026 Poster Session (Board #35), Mon, 8:00 AM-11:30 AM

Single cell analysis of multiple myeloma. *First Author: Guy Ledergor, Weizmann Institute of Science, Rehovot, Israel*

Background: Multiple myeloma (MM) remains mostly incurable despite advances in treatments in the last decade. Major clinical challenges include: capturing inter- and intra- patient heterogeneity, stratification of asymptomatic patients, sensitive and functional identification of residual disease to tailor therapeutic strategies, as well as performing accurate liquid biopsies to mitigate the need for recurrent bone marrow (BM) sampling. **Methods:** To capture BM and circulating plasma cells (PC), we performed single cell RNA-seq (scRNA-seq). Index sorting enabled to link cell surface markers intensity on each cell with its expression profile. Analysis of the transcriptome together with the specific B cell receptor (BCR) using k-nearest-neighbor graphs characterizes the inter and intra tumor heterogeneity of myeloma patients in both the BM and blood at single cell resolution. **Results:** Analysis of more than 30,000 PC sorted from 35 patients and 12 control subjects, created a detailed map of 43 transcriptionally homogeneous subpopulations. These were based on cluster-specific expression patterns of more than 1500 genes. PC from healthy donors clustered together and displayed 4 states representing either long-lived PC or cycling short-lived PC. In contrast, each patient presented a unique PC transcriptional state, with a specific BCR clonotype. We uncover novel overexpressed genes, previously unimplicated in MM, such as *LAMP5*. We identify intra-tumor heterogeneity in 10/35 patients, for example, a patient with a *FRZB* and *SMAD1* gene signature in 68% of PCs and an antimicrobial gene *DEFB1* in the rest of the PC, which share the same BCR clonotype. We define new markers to differentiate normal circulating PC from tumor cells (CTC) in the blood and show that CTC mirror the BM state. Further, we accurately characterize the heterogeneity within MGUS patients into PC with a normal transcriptional state in contrast to small clones with a defined malignant program. Finally, we identify small cancer clones in the setting of minimal residual disease (MRD) following high-dose therapy. **Conclusions:** We show the power of scRNA-seq as a new, high resolution tool, to identify new pathways and potential targets in myeloma, stratify patients based on unique molecular programs, and identify residual disease in both the BM and blood.

8027 Poster Session (Board #36), Mon, 8:00 AM-11:30 AM

Pomalidomide (POM) + low-dose dexamethasone (LoDEX) + daratumumab (DARA) in relapsed and/or refractory multiple myeloma (RRMM) after lenalidomide (LEN)-based treatment (Tx) failure. *First Author: David Samuel DiCapua Siegel, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ*

Background: POM + LoDEX + DARA in RRMM was approved in the US based on a phase 1b trial in heavily pretreated patients (pts; $\geq$ 2 prior lines [median, 4]; ORR, 60%). Data on the use of this regimen in earlier lines of Tx and immediately after LEN-based Tx are limited. Thus, MM-014 (NCT01946477) cohort B was initiated in pts with first- or second-line LEN-based Tx failures immediately before study entry to assess outcomes with POM + LoDEX + DARA sequenced earlier in Tx. **Methods:** Pts with RRMM after 1 or 2 prior lines who received a LEN-based Tx immediately before study and had progressive disease (PD) were eligible. In 28-d cycles (c), pts received POM 4 mg/d on d 1-21 + LoDEX 40 mg/d (20 mg/d if aged $>$ 75 yrs) on d 1, 8, 15, and 22, and DARA 16 mg/kg IV on DEX dosing days of c 1 and 2, then d 1 and 15 of c 3-6, then d 1 of c 7+. Thromboprophylaxis was mandatory. The primary objective was ORR by modified IMWG criteria. **Results:** A total of 46 pts were in the ITT population (median follow-up, 7.8 mos). 13 pts discontinued Tx (PD, 7; AEs, 2; other reasons, 4). Pts were refractory to (n = 36; 78%) or had relapsed after (n = 10; 22%) LEN-based Tx. Median duration of prior LEN-based Tx was 23.6 mos; 20 pts (43%) received LEN 25 mg/d in their last LEN-based Tx. ORR was 76.7% in efficacy-evaluable pts (n = 43), 72.2% in LEN-refractory pts, and 75.0% in pts who received LEN 25 mg/d in their last LEN-based Tx. Efficacy and safety are shown in the Table. At baseline, 10 pts (21.7%) had grade $\geq$ 2 neutropenia. There was 1 each of grade 3/4 pulmonary embolism and peripheral neuropathy. Any-grade infusion-related reactions occurred in 13 pts. Neutropenia (POM and DARA) and infusion-related reactions (DARA only) were primary reasons for dose interruptions. **Conclusions:** These results underscore the importance of POM-based Tx in RRMM after LEN. POM + LoDEX + DARA was safe, with promising activity when sequenced in earlier lines immediately after LEN-based Tx failure. Clinical trial information: NCT01946477.

Efficacy and safety.

Outcomes, %	N = 46
ORR	71.7
CR	4.3
VGPR	21.7
PR	45.7
Minimal response	6.5
Clinical benefit	78.3
SD	8.7
PD	6.5
1-year PFS	76.9
Grade 3/4 TEAEs (occurring in $\geq$ 10%)	
Neutropenia	71.7
Thrombocytopenia	23.9
Anemia	17.4
Infection	28.3

8028 Poster Session (Board #37), Mon, 8:00 AM-11:30 AM

Graft-versus-host disease (GVHD) risk with daratumumab (Dara) therapy post allogeneic transplantation (alloHCT) for multiple myeloma (MM). *First Author: Liana Nikolaenko, City of Hope Medical Center, Duarte, CA*

Background: Daratumumab (Dara) is an antibody targeting CD38+ MM cells that also affects CD38+ non-myeloma cells, including T cells, which mediate GVHD. Regulatory T cells (Tregs) are reduced while helper and cytotoxic T cells are increased in Dara-treated patients. Decreases in Tregs are associated with the development of GVHD. The association between Dara therapy post alloHCT and GVHD was evaluated. **Methods:** Multicenter, retrospective study. All patients who received alloHCT for MM were cross referenced with patients receiving Dara. Demographic data, details of prior MM therapy, conditioning regimen, time from transplant to Dara and time to GVHD were collected. **Results:** AlloHCT were performed between 2001 to 2016. Median time from alloHCT to first dose of Dara was 1.8 years (3.5 months to 15.3 years). Patient demographics are shown in Table 1. Median number of Dara infusions was 12 (range 1-19). A total of 14 patients (41%) developed GVHD post alloHCT: 9 patients had GVHD prior to Dara without relapse of GVHD after Dara, 5 patients developed GVHD after Dara (15%) with 4 of these 5 patients having no prior history of GVHD before Dara. One patient developed acute GVHD during Dara therapy while having history of chronic GVHD. Median time to onset of GVHD from first dose of Dara was 149 days (36 to 149 days). Overall response to Dara-based therapies was 38% (13/34), including 12 SD, 3 MR, 9PR, 2VGPR, 2CR, 4PD and 2 unavailable. Median follow up was 33.2 months (6.4 months to 16.5 years). **Conclusions:** Dara therapy post-alloHCT was well tolerated and did not increase risk of GVHD. These data suggest that Dara is an effective and safe option for use after alloHCT and could be considered in studies of salvage and maintenance post alloHCT.

Age at diagnosis	55 (33-70)
Sex	
Female	14 (41)
Male	20 (59)
Race	
Caucasian	24 (70)
Hispanic	6 (18)
Asian	2 (6)
African-American	2 (6)
Conditioning	
Cy/TBI	2 (6)
Flu/Cy	1 (3)
Flu/Cy/TBI	5 (15)
Flu/Mel	8 (24)
Flu/Mel/ATG	3 (9)
Flu/Mel/Bort	5 (15)
Flu/Mel/Vel/ATG	4 (12)
Flu/Mel/TBI	1 (3)
TBI	3 (9)
Flu/Mel/Bort/TMI	1 (3)
Flu/Bu	1 (3)
GVHD Prophylaxis	
FK/MTX	9 (26)
MMF/Cyclosporine	3 (9)
Tacro/MMF/Cy	5 (15)
Tacro/MTX	13 (38)
Tacro/Siro	2 (6)

8029 Poster Session (Board #38), Mon, 8:00 AM-11:30 AM

A phase 1/2 study of carfilzomib, bendamustine, and dexamethasone (CBD) in newly diagnosed multiple myeloma patients. *First Author: Siyang Leng, Home, Sunnyside, NY*

Background: Carfilzomib and bendamustine have demonstrated efficacy in relapsed refractory myeloma. In this phase 1/2 study, we evaluated the combination of carfilzomib, bendamustine and dexamethasone in newly diagnosed patients. **Methods:** This is an ongoing, open label, single center study. Phase 1 dose escalation followed an up-and-down dosing scheme (Storer's Design D). Carfilzomib was administered at dose levels of 27, 36, 45 and 56 mg/m^2 on days 1,2,8,9,15,16, bendamustine at 70 and 90 mg/m^2 on days 1,2, and dexamethasone at 20 mg on days of carfilzomib and on day 22 of a 28 day cycle. Autologous stem cell transplant (ASCT) eligible patients received 4 cycles of CBD, underwent stem cell harvest, and then received an additional 4 cycles followed by ASCT. ASCT ineligible patients received 8 cycles of CBD. Both groups received maintenance with carfilzomib 36 mg/m^2 on days 1,2,15,16 every 28 days for up to 2 years. **Results:** To date, 18 patients have been treated. Median age was 65 (range 51-74); 12 were male, 7 Hispanic, 2 African American and 2 Asian. One patient was treated at each dose level from 1-4, without DLTs; 14 patients were treated at the maximum dose level. The overall response rate was 100% – 16 (89%) had complete response (CR) / very good partial response (VGPR), with 3 being MRD-negative CR by flow, 3 stringent CR, 1 CR, and 9 VGPR; 2 had partial response (PR). 2 patients with VGPR and 1 with PR are still receiving induction. All patients showed response after 1 cycle. Of the 13 patients who have completed 8 cycles of CBD, 7 underwent ASCT. The 12-month PFS rate was 100%, and median follow-up was 14.8 months. G3/4 hematologic toxicities include neutropenia (28%), thrombocytopenia (22%), anemia (17%), lymphopenia (17%). Notable non-hematologic toxicities (all grades) include infection (44%), creatinine increase (33%), weight loss (28%), and thromboembolic event (22%). Stem cell collection was not impacted. **Conclusions:** CBD appears to be a safe and highly effective induction regimen for myeloma, with an 89% rate of CR/VGPR in our cohort. Clinical trial information: NCT02002598.

8030 Poster Session (Board #39), Mon, 8:00 AM-11:30 AM

Prognostic value of minimal residual disease and polyclonal plasma cells in myeloma patients achieving a complete response to therapy. *First Author: Marcella Tschautscher, Mayo Clinic, Rochester, MN*

Background: Achievement of a complete response (CR) to therapy has been associated with improved outcomes in patients with multiple myeloma (MM). More recently, increasing application of minimal residual disease (MRD) assessment following therapy has shown that MRD negativity is a powerful prognostic factor for survival outcomes. The presence of MRD, even among patients who have achieved a conventional CR, predicts inferior outcomes. Given this, we wanted to examine the impact of the polyclonal plasma cell (pPC) compartment among patients who achieved CR but still have MRD. **Methods:** This is a retrospective cohort study where 460 myeloma patients were identified who met criteria for CR per IMWG criteria and had application of multicolor flow cytometry to the bone marrow (BM) for the purpose of confirming CR. Mono and pPCs were estimated during MRD testing. A Kaplan-Meier model was used to determine OS and the 2-sided log-rank test to compare MRD+ and MRD- groups. TTNT was calculated as the difference from date of confirmed CR and date of next therapy. **Results:** The median duration from diagnosis to CR was 11.7 months. The median follow-up for the entire cohort was 33.5 months (95% CI; 31, 36) from CR; and the median OS was not reached (95% CI; 63 mos, NR). Median TTNT was 31 months (95% CI; 27,36). Among the 460 patients, 70% were MRD-, with a median TTNT of 37.6 months vs 23 months for MRD+ patients ($p < 0.001$); the median OS was not reached for either group, but there was a trend towards better survival for MRD- patients. The improved TTNT with MRD negativity was seen irrespective of prior treatment and SCT status. Among the 139 patients with residual disease, median percentage of pPCs was 65% (2.5 to 98.5), and those with > 95% pPCs had a significantly better TTNT (NR vs 23 months; $p = 0.02$) and a trend towards better OS. **Conclusions:** Achievement of MRD negativity predicts for better response durability and trend toward improved OS among patients in conventional CR treated with modern therapies. The impact seems independent of the type of therapy that results in achievement of CR and MRD negative status. Finally, an increased proportion of pPC predicts for better outcomes within those who have residual tumor cells.

8031 Poster Session (Board #40), Mon, 8:00 AM-11:30 AM

Daratumumab plus bortezomib-melphalan-prednisone (VMP) in elderly (≥75 y) patients (Pts) with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE). *First Author: Michele Cavo, "Seràgnoli" Institute of Hematology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy*

Background: Daratumumab (D) plus VMP (D-VMP) prolonged progression-free survival (PFS) compared with VMP and was well-tolerated in the phase 3 ALCYONE study (NCT02195479). We examined the efficacy and safety profiles of D-VMP vs VMP in elderly (≥75 y) and non-elderly (< 75 y) NDMM pts in ALCYONE. **Methods:** Pts were ineligible for high-dose chemotherapy with ASCT. Pts received up to nine 6-week VMP cycles (V: 1.3 mg/m^2 SC Days 1, 4, 8, 11, 22, 25, 29, 32 [Cycle 1] and Days 1, 8, 22, 29 [Cycles 2-9]; M: 9 mg/m^2 PO and P: 60 mg/m^2 PO Days 1-4 [Cycles 1-9]) ± D (16 mg/kg IV QW for Cycle 1, Q3W for Cycles 2-9, and Q4W for Cycles 10+ [post VMP-treatment phase] until progression). Minimal residual disease (MRD) was assessed by clonoSEQ assay (Adaptive Biotechnologies). **Results:** 706 (350 D-VMP; 356 VMP) pts were randomized, including 211 ≥75 y (104 D-VMP; 107 VMP) and 495 < 75 y (246 D-VMP; 249 VMP) pts. For D-VMP vs VMP, the median duration of study treatment was 14.5 mo vs 12.0 mo for ≥75 y pts and 15.0 mo vs 12.0 mo for < 75 y pts, respectively. After median follow-up of 16.5 months, PFS was prolonged with D-VMP vs VMP in both the ≥75 y (median not reached [NR] vs 20.4 mo; HR 0.53; 95% CI 0.32-0.85) and < 75 y (median NR vs 17.9 mo; HR 0.49; 95% CI 0.36-0.68) pts. ORR and ≥complete response (CR) rates were consistently higher for D-VMP vs VMP in ≥75 y (ORR: 88% vs 70%; ≥CR: 41% vs 24%) and < 75 y (ORR: 92% vs 76%; ≥CR: 43% vs 25%) pts. MRD-negative rates (10^{-5} threshold) also increased with D-VMP vs VMP in ≥75 y (24% vs 8%) and < 75 y (22% vs 6%) pts. Rates of most common grade 3/4 (≥10%) treatment-emergent adverse events, peripheral sensory neuropathy, and infections are in Table. D-associated infusion-related reactions were 36% (9% grade 3/4) in ≥75 y and 24% (3% grade 3/4) in < 75 y pts. **Conclusions:** Efficacy and safety of D-VMP vs VMP in pts ≥75 y of age were consistent with the overall study population. Clinical trial information: NCT02195479.

	≥75 y		< 75 y	
Grade 3/4, %	D-VMP	VMP	D-VMP	VMP
Most common TEAEs				
Neutropenia	52	42	35	38
Thrombocytopenia	51	43	28	35
Anemia	24	23	13	19
Leukopenia	13	9	6	9
Lymphopenia	10	10	7	4
Pneumonia	18	9	9	2
Peripheral sensory neuropathy	0	6	2	3
Infections	28	20	21	13

8032 Poster Session (Board #41), Mon, 8:00 AM-11:30 AM

Carfilzomib and dexamethasone (Kd56) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Updated overall survival (OS), safety, and subgroup analysis of ENDEAVOR. *First Author: Robert Z. Orlowski, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The phase 3 ENDEAVOR trial demonstrated significantly improved PFS and OS with Kd56 vs Vd in RRMM patients (pts; Dimopoulos *Lancet Oncol* 2016 and 2017). We report updated data after additional follow-up. **Methods:** Hazard ratios (HRs) and 95% CIs were estimated using stratified or unstratified Cox proportional hazards models for primary and subgroup OS analyses, respectively. **Results:** 929 pts were randomized (Kd56, n = 464; Vd, n = 465). As of 19-Jul-17, median OS was 47.8 (Kd56) vs 38.8 (Vd) months (mos; HR, 0.76 [95% CI, 0.633–0.915]; median follow-up, 44.3 vs 43.7 mos). OS was longer with Kd56 vs Vd within age subgroups (< 65 years [yrs]: median, 47.8 vs 42.2 mos; HR, 0.79 [95% CI, 0.598–1.031]; 65–74 yrs: median, 49.0 vs 36.2 mos; HR, 0.71 [95% CI, 0.520–0.958]; ≥75 yrs: median, 36.1 vs 23.9 mos; HR, 0.78 [95% CI, 0.506–1.199]). OS was longer with Kd56 vs Vd by prior lines of therapy (1 line: median, 51.3 vs 43.7 mos; HR, 0.77 [95% CI, 0.583–1.018]; 2–3 lines: median, 39.5 vs 28.4 mos; HR, 0.75 [95% CI, 0.589–0.959]) and prior bortezomib (btz) exposure (prior btz: median, 41.8 vs 32.7 mos; HR, 0.85 [95% CI, 0.669–1.082; no prior btz: median, not estimable [NE] vs 42.2 mos; HR, 0.66 [95% CI, 0.496–0.875]). OS was longer with Kd56 vs Vd for high-risk (median, 28.0 vs 22.7 mos; HR, 0.81 [95% CI, 0.580–1.136]) and standard-risk (median, NE vs 43.5 mos; HR, 0.79 [95% CI, 0.618–1.009]) cytogenetics pts. 457 (98.7%, Kd56) and 451 (98.9%, Vd) pts had an adverse event (AE); 379 (81.9%, Kd56) and 324 (71.1%, Vd) had a grade ≥3 AE. Exposure-adjusted pt incidences per 100 pt-yrs (95% CI) of AEs were 1352.07 (1233.62–1481.89) for Kd56 and 1754.86 (1600.15–1924.53) for Vd; for grade ≥3 AEs, these values were 162.31 (146.77–179.50) and 175.90 (157.75–196.13). The most common AEs in the Kd arm (≥ 30% of subjects) were anemia (43.6%), diarrhea (36.7%), pyrexia (32.6%), hypertension (32.4%), fatigue (32.2%) and dyspnea (32.2%). **Conclusions:** With median follow-up of ~44 mos, clinically meaningful OS improvements were observed with Kd56 vs Vd, including in all subgroups examined. The Kd56 safety profile was consistent with previous analyses. Clinical trial information: NCT01568866.

8033 Poster Session (Board #42), Mon, 8:00 AM-11:30 AM

Lack of racial disparity in outcome of African American (AA) and Caucasian patients with symptomatic multiple myeloma (MM) at the Veterans Affairs (VA) hospitals. *First Author: Nathanael Fillmore, VA Boston Healthcare System, Boston, MA*

Background: Recent studies have identified a significant and increasing disparity in survival amongst AA and Caucasian patients diagnosed with MM in the United States, and a concomitant disparity in access to novel chemotherapy and stem-cell transplant. We sought to investigate whether this disparity holds at the VA, which does not use a fee-for-service model. **Methods:** We used the VA's nationwide Corporate Data Warehouse to identify patients diagnosed with MM from 1999 to 2017, as well as their age, race, therapy at induction, and stem-cell transplant status. We compared overall survival between AA and Caucasian using Cox models. We assessed differences in treatment patterns using chi-squared tests. **Results:** We identified 15,717 patients diagnosed with MM, including 3,254 AA and 8,845 Caucasian patients. The median age at diagnosis was 65.6 years for AA and 70.1 for Caucasian (P<1e-15). As age has a substantial effect on overall survival, we adjusted our survival analysis for age at diagnosis. We found no difference in age-adjusted overall survival between AA and Caucasian, measured by hazard ratio of risk of death among AA relative to Caucasian (HR 0.99, 95% CI 0.94-1.05, P=0.69). However, among patients younger than 65 at diagnosis, we observed a significant decrease in age-adjusted risk of death for AA compared to Caucasian patients (HR 0.86, 95% CI 0.79-0.94, P=0.001). In patients >65 years, survival was similar between the 2 groups. The difference in younger population was not explained by access or utilization of the novel agents. We observed no racial disparity at the VA in the use of novel agents at induction (IMiD or PI), with 82.5% of AA patients and 81.5% of Caucasian patients receiving novel therapy (P=0.21); or in use of stem-cell transplant (10.1% of AA and 9.1% of Caucasian patients; P=0.09). **Conclusions:** No racial disparity was observed in overall survival or treatment patterns at the VA. Taken with previous research that does show these disparities in other US healthcare systems, this suggests that these disparities may be due primarily to economic factors, including cost of therapy, rather than factors related to disease biology.

8034 Poster Session (Board #43), Mon, 8:00 AM-11:30 AM

Pre-clinical development of TNB-383B, a fully human T-cell engaging bispecific antibody targeting BCMA for the treatment of multiple myeloma. *First Author: Ben Buelow, TeneoBio, Inc., Menlo Park, CA*

Background: T-cell redirecting therapies such as CAR-T cells and T-cell engaging bispecific antibodies (T-BsAb) targeting B Cell Maturation Antigen (BCMA) have been highly efficacious against relapsed/refractory myeloma (MM) in early phase clinical studies. However, strongly pan-T cell activating T-BsAbs have also been shown to overstimulate T cells, inducing toxicity and possibly decreasing efficacy. We have developed TNB-383B, a fully human BCMA-specific T-BsAb incorporating a low-activating αCD3 that preferentially activates effector over regulatory T cells. TNB-383B mediates T-cell killing of MM *in vitro, ex vivo* and *in vivo* but stimulates minimal cytokine release. **Methods:** *In vitro* and *ex vivo* efficacy studies included T-cell activation by cytokine- and tumor cell kill by calcein-release assays and/or flow cytometry. *In vivo* efficacy of the molecules was evaluated in NSG mice harboring myeloma cells and human PBMCs. Pharmacokinetics and tolerability were assessed in *Cynomolgus*. **Results:** TNB-383B showed T-cell activation and tumor-cell cytotoxicity *in vitro* and *ex vivo*, with markedly reduced cytokine production even at doses that showed maximum tumor cell lysis as compared to a positive control T-BsAb. *In vivo,* TNB-383B reduced tumor load and increased survival. TNB-383B had a T1/2 of ~13-16 days in *Cyno*, consistent with an IgG4 Ab. **Conclusions:** Our results suggest that TNB-383B may have a favorable toxicity profile with comparable or possibly improved efficacy compared to T-BsAbs that incorporate strong, pan T-cell activating anti-CD3 moieties in the treatment of MM.

8036 Poster Session (Board #45), Mon, 8:00 AM-11:30 AM

Molecular underpinnings of clinical disparity patterns in African American (AA) versus Caucasian American (CA) multiple myeloma (MM) patients. *First Author: Elizabeth M. Hill, NCI/NHLBI, Bethesda, MD*

Background: Due to unclear reasons, the AA population, compared to the CA population, has a 2-fold increased incidence of MM, has an earlier average age of diagnosis by 10 years, and has gained less benefit from novel treatments. To better understand underlying biological mechanisms of these disparities, we characterized genetic alterations using a first-in-kind targeted next generation sequencing (NGS) assay called myTYPE, allowing capture of both somatic mutations as well as gene translocations and gains/losses. **Methods:** Bone marrow clot sections were obtained from the NIH Plasma Cell Dyscrasia Racial Disparity Cohort. A total of 91 samples underwent DNA extraction, 81 met minimal quality control (QC) criteria and underwent NGS library preparation. Of these, 74 (51CA, 23 AA) passed all QC and sequenced using the Illumina platform with 100 bp paired end reads and a coverage of 600x. An additional 16 unmatched normal controls were sequenced for somatic analysis. Mutations were manually curated to select somatic based on COMSIC, MMRF, Bolli or truncating databases. myTYPE captures 120 genes including driver mutations, signaling pathways, therapeutic targets, IGH translocations, and copy number variations.**Results:** Of the 74 samples sequenced, 27 patients (37%) had at least one mutation. 12 genes with somatic mutations were identified. KRAS was most common, identified in 16% of patients (14% CA, 22% AA), followed by NRAS (4% CA, 9% AA) and BRAF (2% of CA, 13% AA). Mutations were also observed in FAM46C, DIS3, FGFR3, TP53, RASA2, KLHL6, KDM6A and SP140. Well-defined poor prognosis TP53 somatic mutations were more common in CA (6%) than AA (4%). Conversely, we found higher frequency of poor prognosis chromosomal alterations (1p deletions and 1q gains) in AA (23%) than in CA (13%) patients.**Conclusions:** This proof-of-principle analysis confirms the presence of varying underlying tumor biology between racial groups which likely contributes to the variance in CA and AA clinical outcomes. Our results support the need of future prospective interventional trials designed to capture these molecular characteristics in relation to specific therapies.

8037 Poster Session (Board #46), Mon, 8:00 AM-11:30 AM

Predictors of long-term survival in newly diagnosed multiple myeloma (NDMM) patients (pts) enrolled in the Connect MM registry. *First Author: Cristina Gasparetto, Duke University Medical Center, Durham, NC*

Background: There are limited longitudinal data on disease management & outcomes for long-term survivors of MM. The Connect MM Registry is a US, multicenter, prospective observational cohort study designed to examine diagnostic & treatment (tx) patterns, clinical outcomes & QoL in pts with NDMM. Data from Connect MM were used to identify pt- & disease-specific baseline (BL) characteristics associated with ≥ 6 y overall survival (OS) vs death at < 6 y in pts with NDMM. **Methods:** Adult pts in Cohort 1 (enrolled ≤ 60 days from diagnosis from Sep 2009 - Dec 2011) had sufficient follow-up for evaluation; those censored at < 6 y (study discontinuation, ongoing but survival < 6 y) were excluded. BL characteristics were compared via logistic regression to identify those associated with ≥ 6 y OS ($P < 0.05$). **Results:** As of Feb 2017, median follow-up for Cohort 1 (N = 1493) was 65.4 mo. Median age was 67 y (range 24-94), 57% were male, & 59% were standard/low risk per IMWG criteria. Most pts (91%) had ≥ 1 novel agent in their first drug regimen (1L; Table). BL characteristics associated with ≥ 6 y OS by multivariate analyses were: age (≤ 70 vs > 70), ECOG PS (0-1 vs 2-5), lower ISS stage, platelet count (≤ 150 vs > 150 x 10^9/L), & lack of history of diabetes, del(17p), extramedullary plasmacytoma, or serum-free light chain abnormality. Matrix for predicting OS ≥ 6 y will be included in the presentation. **Conclusions:** This analysis identified pt- & disease-specific BL characteristics associated with ≥ 6 y OS in pts with NDMM. Higher rates of triplet tx, SCT, maintenance (with/without SCT), & higher response rates were observed in pts with ≥ 6 y OS. Clinical trial information: NCT01081028.

	≥ 6 y OS (n = 246)	Death < 6 y[a] (n = 662)
First induction regimen in 1L, n (%)		
Triplet	111 (45)	260 (39)
1 novel tx	160 (65)	452 (68)
2 novel tx	69 (28)	142 (21)
SCT in 1L, n (%)	125 (51)	157 (24)
+ maintenance	89 (36)	89 (13)
no maintenance	36 (15)	68 (10)
No SCT in 1L, n (%)	121 (49)	505 (76)
+ maintenance	62 (25)	123 (19)
no maintenance	59 (24)	382 (58)
Best response to first induction regimen in 1L, n (%)		
Stringent CR	2 (< 1)	2 (< 1)
≥ CR	19 (8)	19 (3)
≥ very good PR	42 (18)	75 (12)
Overall response (≥ PR)	72 (31)	147 (24)
≥ minor response	167 (71)	371 (59)

[a]585 pts were censored at < 6 y and excluded. CR, complete response; PR, partial response

8038 Poster Session (Board #47), Mon, 8:00 AM-11:30 AM

Final results of a phase Ib study of isatuximab (ISA) plus pomalidomide (Pom) and dexamethasone (dex) in relapsed/refractory multiple myeloma (RRMM). *First Author: Joseph Mikhael, Mayo Clinic, Phoenix, AZ*

Background: ISA is a monoclonal antibody targeting CD38-expressing tumor cells. We report final data from a Ph Ib dose-escalation/expansion study of ISA + Pom/dex in pts with RRMM (NCT02283775). **Methods:** Pts with RRMM (≥2 prior MM therapies; includes lenalidomide + a proteasome inhibitor [PI]) received 5, 10, or 20 mg/kg ISA (4 weekly [QW] doses, then every 2 wks until progression/intolerable toxicity), Pom 4 mg (Days 1–21), and dex 40 mg (QW; 20 mg if ≥75 yrs old) in 28-day cycles. Primary objective: recommended dose of ISA + Pom/dex. Secondary objectives included efficacy (IMWG criteria), safety, pharmacokinetics (PK). **Results:** 45 pts received ISA at 5 (n = 8), 10 (n = 31), or 20 (n = 6) mg/kg. Median age 67 (42–82) yrs. Median 3 (2–10) prior lines; 41 (91%), 37 (82%), and 38 (84%) pts refractory to their last regimen, immunomodulatory drugs (IMiDs), or PIs, respectively. 6 pts had high-risk (HR) cytogenetics. Median treatment time: 9.6 mos; 19 (42%) pts remain on treatment. 2 pts (10 mg/kg) discontinued due to AEs (grade [Gr] 5 intestinal perforation [due to underlying MM]; Gr 3 infusion-associated reaction [IAR]). 1 pt at each dose reported a DLT; MTD not reached. Expansion cohort initiated at 10 mg/kg based on efficacy, safety, and PK data. Most common TEAEs, besides IARs/hematologic AEs: fatigue (62%), upper respiratory tract infection (42%), and dyspnea (40%). Gr ≥3 neutropenia occurred in 83% of pts (Gr 4, 56%); all cases reported as AEs resolved with dose modification/growth factor support. IARs occurred in 19 (42%) pts (Gr ≥3, 1 pt): 18 (40%) pts during 1st infusion, 3 (7%) pts at later infusions. Overall response rate (ORR) was 62%; ORR in HR cytogenetics: 33%; IMiD refractory: 57%; PI refractory: 63%. 12 (27%) pts achieved ≥ VGPR (1 CR; 1 sCR). Median time to 1st response, 0.95 mos; median duration of response, 18.7 mos (95% CI 12.5–NC). Median progression-free survival, 17.6 mos (95% CI 6.8–20.5). ISA PK is unaffected by Pom/dex co-administration. **Conclusions:** These final results confirm the promising clinical activity and manageable safety profile of ISA + Pom/dex in heavily pretreated RRMM. A Ph III confirmatory trial is ongoing with results expected later in 2018. Funding: Sanofi Clinical trial information: NCT02283775.

8039 Poster Session (Board #48), Mon, 8:00 AM-11:30 AM

Lenalidomide (LEN) pharmacokinetics (PKs) in multiple myeloma (MM) patients (pts) with various renal functions. *First Author: Yanshuo Cao, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: LEN is a backbone drug used in the treatment of MM. Because over 80% LEN is excreted unchanged in urine, dose modifications for RD are recommended, based on PK evaluation following single dose LEN in non-malignant renal failure. In this analysis, MM pts with varying degrees of RD after single and multiple dosing of LEN were evaluated for PK to validate these dosing recommendations. **Methods:** Previously untreated MM pts received LEN in combination with dexamethasone according to creatinine clearance (CrCL) as recommended by the current LEN label. CrCL was calculated based on 24-hour urine collection. Serial venous blood samples were obtained on Days 1 and 17 and analyzed for LEN. PK parameters were calculated using non-compartmental methods. **Results:** A total of 25 pts were enrolled, 9 pts with normal renal function (CrCl ≥ 60 ml/min), 8 with moderate RD (30 ≤ CrCl < 60 ml/min), and 8 with severe RD (CrCL < 30 ml/min or on dialysis). Median age: 59 years (range: 39-69); male/female: 16/9. After a single dose, LEN half-life increased with RD (4.1 vs 6.7 vs 11.1 hours, $p < 0.01$). Plasma LEN concentrations were lowest in moderate RD, resulting in significantly lower maximum concentration (Cmax) and area under concentration-time curve (AUC). LEN clearance decreased with more advanced RD, and correlated with calculated CrCL, with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula providing the best correlation compared to the Modification of Diet in Renal Disease (MDRD) formula and the Cockcroft-Gault formula. There was no LEN accumulation between Day 1 and Day 17 in pts with normal renal function or moderate RD. Cmax and AUC were significantly lower on Day 17 for pts with severe RD (413.8 ng/ml vs 71.1 ng/ml, $p < 0.0001$, and 4946 ng×hr/ml vs 538 ng×hr/ml, $p = 0.002$). **Conclusions:** MM pts with moderate RD are significantly under-dosed with the current LEN dosing recommendation. LEN PKs after multiple doses are similar for pts with normal or moderate RD, but those with severe RD may benefit from therapeutic drug monitoring and dose adjustment. The CKD-EPI formula should be used to calculate CrCL and LEN dose determination. The current LEN dose recommendation should be revised for pts with moderate RD. Clinical trial information: NCT01270932.

8040 Poster Session (Board #49), Mon, 8:00 AM-11:30 AM

Extended 5-y follow-up (FU) of phase 3 ELOQUENT-2 study of elotuzumab + lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma (RRMM). *First Author: Sagar Lonial, Emory University, Winship Cancer Institute, Atlanta, GA*

Background: The immunostimulatory monoclonal antibody elotuzumab exhibits a dual mechanism of action, directly activating natural killer cells and mediating myeloma cell death via antibody-dependent cell-mediated cytotoxicity. In ELOQUENT-2 (NCT01239797), ELd showed sustained reduction in risk of disease progression or death at 2- (30%), 3- (27%), and 4-y (29%) FU vs Ld, and a favorable trend in overall survival (final analysis at 427 deaths). Here we present progression-free survival (PFS) data at 5 y, a milestone timepoint in cancer survival analyses. **Methods:** RRMM patients (pts) randomized 1:1 to ELd or Ld in 28-d cycles until disease progression/unacceptable toxicity. Coprimary endpoints: PFS and overall response rate (ORR) per independent review committee. **Results:** In all, 646 pts were randomized to ELd (n = 321) and Ld (n = 325). At database lock (Nov 29, 2017), 13% (ELd) vs 7% (Ld) of pts remained on treatment; discontinuation was mostly due to disease progression (55 vs 56%). At 5-y FU (minimum 60 mo), ELd showed 27% reduction in risk of progression or death vs Ld (HR 0.73, 95% CI 0.60–0.87) and relative improvement of 50% in PFS rate at 5 y (18 vs 12%). Pts with ≥very good partial response (ELd 36% vs Ld 30%) had the greatest reduction in risk of progression/death (HR 0.63, 95% CI 0.44–0.89). ORR was 79% (ELd) vs 66% (Ld). G3–4 AEs included blood and lymphatic system disorders (ELd vs Ld: 46 vs 46%), infections (35 vs 27%), vascular diseases (11 vs 8%), second primary malignancies (SPMs; 10 vs 6%), and cardiac disorders (5 vs 8%). Higher rate of any-grade infection (84 vs 75%) and SPMs (17 vs 11%) may reflect longer median duration of treatment with each agent of the ELd vs Ld regimens (E/L/d vs L/d: 17/17/17 vs 12/12 mo). Fewer deaths occurred with ELd than Ld (193 vs 208), mostly due to disease progression. **Conclusions:** Elotuzumab (+ Ld) has the longest median FU of an immuno-oncology agent in MM. At the milestone timepoint of 5 y, ELd showed sustained, durable clinically relevant improvement in PFS, a 27% reduction in the risk of progression or death, and a safety profile with minimal incremental AEs with ELd vs Ld. Study funding: BMS. Writing support: L Yee, Caudex, funded by BMS. Clinical trial information: NCT01239797.

8041 Poster Session (Board #50), Mon, 8:00 AM-11:30 AM

Treatment (tx) journeys in newly diagnosed multiple myeloma (NDMM) patients (pts): Results from the Connect MM Registry. *First Author: Sundar Jagannath, Mount Sinai Hospital, New York, NY*

Background: Real-world longitudinal data on tx sequencing & outcomes are limited. The Connect MM Registry is a US, multicenter, prospective observational cohort study designed to examine diagnostic & tx patterns, clinical outcomes & QoL in pts with NDMM. Using visual tools (Sankey Plots), tx sequences & transitions were longitudinally assessed in pts with NDMM from Connect MM who did or did not receive stem cell transplant (SCT, NSCT). **Methods:** Adult pts were enrolled ≤ 60 days from diagnosis in Cohorts 1 (n = 1493; 2009-2011) & 2 (n = 1518; 2012-2016). Tx were classified as containing: 1) immunomodulatory agents, 2) proteasome inhibitors (PI), 3) IMiD® agent + PI, 4) non-IMiD/PI agents (other), 5) tx gaps. Data is presented within Sankey plots, a type of flow diagram in which the proportional flow between variables (or nodes) is visualized. Flows between tx from first to last lines of tx, discontinuation, or death, were visually depicted & median progression-free survival (PFS) for lines 1, 2 & 3 of tx were examined. **Results:** As of Feb 2017, 966 SCT & 1941 NSCT pts have been treated (Table). Points of tx transitions were represented by nodes on the plots corresponding to a change in regimen, such as maintenance (or not), line 2 tx, line 3 tx, discontinuation or death. Substantial heterogeneity of treatment was observed. The most frequent treatment flow among SCT pts was IMiD agent + PI → IMiD agent → Ongoing (O) → Line Not Yet Reached (LNR) (16%); & for NSCT pts was PI → PI → O → LNR (8%). Outcomes per line of therapy were assessed. Median 1st PFS was nearly twice as long in all SCT pts compared to all NSCT pts. In SCT pts, median 1st, 2nd, & 3rd PFS measured from line start were 44.0, 8.3, & 4.5 mo; in NSCT pts, median 1st, 2nd, & 3rd PFS were 21.5, 7.3, & 5.8 mo, respectively. **Conclusions:** These real-world registry data depict the therapeutic journeys of pts with MM. The PFS by line data are similar to clinical trials of pts with MM. Clinical trial information: NCT01081028.

	SCT (n = 966)	NSCT (n = 1941)
Median follow-up, mo	31.8	37.5
Firstline (1L), n (%)		
PI	417 (43)	946 (49)
IMiD agent	88 (9)	367 (19)
IMiD agent + PI	450 (47)	525 (27)
Other	11 (1)	103 (5)
MT after 1L, n (%)		
Yes	620 (64)	511 (26)
No	290 (30)	393 (20)
Remain on initial tx	55 (6)	1037 (53)

8042 Poster Session (Board #51), Mon, 8:00 AM-11:30 AM

Health-related quality of life in patients with newly diagnosed multiple myeloma who are ineligible for stem cell transplantation: Results from the ALCYONE trial. *First Author: Katharine Gries, Janssen Research & Development, LLC, Raritan, NJ*

Background: ALCYONE, an ongoing multicenter, open-label, Phase 3 trial of subjects with newly diagnosed multiple myeloma not eligible for high-dose chemotherapy with stem cell transplantation due to coexisting conditions or age ≥ 65 years, demonstrated significant progression-free survival (PFS) with daratumumab, bortezomib, melphalan, and prednisone (D-VMP) treatment compared with VMP alone. Measuring patient-reported outcomes (PROs) alongside disease progression provides the patient perspective on quality of survival and the value of health-related quality of life (HRQoL) for treatment decisions. **Methods:** The European Organization for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) and EuroQol Questionnaire (EQ-5D-5L) visual analog scale (VAS) were completed using an electronic device (ePRO) at baseline and every 3 months during treatment; interim results presented for first 12 months. Key secondary endpoints included EORTC QLQ-C30 Global Health Status (GHS) and VAS scores. Treatment differences were assessed using repeated measures, mixed-effects model. Percent subjects achieving meaningful improvement based on established clinically important differences was summarized. **Results:** Study population included D-VMP (n = 350) and VMP (n = 356) subjects. Compliance rates > 90% at baseline and > 70% through month 12. Significantly better HRQoL in the D-VMP arm was observed at month 3 for GHS (p = 0.026) [Table]. Meaningful improvement in GHS was reported in 59.7% of D-VMP subjects compared to 52.0% VMP subjects (OR: 1.37; 95% CI: 1.02, 1.85). Similar HRQoL improvements were observed with the VAS. **Conclusions:** Patients experienced meaningful improvement in HRQoL over the course of therapy with more achieving meaningful change when treated with D-VMP. Improvements in HRQoL were consistent with the clinical benefit showing superior PFS of D-VMP over VMP alone. Clinical trial information: NCT02195479.

GHS Change from baseline.

	D-VMP		VMP	
	n	LS Means (95% CI)	n	LS Means (95% CI)
Month 3	261	7.6 (5.3, 9.8)	244	4.1 (1.8, 6.5)
Month 6	233	8.7 (6.4, 11.1)	212	8.9 (6.5, 11.4)
Month 9	226	10.7 (8.3, 13.1)	189	10.4 (7.8, 13)
Month 12	220	11.5 (9.1, 13.9)	179	10.5 (7.9, 13.2)

8043 Poster Session (Board #52), Mon, 8:00 AM-11:30 AM

Real-world evidence of cardiac hospitalizations in carfilzomib- and non-carfilzomib-treated multiple myeloma patients in the United States. *First Author: Joseph Mikhael, International Myeloma Foundation, North Hollywood, CA*

Background: Approximately 30% of multiple myeloma (MM) patients (pts) are hospitalized for cardiac events after MM diagnosis. Carfilzomib (K), a 2nd generation proteasome inhibitor, was approved to treat MM in 2012. **Methods:** We conducted a matched retrospective claims-based cohort study of MM pts who initiated K or non-K treatment (tmt) between 2012-2015 using Truven MarketScan. Pts were > 18 yrs and had ≥1 yr baseline (BL) data before MM diagnosis. Line of therapy (LOT) and regimens were identified using drug prescription claims. Index LOT was defined as first K-containing LOT. Pts who received non-K regimens were matched 2:1 to K pts on age, sex, and index LOT. Hospitalizations were identified using diagnosis codes in claims during index LOT. Any cardiac hospitalizations (CH) included new and existing cardiac conditions defined as having a cardiac code (arrhythmia, heart failure, ischemic heart disease, cardiomyopathy, hypertension) as primary/secondary diagnoses on the claim; primary CH (PCH) had a cardiac code as primary diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated, adjusting for tmt duration and BL conditions. **Results:** 498 K and 996 non-K pts were identified (median age 61 and 62 yrs, respectively). In both cohorts, 59% were male; 6%, 30%, and 64% were treated in LOT 1, 2, and 3+. Overall, there was no difference in BL cardiac history (84.9% and 84.1%, respectively). Median tmt duration was 105 and 158 days for K- and non-K pts, respectively. 34% of pts in each cohort were hospitalized. Any CH occurred in 16% and 12% of K- and non-K pts. Unadjusted OR (95% CI) for CH in K pts vs non-K pts was 1.47 (1.1–2.0). When adjusted for tmt duration, OR (95% CI) of CH in K pts vs non-K pts was 1.1 (0.8–1.5). Similar hospitalization risks were seen when additionally adjusting for BL conditions. PCH occurred in 2% and 3% of K and non-K pts, respectively (unadjusted OR [95% CI] 0.7 [0.4–1.4]; adjusted OR [95% CI] 0.55 [0.3–1.1]). **Conclusions:** In real world pts, the risk of cardiac-related hospitalizations during tmt was similar for K- and matched non-K treated pts when adjusted for tmt duration and BL conditions. Selection bias may impact the risk estimates.

8044 Poster Session (Board #53), Mon, 8:00 AM-11:30 AM

The MD Anderson modified cyclophosphamide, bortezomib, doxorubicin, and dexamethasone (mCBAD) for the treatment of newly diagnosed (NDMM) and relapsed/refractory multiple myeloma (RRMM). *First Author: Samer Tabchi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MM follows a clinical course leading to refractoriness and limited treatment options in RRMM. Aggressive NDMM needs rapid cytoreduction for disease control, which may not be possible with standard novel therapies. We report on a highly effective therapy that offers a salvage option for these patients. **Methods:** We searched our medical database for MM patients who received mCBAD from 2010-2016 – 28 day cycle of cyclophosphamide 350 mg/m^2 IV twice daily + mesna 400mg/m^2 IV daily (days 1-4), bortezomib 1.3 mg/m^2 SQ (days 1, 4, 8, 11), doxorubicin 9 mg/m^2 IV (days 1-4) , dexamethasone 40 mg PO daily (days 1-4, 9-12, 17-20). IMWG criteria were used for response assessment. Descriptive statistics, Fisher's exact test, Chi-square, Wilcoxon rank sum, and Kaplan-Meier were used for statistical purposes. **Results:** 80 patients met the inclusion criteria. Baseline characteristics, response, adverse events, PFS/OS are summarized in Table 1. Median follow-up for the censored observations was 21.3 months (1.35 – 69.22). **Conclusions:** mCBAD offers excellent response rates (ORR > 90%) and favorable PFS/OS in highly refractory high risk MM. It is also an excellent salvage regimen with about half of patients undergoing subsequent transplant. Patient selection is required due high treatment related mortality.

	NDMM (n = 15)	RRMM (n = 65)
Age, median (range)	56 (36 -74)	65 (22 -75)
ISS, n(%)		
I	1 (7.1)	15 (24.6)
II	1 (7.1)	15 (24.6)
III	12 (85.7)	31 (50.8)
FISH, n(%)		
t(4:14)	2 (14.3)	6 (9.5)
t(14;16)	0	2 (3.2)
deletion 17p	2 (14.3)	21 (33.3)
# cycles received, (%)		
≤2	80%	80%
≥3	20%	20%
# prior therapies, median (range)	0	2 (1 - 7)
Prior ASCT, n (%)	0	24 (36.9)
ORR^, n (%)	15 (100)	54 (91.5)
CR	3 (20)	4 (6.8)
VGPR	4 (26.7)	13 (22)
PR	8 (53.3)	37 (62.7)
PD	0	5 (8.5)
Adverse events*, n(%)		
Neuropathy	3 (20)	20 (31)
Febrile neutropenia	2 (13.3)	18 (27.7)
Infection	5 (33.3)	26 (40.6)
Mortality	0	8 (16%)
PFS, mo (95% CI)	19.6 (10.3 - NR)	6 (3.9- 7.2)
PFS (followed by ASCT)	N/A	8.95 (6.9-15.9) (n = 28)
PFS (not followed by ASCT)	N/A	3.2 (2.2 - 4.2) (n = 34)
OS mo (95% CI)	35.4 (18.1 - NR)	15.8 (9.3 - 23)

**related to treatment, ^ best response - 59 evaluable RRMM, ASCT = autologous transplant*

8045 Poster Session (Board #54), Mon, 8:00 AM-11:30 AM

Duration of complete response (DurCR) impacts overall survival (OS) in multiple myeloma (MM). *First Author: Surbhi Sidana, Mayo Clinic, Rochester, MN*

Background: DurCR has a direct impact on progression free survival in MM, but its impact on OS is not well described. **Methods:** We retrospectively analyzed 351 patients with MM from 2004-16 who achieved CR (IMWG criteria) with first line therapy to assess impact of DurCR (time from achievement to loss of CR) on OS. **Results:** The table lists baseline characteristics. Loss of CR was experienced by 68% (239) patients, with (1) symptomatic progression in 25% (59); (2) biochemical progression in 24% (58); (3) two consecutive positive immunofixation or rise in monoclonal protein not meeting progression criteria in 37% (88); (4) two abnormal FLC ratios in light chain MM in 14% (34). In group 3, progression was seen in 73/88 (85%) patients (13 symptomatic, 60 biochemical) with median time from loss of CR to progression of 7 months and in 21/34 (62%) patients in group 4 (3 symptomatic, 18 biochemical) with median time of 4 months. After median follow-up of 72 months, median OS from start of therapy with DurCR $\geq$ 24 (n = 179, 51%) vs. $<$ 24 months (n = 172, 49%) was 150 vs. 80 months, $p < 0.001$. Estimated 5 and 10 year OS in DurCR $\geq$ 24 was 95% and 70% and in DurCR $<$ 24 was 66% and 25%, respectively. Landmark analysis for patients alive at 24 months from start of treatment showed similar results (DurCR $\geq$ 24 vs. $<$ 24, median OS: 150 vs. 83 months, $p < 0.001$). Among patients who experience loss of CR, OS from loss of CR was higher in patients with DurCR $\geq$ 24; 82 vs 56 months, p = 0.005. On multivariate Cox Proportional hazards model, DurCR remained a significant predictor of OS from start of treatment (CR $<$ 24 months vs. $\geq$ 24 months, HR: 4.0 (2.4-7.0), $p <$ 0.001), after adjusting for revised ISS, age $\geq$ 65 years, ASCT and maintenance therapy. **Conclusions:** DurCR is an important independent predictor of OS in MM, with estimated 5 and 10 year OS with DurCR $\geq$ 24 months being 95% and 70%, respectively. Importantly, majority of patients who experience loss of CR meet criteria of progression within median of 4-7 months.

	Median (IQR) or n (%)
Age	61 years (54-66)
Males	198 (56)
High risk FISH: del17p, t(4;14),t(14;16) & t(14;20)	58/283 (21)
ISS N = 295	115/96/84 (39/33/28)
R-ISS N = 230	61/141/28 (27/61/12)
BMPCs	50% (30-70)
ASCT	269 (77)
Maintenance	133 (39)
Time to CR	8 months (5-9)
Duration of CR	24 months (13-42)

8046 Poster Session (Board #55), Mon, 8:00 AM-11:30 AM

Impact of obesity on response in 751 myeloma patients receiving lenalidomide, bortezomib, and dexamethasone (RVd) induction. *First Author: R Donald Harvey, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Obesity is a putative risk factor for the development of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM). Induction regimens for MM have evolved; and lenalidomide, bortezomib, and dexamethasone (RVd) produces an overall response rate of 82%. Response, tolerability and therapy duration are related to agent dose, dose intensity, and comorbidities, which may be higher in the obese. We analyzed the effect of anthropometric measures on response and therapy duration in patients (pts) receiving RVd induction. **Methods:** Height (cm), weight (kg), body surface area (BSA), and body mass index (BMI) were obtained from a database of 751 pts receiving RVd. Demographics including sex, self-reported race, ISS stage at diagnosis, and cytogenetic risk category were analyzed with anthropometric data in a multivariate model with response per IMWG criteria, progression-free survival (PFS) and overall survival (OS). **Results:** Anthropometric measures were available in 746/751 (99%) pts. Of 746 pts analyzed, 54% were male, 57% white, and 30% black. Median BMI (kg/m^2) was 28 (range 17-53); BMI per category was underweight ($\leq$ 18.5) 0.9%, normal (18.5- $<$ 25) 25.7%, overweight (25- $<$ 30) 35.7%, obese (30-40) 32.3%, and morbidly obese ($>$ 40) 5.3%. Median BSA (m^2) was 1.94 (range 1.29-2.70). Median BMI and BSA were significantly higher in men ($p < 0.05$). Morbid obesity was more common in black versus white pts (8.4 vs 3.8%, p = 0.017) and women versus men (7.9 vs 3%, p = 0.03). Pts with BMI $\geq$ 40 had an estimated OS of 81 vs 98 months compared to pts with BMI $<$ 40 (p = 0.071); unadjusted hazard ratio (HR) 1.47 (95% CI: 0.56-3.49). Response of VGPR or better did not show a significant association with higher BSA ($>$ 2.25) (80.3 vs 70.3%, p = NS). On multivariate analysis, PFS and OS showed no association with BMI or BSA. ISS stage 3 disease (HR 2.1; 95% CI 1.4-3.4) and high risk cytogenetics (HR 2.2; 95% CI 1.5-3.7) were significantly associated with shorter OS ($p < 0.001$). **Conclusions:** Obesity does not significantly impact depth or duration of response with RVd induction. We advocate use of full dose RVd regardless of BSA or BMI in pts with acceptable performance status and managed comorbid conditions.

8047 Poster Session (Board #56), Mon, 8:00 AM-11:30 AM

Relationship of acquired resistance of myeloma cells to bortezomib with Lyn and Src induced inhibition of PP2A and effect of treatment with the tyrosine kinase inhibitor dasatinib. *First Author: Barry Paul, Duke University, Chapel Hill, NC*

Background: Multiple Myeloma (MM) is the second most common hematologic malignancy in the United States. Proteasome inhibitors—especially bortezomib (BTZ)—are a mainstay of treatment in MM, but nearly all patients eventually develop resistance to these agents. We hypothesize that resistant cells are escaping BTZ induced cell killing via dedifferentiation to a more primitive state resulting in inhibition of the tumor suppressive activity of PP2A. **Methods:** MM cell lines (RPMI-Dox, MM1R, and OPM1) were grown in media with increasing concentrations of BTZ over time to select for resistance, and then treated with dasatinib. MTT assays were conducted to confirm BTZ resistance. Sensitive and resistant cells were harvested for protein and RNA and evaluated through standard qRT-PCR, flow cytometry, and immunoblotting methods to determine levels of PP2A-C, Src, and Lyn, as well as the differentiation markers CD138 and IRF4. **Results:** MTT assays verified significant resistance in cells grown with BTZ (mean IC_{50} 225.80 $\pm$ 49.76 nM) compared to parental cells (mean IC_{50} 7.02 $\pm$3.97 nM). Immunoblotting confirmed differential phosphorylation of the Y307 inhibitory site of PP2A-C in the resistant cells. Levels of Src and Lyn RNA and protein were increased in the resistant cells, and treatment with the multikinase inhibitor dasatinib selectively increased cell death in the resistant cells (IC_{50} 1.31 $\pm$0.11 nM). Additionally, expression of the differentiation markers CD138 and IRF4 was absent in the BTZ resistant cells while being appropriately expressed in the parental cells. **Conclusions:** Our experiments show that inhibition of PP2A plays a significant role in acquired resistance to BTZ and that this process is primarily driven by increased expression of Src and Lyn. Inhibition of Src and Lyn activity with dasatinib was able to overcome this effect and selectively resensitize the resistant cells. Our data also imply that the resistant cells may be dedifferentiating to a more primitive state as evidenced by absent IFR4 and CD138 expression. These data suggest a role for kinase inhibitors in myeloma patients with acquired resistance to BTZ.

8049 Poster Session (Board #58), Mon, 8:00 AM-11:30 AM

Quality of life and cancer worry in a follow-up cohort of patients with asymptomatic monoclonal gammopathies. *First Author: Michelle Ann Theobald Hildebrandt, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM) are monoclonal gammopathies that precede multiple myeloma (MM). Although considered asymptomatic, patients diagnosed with these conditions are at greatly increased risk of developing MM. There is currently limited to no information on quality of life (QOL) or cancer worry/anxiety burden for patients with MGUS and SMM. **Methods:** We implemented a longitudinal QOL and cancer-related worry assessment in an observational cohort study of MGUS and SMM patients at MD Anderson Cancer Center (expected total enrollment of N = 200). Questionnaires included the QLQ-C30 cancer QOL tool and the MY20 myeloma-specific module, as well as questions to measure cancer worry. In this preliminary data analysis, a total of 46 patients completed the baseline questionnaires (MGUS = 17; SMM = 29). **Results:** Overall, individuals with MGUS have a worse QOL compared to SMM patients with MGUS patients reporting a $>$ 12 point lower Global QOL score (71.6 vs 83.9; P = 0.035). Significant differences were also observed for Physical Functioning (P = 0.012), Nausea/Vomiting (P = 0.045), and Pain (P = 0.027). For myeloma-specific QOL and symptoms, MGUS patients again reported higher levels of Back Pain (P = 0.017), Burning/Sore Eyes (P = 0.021), Restlessness/Agitation (P = 0.026), and Tingling in Hands/Feet (P = 0.031) compared to SMM patients. This increase in reported QOL burden corresponded to MGUS patients less feeling in control of their MM risk compared to SMM patients (P = 0.0038). **Conclusions:** Patients with MGUS self-reported a high QOL burden that was often greater than SMM patients and more closely in line with MM-specific or overall cancer reference values. Further, a sense of loss of control of their MM risk is heightened in MGUS patients. Together, even though MGUS is considered clinically asymptomatic, patients diagnosed with this condition are experiencing reduced QOL is impacting their overall well-being. These results suggest potential opportunities for interventional strategies to improve the lives of patients with monoclonal gammopathies. This work was supported in part by MD Anderson's Cancer Center Support Grant P30 CA016672.

8050 Poster Session (Board #59), Mon, 8:00 AM-11:30 AM

Comparative analysis of outcomes in African American (AA) and white (W) patients (pts) with multiple myeloma (MM) treated with lenalidomide (LEN) or pomalidomide (POM). *First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL*

Background: AA are ≈2-fold more likely to develop MM, and racial and ethnic minorities may not have similar access to novel MM treatment (Tx). Outcomes are often worse in AA vs W pts with cancer, but data are mixed in MM. Thus, we compared outcomes in AA and W pts treated with LEN or POM. **Methods:** We performed a subgroup analysis with data from 4 clinical trials. E4A03 (Rajkumar et al. *Lancet Oncol* 2010) used LEN + high- or low-dose dexamethasone (LEN-D or LEN-d) as a first-line MM Tx. CALGB 100104 (McCarthy et al. *NEJM* 2012) studied LEN or placebo (PBO) maintenance after transplant. MM-009 (Weber et al. *NEJM* 2007) and MM-002 (Richardson et al. *Blood* 2014) used LEN-D or PBO-D and POM or POM-d, respectively, for relapsed/refractory MM. We compared baseline characteristics and Tx outcomes in AA vs W pts from the LEN-d arm of E4A03, all arms of CALGB and MM-009, and the combined POM and POM-d arms of MM-002. **Results:** Detailed results are in the Table. Baseline characteristics were generally similar in each trial. PFS/OS was similar in AA and W pts treated with LEN or POM except in the MM-002 trial, where PFS was longer in AA pts. Neutropenia was the most common hematologic Tx-emergent adverse event across the studies. **Conclusions:** Tx with LEN or POM resulted in similar or better outcomes in AA vs W pts in multiple Tx settings, emphasizing the importance of equitable access to Tx.

	E4A03		CALGB 100104				MM-009				MM-002	
	AA	W	AA	W			AA	W			AA	W
Tx, n	LEN-d 24	LEN-d 194	LEN 40	PBO 44	LEN 175	PBO 171	LEN-D 25	PBO-D 17	LEN-D 141	PBO-D 148	POM ± d 33	POM ± d 178
Median age, yrs	66.3	65.3	55.0	56.5	59.0	58.0	63.0	59.0	64.0	62.0	60.0	64.0
Male, %	54	55	43	52	55	58	40	12	63	64	52	54
Median PFS, mos	18.7	21.6	72.0	37.0	56.9	28.8	9.2	3.7	13.1	4.6	5.6	2.8
HR[a] (95% CI)	0.98 (0.47-2.05)			1.07 (0.66-1.73)				1.30 (0.75-2.25)			0.56 (0.35-0.89)	
P	.96			.78				.36			.01	
Median OS, mos	40.4	39.2	NR	81.6	NR	72.9	44.0	41.3	36.5	29.4	17.4	14.2
HR[a] (95% CI)	1.72(0.68-4-.36)			1.33 (0.68-2.60)				1.15 (0.64-2.07)			0.69 (0.44-1.08)	
P	.25			.41				.63			.11	
ORR, %	63	67	88	89	90	84	72	6	57	20	30	26
Neutropenia, %	4	3	85	50	74	51	52	12	46	7	36	48
Anemia, %	4	2	28	11	21	14	48	18	33	19	15	35
Thrombocytopenia, %	0	1	58	36	72	55	28	18	25	8	15	25
Leukopenia, %	0	1	28	14	22	16	8	6	8	1	3	17

[a]HR: AA vs W in LEN/POM arms. NR, not reached.

8051 Poster Session (Board #60), Mon, 8:00 AM-11:30 AM

Association of venous thromboembolism with increased mortality in patients with multiple myeloma. *First Author: Martin W. Schoen, Saint Louis University School of Medicine, St. Louis, MO*

Background: Previous studies have demonstrated conflicting results regarding the effect of venous thromboembolism (VTE) on survival in patients with multiple myeloma (MM). In order to understand the impact of VTE on survival in MM, we studied outcomes in a nationwide population of United States Veterans with MM. **Methods:** Patients with newly diagnosed MM treated within the Veterans Health Administration (VHA) system between September 1, 1999 and 2013 were identified within the VHA Central Cancer Registry. Patients who did not receive treatment within 6 months of diagnosis were excluded. Age, sex, race, body mass index (BMI), comorbidities, treatment (including transplant status), hemoglobin (HGB), albumin, and renal function were included. VTE was identified using an algorithm consisting of a combination of ICD-9 codes and VTE treatment. Cox proportional hazards regression modeling was used to assess the association between VTE as a time-varying exposure and overall survival while controlling for known prognostic factors. **Results:** The analytic cohort consisted of 4797 patients, of which 641 developed VTE after MM diagnosis (15.4%). After controlling for age, race, BMI, medical comorbidities, baseline lab characteristics, year of diagnosis, and initial treatment with a novel agent (thalidomide, lenalidomide, or bortezomib), patients with MM and VTE had an increased risk of death at 2 years (Hazard Ratio [HR] 1.28, 95% CI 1.09-1.52) and 5 years (HR 1.17, 95% CI 1.04-1.31) but not at one year (HR 1.15, 95% CI 0.90-1.49). Landmark analyses of patients surviving at least 6 months showed VTE continued to be a risk factor for death at 2 years (HR 1.23, 95% CI 1.05-1.45) and 5 years (HR 1.17, 95% CI 1.04-1.32). **Conclusions:** After controlling for known MM prognostic factors, VTE was significantly associated with increased mortality in the 2-years following MM diagnosis. Whether the observed increase in mortality is a direct result of VTE could not be determined in this study. Further study of MM patients with a high-risk for VTE, including studies of thromboprophylaxis, could clarify the significance of this association.

8053 Poster Session (Board #62), Mon, 8:00 AM-11:30 AM

Daratumumab-based therapies in patients with AL amyloidosis. *First Author: Jithma P. Abeykoon, Department of Internal Medicine, Mayo Clinic, Rochester, MN*

Background: Treatment options for patients (pts) with relapsed/refractory (RR) AL amyloidosis are limited. Daratumumab (dara) has been approved as monotherapy (DMT) or combination therapy (DCT) for multiple myeloma (MM). Data for dara-based therapy (DBT) in AL are sparse. **Methods:** We studied pts with RR AL without coexisting MM seen at Mayo Clinic from 11/2015 to 02/2018 & treated with DBT. Hematologic response (HR) & organ response (OR) were defined per Consensus criteria. All time to event analyses were done from the time of DBT initiation. Pts with dFLC < 4 mg/dL at the time of start of DBT were considered non evaluable (NE) for HR other than disease progression. DCT included dara, pomalidomide & dexamethasone (dex) (35%), dara, lenalidomide & dex (26%), dara, bortezomib & dex (22%) & other DBT regimens (17%). **Results:** 45 pts (DMT, n = 22; DCT, n = 23) received DBT; median age at DBT initiation was 64 years (range: 46-82). Data for HR assessment were available in 44 pts & 31 were evaluable for HR. HR & end points are outlined in Table 1. Among 13 NE pts, response improved to CR in 5 (38%) while remaining 8 continued to be NE. Of these 13 pts, 77% reached dFLC < 1 mg/dL at last follow up (FU). Cardiac, renal & liver involvement was observed in 59%, 43% & 7% of pts. Cardiac, renal and liver OR was 46%, 32%, 0%, respectively. At last FU, 31 pts were on DBT. Three (7%) pts had disease progression. Hematologic toxicity (HT) from DBT included anemia ≤2 grade (Gr =) 69%, 3 Gr 3%; thrombocytopenia 1 Gr 38%; neutropenia ≤2 Gr21% & > 2 Gr 7%. Non-HTs included fatigue (23%), infusion reactions (21%), & treatment-emergent neuropathy (14%). **Conclusions:** DBT is safe & effective in heavily pretreated pts with AL. HR is achieved rapidly with DBT, particularly with DCT.

	Entire cohort, N = 45	DMT, N = 22[a]	DCT, N = 23[b]
Median prior lines of therapy, n (range)	3 (1-8)	3 (1-5)	3 (1-8)
ORR /CR/ VGPR/ PR, (%)	84 / 19 / 61 / 3	77/14/ 64/ 0	88/ 22 / 59 / 6
Time to 1st/ best response, m (CI)	2 (2-5) / 6 (5-8)	4 (2-6) / 6 (2-9)	2 (1-3) / 6 (2-12)
Median FU, m (CI)	10 (8.5-13)	8.5 (5.7-10.4)	13.1 (9.1-19.1)
PFS, m (CI)	NR (NR- NR)	NR (13-NR)	16 (NR-NR)
Duration of response, m (CI)	NR (13-NR)	NR (NR-NR)	NR (13-NR)
OS, m (CI)	NR (17-NR)	NR (13-NR)	NR (15.5-NR)

[a]14 evaluable for HR, [b]17 evaluable for HR, CI: 95% Confidence Interval, NR: Not Reached, m: months

8054 Poster Session (Board #63), Mon, 8:00 AM-11:30 AM

Characteristics and outcomes of primary plasma cell leukemia in the era of novel agents: Single center experience. *First Author: Iman Aboudalle, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Plasma cell leukemia (PCL) is a rare and aggressive disease characterized by a clonal proliferation of plasma cells in bone marrow and blood. PCL can present as *de novo* disease without underlying multiple myeloma. The purpose of this study is to describe the clinical characteristics and outcomes of primary (p) PCL in the era of novel agents. **Methods:** This is a retrospective study of patients (pts) with pPCL treated at The University of Texas MDACC from 01/1998-12/2017. The Kaplan Meier method was used to estimate progression free survival (PFS) and overall survival (OS). Univariate and multivariate Cox proportional hazards models were used to evaluate the associations between a continuous variable and important prognostic covariates, respectively, with time to event endpoints. **Results:** We identified 77 pts with pPCL as defined by International Myeloma Working Group (IMWG) criteria. 64 (83%) pts were treated with immunomodulatory drugs (IMiD) and/or proteasome inhibitors (PI) during induction. Overall response rate was 70% (45 pts) by IMWG response criteria in pts treated with novel agents. 30 pts received consolidation with autologous stem cell transplantation (ASCT). For all pts, median PFS was 11.1 months (mos) (95% CI: 8.6-14.8), with 8 pts presenting with leptomeningeal disease at the time of relapse. Median OS (mOS) from the time of diagnosis was 19.1 mos (95% CI: 15.3-26.1) with a median follow-up of 20 mos. The mOS for pts receiving ASCT was 33.6 mos (95% CI: 22.6-40.2). Pts who underwent ASCT had significantly prolonged mOS (HR=0.2, 95% CI: 0.11-0.45; p<0.0001) on multivariate analysis. The main cause of death was disease progression in 84% of pts. **Conclusions:** pPCL prognosis can be improved with the incorporation of novel agents and early consolidation with ASCT.

Baseline characteristics.

No. of pts	77
Median age in years (range)	58 (31-85)
Sex, M/F	46/31
Extramedullary disease, N (%)	15 (23)
R-ISS, N (%)	
I	2 (3)
II	28 (36)
III	27 (35)
Unknown	20 (26)
Del 17p, N (%)	
Yes	19 (25%)
No	27 (35%)
Unknown	31 (40%)
Induction treatment, N=72	N (%)
Chemotherapy	8 (11)
IMiD Doublet	4 (6)
IMiD-Chemotherapy	1 (1)
PI Doublet	5 (7)
PI-Chemotherapy	25 (35)
PI-IMiD Triplet	21 (29)
PI-IMiD-Chemotherapy	8 (11)

TPS8055 Poster Session (Board #64a), Mon, 8:00 AM-11:30 AM

Phase III (IMROZ) study design: Isatuximab plus bortezomib (V), lenalidomide (R), and dexamethasone (d) vs VRd in transplant-ineligible patients (pts) with newly diagnosed multiple myeloma (NDMM). *First Author: Robert Z. Orlowski, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Pts with transplant-ineligible NDMM require therapies which prolong survival and improve quality of life. The combination of VRd significantly improves progression-free (PFS) and overall survival compared with Rd in NDMM, and has an acceptable safety profile. Combining VRd with a monoclonal antibody (mAb) may further improve efficacy. Isatuximab (ISA) is an anti-CD38 mAb that demonstrates antitumor and immunomodulatory activities with strong potentiation when combined with V and R in MM xenograft models. Here we describe a Phase III, randomized, open-label, multicenter study (NCT03319667; IMROZ), evaluating clinical benefit of ISA plus VRd vs VRd in pts with transplant-ineligible NDMM. **Methods:** Approximately 440 adult pts with symptomatic MM (International Myeloma Working Group [IMWG] criteria) will be randomly assigned, according to Revised International Staging System criteria (I or II vs III vs unknown) and age ($<$ 70 vs $\geq$70 years), in a 3:2 ratio to ISA (10 mg/kg on Days 1, 8, 15, 22, 29 in Cycle 1; every 2 weeks [Q2W] thereafter), plus V (1.3 mg/m^2 on Days 1, 4, 8, 11, 22, 25, 29, 32), R (25 mg on Days 114, Days 2235), and d (20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, 33), or VRd alone for 4 6-week cycles (induction phase). After Cycle 4, pts will receive Rd with or without ISA in 4-week cycles (R on Days 121; d weekly; ISA Q2W) until disease progression, unacceptable adverse events (AEs), or pt decision to discontinue (continuous phase). ISA will be reduced to monthly dosing from Cycle 18. Pts who progress on Rd can cross-over to ISA plus Rd. Primary endpoint is PFS (IMWG criteria) assessed by a blinded independent review committee, and analyzed with a 1-sided stratified log-rank test. Key secondary endpoints include rate of very good partial response or better, minimal residual disease negativity rate, and complete response rate. Safety evaluations include AEs, laboratory parameters, vital signs, and physical examination. The IMROZ study is currently enrolling pts; recruitment is planned in approximately 100 countries worldwide, including Japan and China. Study funding: Sanofi. Clinical trial information: NCT03319667.

TPS8056 Poster Session (Board #64b), Mon, 8:00 AM-11:30 AM

A phase 3 randomized, controlled, open-label study of selinexor, bortezomib, and dexamethasone (SVd) versus bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma (RRMM). *First Author: Sosana Delimpasi, General Hospital of Athens, Athens, Greece*

Background: Selinexor is an oral, selective inhibitor of nuclear export that specifically blocks exportin 1, leading to the nuclear accumulation & reactivation of tumor suppressor proteins. Twice weekly (BIW) bortezomib in combination with dexamethasone (Vd) is an established therapy in relapsed and refractory multiple myeloma (RRMM). While the activity of bortezomib (bort) BIW in combination with other agents is efficacious, prolonged use is limited due to peripheral neuropathy (PN) (50-60%) as well as acquired resistance to bort. Preclinical studies have shown that selinexor, when combined with bort, can restore sensitivity of bort-resistant MM, inhibiting tumor growth and increasing survival in murine MM xenografts. In a Ph 1b/2 study, the combination of weekly selinexor with weekly bort and dex (SVd) was well tolerated and highly active with an ORR of 83% in patients (pts) with PI non-refractory MM, furthermore PN was limited to 14%. In addition, in pts with PI refractory MM, an ORR of 43% was observed, supporting selinexor can resensitize myeloma to PI based therapies. **Methods:** The BOSTON trial (NCT03110562) is a global Ph III study of selinexor in combination with weekly bort and dex (QW SVd) vs BIW bort in combination with dex (BIW Vd), in pts with RRMM who have received 1 to 3 prior anti-MM regimens. The QW regimen of SVd may provide for a higher ORR and improved duration of response as well as provide for a considerable reduction (~40%) in overall bort dose vs BIW Vd arm, which may be associated with better tolerability (e.g., PN) compared with second-line Vd-based regimens. After progressive disease is confirmed by an Independent Review Committee, pts in the Vd arm may crossover to SVd. Crossover to Sd is allowed as compassionate use for pts who are not able to tolerate continued treatment with bort. Progression Free Survival (PFS) and ORR are primary endpoints. Secondary endpoints include overall survival and duration of response. An ORR primary analysis is planned after the last pt randomized has had the opportunity to complete at least 2 MM evaluations. Clinical trial information: NCT03110562.

TPS8057 Poster Session (Board #65a), Mon, 8:00 AM-11:30 AM

Randomized, open-label, phase 2/3 study of daratumumab (DARA) with or without JNJ-63723283, an anti-PD-1 monoclonal antibody, in relapsed/refractory multiple myeloma (RRMM). *First Author: Jan Van Droogenbroeck, Department of Hematology, AZ St.-Jan Brugge-Oostende AV, Brugge, Belgium*

Background: DARA, a human CD38 monoclonal antibody, is approved for treatment of RRMM. DARA produces deep clinical responses in RRMM and induces T-cell expansion through reduction of immune suppressive cell populations (CD38$^+$ myeloid-derived suppressor cells and regulatory T and B cells). JNJ-63723283 (JNJ-283) is a fully human monoclonal antibody that binds to PD-1 and enhances the induction of T cell-mediated pro-inflammatory cytokines and reduces tumor volume in preclinical models. JNJ-283 in combination with DARA may improve clinical responses in RRMM by enhancing the anti-tumor and immunomodulatory effects of DARA through PD-1 blockade. This study will assess the efficacy, safety, and pharmacokinetics of DARA $\pm$ JNJ-283 in patients (pts) with RRMM. **Methods:** This is an ongoing, multiphase, multicenter study of DARA (16 mg/kg intravenous [IV] QW for Cycles 1-2, Q2W for Cycles 3-6, and Q4W thereafter; 28-d cycles) $\pm$ JNJ-283 (240 mg IV Day 2 and 15 of Cycle 1 and then Q2W thereafter). Eligible pts ($\geq$18 years of age) must have received $\geq$3 prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD), or have disease that is double refractory to both a PI and an IMiD. Pts must have demonstrated evidence of response to $\geq$1 prior treatment regimen. Pts previously treated with anti-CD38 therapy, including DARA, or anti-PD-1 and anti-PD-L1 antibodies are excluded. Approximately 6 pts will be enrolled in Part 1 (safety run-in cohort of DARA + JNJ-283). If $<$ 2 pts experience a dose-limiting toxicity, the study will proceed to Part 2 (Phase 2) in which 80 pts will be randomized 1:1 to the 2 treatment arms. The primary endpoint is overall response rate, and secondary endpoints include safety, $\geq$complete response and $\geq$very good partial response rates, duration of response, time to response, progression-free survival, overall survival, minimal residual disease, and pharmacokinetics/immunogenicity of DARA and JNJ-283. Enrollment of an additional 300 pts into Part 3 (Phase 3) will be considered if the primary efficacy endpoint is met and DARA plus JNJ-283 is deemed safe in Part 2. Clinical trial information: NCT03357952.

TPS8058 Poster Session (Board #65b), Mon, 8:00 AM-11:30 AM

Randomized, open-label, non-inferiority, phase 3 study of subcutaneous (SC) versus intravenous (IV) daratumumab (DARA) administration in patients with relapsed or refractory multiple myeloma (RRMM): COLUMBA. *First Author: Saad Zafar Usmani, Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute/Carolinas Healthcare System, Charlotte, NC*

Background: DARA, a human IgG1κ monoclonal antibody that targets CD38, induces deep and durable responses in patients with RRMM. In a phase 1b RRMM study, a SC co-formulation of DARA with recombinant human hyaluronidase (rHuPH20; DARA SC) was found to be well tolerated with low infusion-related reaction (IRR) rates. Moreover, response rates were similar to those observed historically with DARA IV. The phase 3 COLUMBA study will compare the efficacy, pharmacokinetics, and IRRs of DARA SC versus DARA IV in patients with RRMM. **Methods:** This is an ongoing phase 3, randomized, open-label, multicenter, non-inferiority study of DARA SC (1,800 mg DARA in combination with rHuPH20 [2,000 U/mL] administered by manual push [15 mL] over 3-5 minutes at alternating left/right abdominal sites) versus DARA IV (16 mg/kg IV infusion) weekly for Cycles 1-2 (28-day cycles), every 2 weeks for Cycles 3-6, and every 4 weeks thereafter until disease progression or unacceptable toxicity. Pre- and/or post-infusion medications include paracetamol, diphenhydramine, methylprednisolone, and an optional leukotriene inhibitor. Eligible patients ($\geq$18 years) with RRMM must have received $\geq$3 prior lines of therapy, including a proteasome inhibitor (PI; $\geq$2 cycles or 2 months of treatment) and an immunomodulatory drug (IMiD; $\geq$2 cycles or 2 months of treatment), or must be double refractory to both a PI and an IMiD. The co-primary endpoints are overall response rate and maximum C_{trough} concentration of DARA on Cycle 3 Day 1. Secondary endpoints include IRR rates, progression-free survival, $\geq$very good partial response and $\geq$complete response rates, time to next therapy, overall survival, time to response, and duration of response. Approximately 480 patients will be enrolled and randomly assigned (1:1) to the 2 treatment groups. Randomization will be stratified by body weight at baseline ($\leq$65 kg, 66 kg to 85 kg, $>$ 85 kg), number of prior lines of therapy ($\leq$4 prior lines versus $>$ 4 prior lines), and type of myeloma (IgG versus non-IgG). Clinical trial information: NCT03277105.

TPS8059 Poster Session (Board #66a), Mon, 8:00 AM-11:30 AM

Pomalidomide and dexamethasone (pom-dex) with or without daratumumab (DARA) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): A multicenter, randomized, phase 3 study (APOLLO). *First Author: Pieter Sonneveld, Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: DARA, a human IgGκ monoclonal antibody targeting CD38, is approved in the United States and Europe for use as a monotherapy and in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone in pts with RRMM. In a phase 1b study, DARA + pom-dex demonstrated efficacy and tolerability in pts with RRMM, leading to the approval of this regimen for pts with RRMM in the United States. This phase 3 study will evaluate the efficacy and safety of DARA + pom-dex versus pom-dex alone in RRMM. **Methods:** This is an ongoing multicenter, open-label, phase 3 study of DARA + pom-dex versus pom-dex alone. RRMM pts who have received prior antimyeloma therapy, including a proteasome inhibitor and a lenalidomide-containing regimen, have responded to prior therapy, and have progressed on or after their last regimen, are eligible. Pts who have received only 1 prior line of therapy must have progressed ≤60 days of completing the lenalidomide-containing regimen. All pts will receive pom 4 mg orally on Days 1-21 of a 28-day cycle + dex 40 mg QW (20 mg for pts ≥75 year of age). Following a protocol amendment, pts in the DARA group will receive subcutaneous DARA (1,800 mg co-formulated with recombinant human hyaluronidase [rHuPH20]) QW in Cycles 1-2, Q2W in Cycles 3-6, and Q4W thereafter. All pts will receive preinfusion medications (including diphenhydramine, paracetamol, dexamethasone, and an optional leukotriene inhibitor), and postinfusion medications (diphenhydramine, lung disease control medications, and a short-acting β2 adrenergic receptor agonist) will be recommended for pts with a higher risk of respiratory complications. Progression-free survival is the primary endpoint. Secondary endpoints include safety, overall survival, overall response rate, duration of response, and minimal-residual-disease-negative rate. Approximately 302 pts will be enrolled across 11 countries. Clinical trial information: NCT03180736.

TPS8060 Poster Session (Board #66b), Mon, 8:00 AM-11:30 AM

Phase III (IKEMA) study design: Isatuximab plus carfilzomib and dexamethasone (Kd) vs Kd in patients with relapsed/refractory multiple myeloma (RRMM). *First Author: Thomas G. Martin, University of California at San Francisco, San Francisco, CA*

Background: Multiple myeloma (MM) remains an incurable disease requiring multiple lines of therapy, in which carfilzomib-based treatments are a standard of care. Isatuximab (ISA), an anti-CD38-targeted monoclonal antibody with antitumor and immunomodulatory activities in preclinical models of MM, has shown clinical activity as monotherapy and in combination with current standard of care in patients (pts) with RRMM. **Methods:** This Phase III, prospective, randomized, open-label study (NCT03275285; IKEMA) will evaluate the clinical benefit of ISA in combination with Kd versus Kd alone in pts with RRMM, who have received 13 prior lines of therapy. Pts who have received prior carfilzomib therapy, have primary refractory disease, or have free light chain measurable disease only will be excluded. Approximately 300 pts will be randomized according to 2 stratification factors (prior lines of therapy: 1 vs > 1; revised international staging system at baseline: I or II vs III vs unknown) in a 3:2 ratio to receive either ISA (10 mg/kg weekly in Cycle 1 then once every 2 weeks thereafter) in combination with carfilzomib (56 mg/m^2 on Days [d] 1, 2, 8, 9, 15, and 16, 20 mg/m^2 on d 1 and 2 of Cycle 1) and dexamethasone (20 mg on d 1, 2, 8, 9, 15, 16, 22, and 23) or Kd in 28-d cycles until disease progression, pt choice, or unacceptable toxicity. The primary endpoint is progression-free survival (PFS) according to International Myeloma Working Group Criteria. Key secondary endpoints include overall response rate, rate of very good partial response or greater, minimal residual disease negativity rate, complete response rate, and overall survival. Other secondary endpoints include safety, duration of response, time to progression, PFS2, pharmacokinetics, and quality of life. Safety evaluations will include adverse events and laboratory parameters, vital signs, and physical examination. The IKEMA study is currently enrolling pts; recruitment is planned in 16 countries worldwide. Study funding: Sanofi. Clinical trial information: NCT03275285.

TPS8061 Poster Session (Board #67a), Mon, 8:00 AM-11:30 AM

A phase 1/2, multicenter, dose-escalation and expansion study of combination therapy with venetoclax, daratumumab, and dexamethasone (with and without bortezomib) in subjects with relapsed or refractory multiple myeloma. *First Author: Orlando Bueno, AbbVie Inc., North Chicago, IL*

Background: Despite the introduction of new compounds to manage relapsed/refractory (R/R) multiple myeloma (MM) over the last decade, none are curative. Trials investigating novel agents or combinations are critical to advancing therapy. Overexpression of BCL-2 may contribute to the pathogenesis of t(11;14)-positive MM. Venetoclax (Ven) is a selective, potent, orally bioavailable BCL-2 inhibitor with activity in R/R t(11;14)-positive MM. Daratumumab, bortezomib, and dexamethasone is an FDA-approved triplet for MM. The addition of Ven to this regimen (± bortezomib) may result in additive antitumor effects via complementary mechanisms. **Methods:** This phase 1/2, multicenter study of Ven, daratumumab, and dexamethasone, with or without bortezomib, in R/R MM (NCT03314181) will have 2 parts, each with a dose-escalation and dose-expansion phase. Part 1 will evaluate Ven, daratumumab, dexamethasone (VenDd) in t(11;14)-positive patients who have had ≥ 3 prior therapies including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to both. The dose escalation phase will evaluate safety and tolerability; the randomized, blinded, expansion phase will assess the objective response rate of VenDd versus placebo-Dd. Part 2 will examine VenDd and bortezomib (VenDVd) in patients who have received 1 to 3 prior therapies and are not PI-refractory. The dose escalation phase will evaluate safety and tolerability; the single-arm, open-label expansion phase will assess efficacy per the International Myeloma Working Group (IMWG) criteria. A Bayesian Optimal Interval (BOIN) design will be used to guide dose escalation/de-escalation decisions in Parts 1 and 2. Secondary objectives will include progression free survival, duration of response, time-to-progression, minimal residual disease negativity, and pharmacokinetics and immunogenicity profiles of the Ven/daratumumab combinations. Exploratory objectives include evaluation of pharmacodynamic and predictive biomarkers associated with outcomes. Clinical trial information: NCT03314181.

TPS8062 Poster Session (Board #68b), Mon, 8:00 AM-11:30 AM

Randomized, open-label, phase 3 study of subcutaneous daratumumab (DARA SC) versus active monitoring in patients (Pts) with high-risk smoldering multiple myeloma (SMM): AQUILA. *First Author: S.Vincent Rajkumar, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Current guidelines for SMM recommend active monitoring for progression to symptomatic MM before initiating treatment as standard of care. Earlier treatment may benefit pts with SMM at high risk of progression. DARA, a CD38-targeted monoclonal antibody, is approved as monotherapy and in combination with standard of care for relapsed/refractory MM (RRMM). In a phase 1b RRMM study, a SC co-formulation of DARA with recombinant human hyaluronidase (rHuPH20; DARA SC) showed low infusion reaction rates and similar response rates to those seen with intravenous (IV) DARA in RRMM. Given the encouraging single-agent activity of IV DARA observed in a phase 2 SMM study (12-month PFS rate: 95%), we hypothesized that DARA SC may delay progression of high-risk SMM to MM compared with active monitoring. **Methods:** AQUILA is an ongoing, phase 3, randomized, open-label, multicenter study of DARA SC (1,800 mg DARA + rHuPH20 [2,000 U/mL] administered by manual injection (15 mL) over approximately 5 minutes at alternating abdominal locations QW for Cycles 1 and 2, Q2W for Cycles 3-6, and Q4W thereafter for up to 39 cycles or 36 months; 28-d cycles) versus active monitoring (no study medication). Eligible pts (≥18 y) have had a confirmed diagnosis of SMM for ≤5 y, have factors indicating a high risk of progression (clonal bone marrow plasma cells [BMPCs] ≥10% + ≥1 of the following: serum M protein ≥30 g/L, IgA SMM, immunoparesis with reduction of 2 uninvolved Ig isotypes, serum involved: uninvolved free light chain ratio ≥8- < 100, or clonal BMPCs > 50%- < 60% with measurable disease), and have an ECOG performance status of ≤1. The primary endpoint is PFS as assessed by an independent review committee. Secondary endpoints include time to biochemical or diagnostic (SLiM-CRAB) progression, ORR, complete response rate, duration of and time to response, time to first-line treatment for MM, progression-free survival on first-line treatment for MM (PFS2), incidence of MM with adverse prognostic features, and OS. Disease will be evaluated per International Myeloma Working Group response criteria. Approximately 360 pts will be randomized (1:1) to the 2 arms. Clinical trial information: NCT03301220.

8500 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Phase II trial of concurrent chemoradiation with consolidation pembrolizumab in patients with unresectable stage III non-small cell lung cancer: Hoosier Cancer Research Network LUN 14-179. *First Author: Greg Andrew Durm, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Concurrent chemoradiation (CRT) has been the standard Rx for pts with unresectable stage III NSCLC. A recent phase III trial (PACIFIC) of consolidation durvalumab [PDL-1 inhibitor] demonstrated improved median PFS vs. placebo (16.8 vs. 5.6 mo, HR 0.52, $p < 0.001$). 12-mo (55.9% vs. 35.3%) and 18-mo (44.2% vs. 27%) PFS were also improved. Toxicity was manageable with a grade 3-4 pneumonitis rate of 3.4%, and 4 patients experienced grade 5 pneumonitis. We report the results of a phase 2 trial of consolidation pembrolizumab [PD-1 inhibitor] following concurrent CRT in patients with unresectable stage III NSCLC. **Methods:** After completion of CRT with carbo/pac, cis/etop, or cis/pemetrexed + 59-66.6 Gy XRT, those pts w/o PD after 4-8 weeks off CRT received pembro 200 mg IV q3wk for up to 1 yr. The primary endpoint was time to metastatic disease or death [TMDD]. Key secondary endpoints included PFS, OS, and toxicity. **Results:** 93 pts enrolled [92 eligible for efficacy analysis]. Median f/u was 16.4 mo and median age 66 (45-84). 64.1% male and 35.9% female. Stages were 59.8% IIIA and 40.2% IIIB. 55.4% non-SqCC and 43.5% SqCC with 1 mixed histology. 94.6% were current/former smokers. Chemo regimens included carbo/pac (71.7%), cis/etop (26.1%), cis/pemetrexed (2.2%). Median number of cycles of pembro was 13.5 [1-19]. 16% received < 4 cycles; 84% received ≥ 4 cycles; 37% completed 1 yr pembro. Median TMDD was not reached (95% CI 18.7-NR), but the estimates of 1-yr and 2-yr OS were 80.5% and 68.7% respectively. Median PFS was 15.4 months (95% CI 10.4-NR). 12, 18, and 24-month PFS were 59.9%, 49.5%, and 45.4% respectively. 16 (17.2%) pts developed G$\geq$2 pneumonitis, 5 (5.4%) had G3-4 pneumonitis. There was 1 pneumonitis-related death. In those developing pneumonitis, the median time was 8.4 wks [1.1-48.2]. No other G 3/4 toxicities exceeded 5% except dyspnea (5.4%). **Conclusions:** Consolidation pembrolizumab following CRT substantially improves TMDD and PFS compared with historical controls. Prelim OS data is promising and suggests a substantial gain in outcomes of patients with stage III NSCLC is possible with consolidation pembrolizumab. Clinical trial information: NCT02343952.

LBA8501 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Genome-wide sequencing for early stage lung cancer detection from plasma cell-free DNA (cfDNA): The Circulating Cancer Genome Atlas (CCGA) study. *First Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

8502 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

Pragmatic study of a lymph node (LN) collection kit for non-small cell lung cancer (NSCLC) resection. *First Author: Raymond U. Osarogiagbon, Baptist Cancer Center, Memphis, TN*

Background: Surgical resection is the best curative modality for NSCLC, but overall survival (OS) rates vary with quality of pathologic (p) LN staging. We studied the impact of a pre-labeled LN collection kit on pLN staging quality, operative (OP) complications and OS. **Methods:** Prospective, population-based multiple baseline, staggered implementation study involving all patients undergoing curative-intent NSCLC resection in all 11 eligible hospitals (with $\geq$5 resections/yr) in 4 contiguous Hospital Referral Regions in E. Arkansas, N. Mississippi, W. Tennessee. After 12 months of prospective baseline observation, institutions sequentially implemented the kit in 3 balanced cohorts 3 months apart. We examined OS with Kaplan-Meier method, logrank test. Crude (HR) and adjusted Hazard Ratios (aHR) with 95% CI from Cox Models are adjusted for surgeon clustering, controlled for: age, sex, histology, tumor grade, extent of resection, pT, pM, number of comorbidities. **Results:** Of 1,171 OPs by 32 surgeons from 2014-2017, LN kit used in 650 (56%) OPs by 20 surgeons. Kit cases were older v non-kit cases (mean 68 v 67 years, $p = .026$). Race ($p = .12$), sex ($p = .089$), insurance ($p = .52$), clinical stage distribution ($p = .18$) were similar between groups. Comparing kit v non-kit cases, median OP time was 124 v 144 min ($p < .0001$), transfusion 9 v 5% ($p = .02$), all other periOP complication rates were similar, incomplete (non-R0) resection rates 3 v 4% ($p = .39$). LN staging quality: pNX rate 0 v 7%; no mediastinal LN 2 v 18%; attainment of NCCN quality criteria (R0 + anatomic resection + $\geq$1 N1 + $\geq$3 mediastinal LN stations) 77 v 31% ($p < .0001$ for all); 60-day readmission 15 v 13% ($p = .35$); 60 day mortality 3% v 5% ($p = .02$). With 20 months median follow up, 3-year OS was 80% in kit v 73% in non-kit cases ($p = .005$). Kit cases had $>$ 30% reduction in both HR (.67 [.50 - .89], $p = .005$) and aHR (.57 [.42 - .77], $p < .001$). In sensitivity analyses excluding sub-lobar resections, 60-day mortality, and non-adopting surgeons (to evaluate the possible impact of higher performing surgeons using the kit), aHR ranged from .54 to .61 (all $p < .013$). **Conclusions:** A LN collection kit improves staging quality and OS without adding to morbidity of curative NSCLC resection.

8503 **Oral Abstract Session, Mon, 8:00 AM-11:00 AM**

DREAM: A phase II study of durvalumab with first line chemotherapy in mesothelioma—First results. *First Author: Anna K. Nowak, School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Crawley, Australia*

Background: DREAM is an open-label, single arm, multi-centre, phase II trial with a safety run in designed to determine the activity, safety and tolerability of durvalumab combined with cisplatin and pemetrexed as first line therapy in malignant pleural mesothelioma (MPM). ANZ Clinical trial registry number: ACTRN12616001170415. **Methods:** Chemotherapy-naïve patients with MPM of all histological subtypes, planned for first-line cisplatin and pemetrexed who had not received prior radiotherapy and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 were eligible. Patients received durvalumab (1125mg), cisplatin (75mg/m^2) and pemetrexed (500mg/m^2) 3-weekly for a maximum of 6 cycles, followed by durvalumab alone (1125 mg 3-weekly) until progression or to 12 months total therapy. Primary endpoint was progression-free survival at 6 months (PFS6). The design provides $>$90% power if the true PFS6 rate is 65%, with 5% type I error using an expected PFS6 from standard treatment of 45%. Matching tissue and bloods were collected for translational research. **Results:** Between Dec 2016 to Sep 2017 54 participants were recruited. The median age was 68 (42-82) with 82% male and 60% ECOG 0. They received a median of 6 cycles of chemotherapy (range 1-6) and 7 of durvalumab (given with and without chemotherapy) (range 1-18). The 6-patient safety run in confirmed the tolerability of chemoimmunotherapy. In the first 31 evaluable patients (pre-specified primary interim analysis), PFS6 based on modified RECIST (mRECIST) for MPM was 71%. The objective response rate (ORR) was 61% using mRECIST and 53% using iRECIST. Thirty-one patients (57%) experienced adverse events (AEs) that were grade $\geq$3. Nineteen patients (35%) had immune-related (ir) AEs including 2 grade 3 irAEs. **Conclusions:** In MPM, adding durvalumab to first line treatment with cisplatin and pemetrexed had higher rates of PFS6 and ORR than expected for chemotherapy alone, with acceptable tolerability. The final result of PFS6 for all 54 patients will be reported in late 2018. Clinical trial information: ACTRN12616001170415.

8504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Inherited predisposition to malignant mesothelioma (MM) due to mutations in DNA repair genes. *First Author: Raffit Hassan, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Bethesda, MD*

Background: Identifying the profile of DNA repair genes predisposing to MM will enable treatment options for patients (pts) and risk assessment for their families. **Methods:** In this prospective study of the natural history of MM (NCT01950572) we enrolled 239 consecutive pts independent of site of disease, family history of cancer, age at diagnosis, ethnicity, or asbestos exposure. Germline DNA was sequenced for all 239 pts, identifying mutations of all classes in 73 DNA repair genes. Tumor DNA from 12 pts with germline *BAP1* mutations was evaluated by whole exome sequencing. **Results:** Of the 239 pts, 29 (12%) carried a pathogenic germline mutation in a DNA repair gene: *BAP1* (N = 17 pts), *CHEK2* (N = 5), *PALB2* (N = 2), and *BRCA2*, *MLH1*, *POT1*, *TP53,* and *MRE11A* (N = 1 each). Pts with mutations were more likely to be female (P = 0.02) and to have been diagnosed with another cancer (P = 0.009). Pts with germline mutations were more likely to have a 1° relative with a diagnosis of MM (P < 0.0001), melanoma (P = 0.003), or breast cancer (P = 0.022). Pleural MM pts with germline mutations had better overall survival than pts without mutations (median 7.9 vs 2.1 years, P = 0.003). There was no difference in history of asbestos exposure between pts with or without mutations (P = 0.64). Tumors from all 12 pts with germline *BAP1* mutations carried a second somatic event likely to lead to complete loss of BAP1 function. Five tumors had somatic stop mutations, 2 somatic missense mutations, 4 somatic loss of part or all of the *BAP1* locus and 1 copy neutral loss of the wildtype *BAP1* allele (LOH). **Conclusions:** Among unselected MM pts, 7% carried a pathogenic mutation in *BAP1* and 5% carried a pathogenic mutation in another DNA repair gene, which have not been previously described in MM. Analysis of more pts is important to evaluate if increased MM risk is conferred by any of these genes. Mutation carriers and their 1° relatives were at increased risk of developing MM, melanoma, or breast cancer. Genetic testing for germline mutations in DNA repair genes should be considered for MM pts since it has implications for both pts and their relatives. Finally, we suggest that, pts with *BAP1*-null tumors due to both germline and somatic mutations could be sensitive to PARP inhibitors. Clinical trial information: NCT01950572.

8505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Impact on health-related quality of life of the addition of bevacizumab to cisplatin-pemetrexed in malignant pleural mesothelioma in the MAPS phase III trial. *First Author: Virginie Westeel, University of Franche-Comté, Besancon, France*

Background: The IFCT-GFPC-0701 MAPS phase III trial highlighted a significant improvement in overall survival with the addition of bevacizumab to the standard first-line chemotherapy regimen, cisplatin plus pemetrexed, in advanced malignant pleural mesothelioma. We present the results of health-related quality of life (HRQoL), a secondary endpoint of MAPS. **Methods:** HRQoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 and the Lung Cancer specific module QLQ-LC13 at randomization and then every 9 weeks until progression. HRQoL deterioration-free survival (QFS), used to analyze longitudinal HRQoL data, was defined as the interval between randomization and the occurrence of the first clinically important deterioration of at least 5 points or death. Univariate and multivariate cox regression models were done to analyze variables associated with the QFS, including treatment arm. **Results:** A total of 448 patients were included in the MAPS trial between 2008 and 2014. At baseline, 428 patients (95.5%) completed the HRQoL questionnaire. We showed that the addition of bevacizumab to cisplatin and pemetrexed significantly improved QFS for two HRQoL dimensions: pain (Hazard Ratio (HR) = 0.81, 95% CI 0.67–0.99; p = 0.041) and peripheral neuropathy (HR 0.73, 95% CI 0.6–0.89, p = 0.002). A performance status 0-1, a hemoglobin level > 14g/dl and epithelioid histology were also associated with a longer QFS. **Conclusions:** This study shows that adding bevacizumab to standard chemotherapy in patients with advanced malignant pleural mesothelioma not only enhanced progression-free survival and overall survival, but resulted in a significant improvement in HRQoL. Clinical trial information: NCT00651456.

8506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *First Author: Hyun Cheol Chung, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea, Republic of (South)*

Background: The antitumor activity of pembrolizumab, an IgG4 anti-PD-1 monoclonal antibody, was evaluated in patients (pts) with SCLC in KEYNOTE-158 (NCT02628067), a phase 2 basket study of 11 cancer types. **Methods:** Enrolled pts were aged ≥18 y with advanced SCLC; had measurable disease per RECIST v1.1; ECOG PS ≤1; incurable disease with prior failure of, progression on, or intolerance to standard therapy; and evaluable tumor samples for PD-L1 (PD-L1 IHC 22C3 pharmDx assay [Agilent Technologies]) and other biomarkers. Pembrolizumab 200 mg Q3W was administered for 2 y or until disease progression or intolerable toxicity. The primary endpoint was ORR. DOR, PFS, and OS were secondary endpoints and were estimated by the Kaplan-Meier method. Tumor imaging was performed every 9 wks for the first year, then every 12 wks. Response was assessed per RECIST v1.1 by independent central radiologic review. PD-L1–positive was defined as PD-L1 combined positive score ≥1. **Results:** Among 107 SCLC pts, median age was 63 y (range, 24–84) and 85 (79%) had 1–2 prior therapies. At the data cutoff date (Aug 23, 2017), 36 pts (34%) were continuing on-study; median follow-up was 10.1 mo (range, 0.5–17.5). Tumors were PD-L1–positive in 42 pts (39%) and PD-L1–negative in 50 (47%); 0 had microsatellite instability-high (MSI-H) tumors and 83 (78%) had microsatellite-stable (MSS) tumors. ORR was 18.7% (20/107; 95% CI, 11.8–27.4) overall, 35.7% (15/42; 95% CI, 21.6–52.0) in pts with PD-L1–positive tumors, and 6.0% (3/50; 95% CI, 1.3–16.5) in pts with PD-L1–negative tumors. Overall, median DOR had not been reached (range, 2.1+ to 13.2+ mo); 12 pts (77%) had DOR ≥9 mo. Median PFS was 2.0 mo (95% CI, 1.9–2.1) in all pts, 2.1 mo (95% CI, 2.0–9.9) in pts with PD-L1–positive tumors, and 1.9 mo (95% CI, 1.6–2.0) in pts with PD-L1–negative tumors. Median OS was 9.1 mo (95% CI, 5.7–14.6) overall, 14.6 mo (5.6–not estimable) in pts with PD-L1–positive tumors, and 7.7 mo (95% CI, 3.9–10.4) in pts with PD-L1–negative tumors. Treatment-related AEs occurred in 63 pts (59%) and led to 4 discontinuations and 1 death (pneumonia). **Conclusions:** Pembrolizumab has shown promising antitumor activity and durable responses in advanced SCLC, especially in pts with PD-L1–positive tumors. Clinical trial information: NCT02628067.

8507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Efficacy and safety of rovalpituzumab tesirine in patients With DLL3-expressing, ≥ 3rd line small cell lung cancer: Results from the phase 2 TRINITY study. *First Author: David Paul Carbone, Ohio State University, Columbus, OH*

Background: Small cell lung cancer (SCLC) accounts for ~15% of lung cancer with no approved therapies in ≥ 3rd line (3L) patients (pts). In 3L pts, historical data demonstrate a median overall survival (mOS) of 4.7 mo and a best overall response of 18%; no historical data exist for objective response rate (ORR). Rovalpituzumab tesirine (Rova-T™) is an antibody-drug conjugate targeting Delta-like 3 protein (DLL3), an atypical Notch ligand that is highly expressed in SCLC but not normal tissue. A Ph1 study showed that Rova-T has antitumor activity in pts with recurrent SCLC and high DLL3 expression, and a manageable safety profile. **Methods:** TRINITY was an open-label, single-arm, Ph2 study of Rova-T in adult pts with DLL3-expressing SCLC (NCT02674568). Eligibility: ≥ 2 prior systemic regimens including ≥ 1 platinum-based regimen; ECOG 0-1; stable CNS disease. Pts received 0.3 mg/kg Rova-T intravenously on Day 1 of a 6-week cycle for 2 cycles. DLL3-high (hi) pts had ≥ 75% tumor cells positive by immunohistochemistry; DLL3-positive (pos) pts had ≥ 25%. Primary endpoints: confirmed ORR, overall survival (OS). **Results:** Interim analysis (6 Oct 17) included 199 pts, of which 64% were 3L. Common drug-related adverse events (AEs) were fatigue (32%), photosensitivity (31%), pleural effusion (26%), peripheral edema (26%), thrombocytopenia (23%). Drug-related Grade 3/4 AEs were thrombocytopenia (15%), photosensitivity (7%), pleural effusion (7%), fatigue (5%). In DLL3-hi 3L pts, median progression-free survival (mPFS) = 4.1 mo, mOS = 6.7 mo. **Conclusions:** Rova-T demonstrated antitumor activity and a favorable benefit:risk profile in ≥ 3L SCLC pts, with clinically meaningful mOS and mPFS. Updated analysis will be shown at presentation. Clinical trial information: NCT02674568.

	DLL3-hi		DLL3-pos	
n (%)	3L N = 85	≥ 3L N = 140	3L N = 103	≥ 3L N = 165
Best Overall Response				
IA	27 (32)	39 (28)	31 (30)	45 (27)
IRC	24 (28)	32 (23)	27 (26)	36 (22)
ORR				
IA	20 (24)	30 (21)	23 (22)	35 (21)
IRC	15 (18)	20 (14)	17 (17)	23 (14)
Clinical Benefit Rate*				
IA	59 (69)	100 (71)	67 (65)	111 (67)
IRC	60 (71)	105 (75)	67 (65)	117 (71)

IA, investigator assessment; IRC, independent radiology committee
*complete response + partial response + stable disease

8508 Poster Discussion Session; Displayed in Poster Session (Board #114), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Final overall survival for CSLC 0501: Phase 3 study of adjuvant versus neoadjuvant chemotherapy with docetaxel combined carboplatin for resectable stageIB-IIIA non-small cell lung cancer. *First Author: Xue-ning Yang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Adjuvant or neoadjuvant chemotherapy increased 5% survival compared with surgery alone for completely resected stage II-IIIa NSCLC. No significant difference in overall survival among adjuvant vs neoadjuvant vs surgery was found in NATCH study. Clinical issue is how to select adjuvant or neoadjuvant therapy for resectable NSCLC. **Methods:** Patients with stage IB-IIIA NSCLC were eligible. Adjuvant or neoadjuvant chemo regimen was designed as 3 cycles DC (Docetaxel: 75mg/m2, Carboplatin:AUC = 5 on day 1 every 3wks). The primary end point was 3yrs disease Free Survival (DFS) rate; secondary end points were 3yrs and 5yrs Overall Survival (OS) and Safety. The trial was closed early due to stage IB was not eligible since 2008 and slow accrual. The preliminary results were reported at 2013 ASCO & 2016 ESMO. **Results:** 214 patients were screened from 13 sites from March 2006 to May 2011, 198 patients were randomized. 97 were assigned to neoadjuvant (N) arm and 101 to the adjuvant (A) arm. Stage Ib, II and IIIa were 32.5%, 40.6% and 26.9%, respectively. 100% cases received neoadjuvant chemo and 85.1% completed the planned adjuvant chemotherapy. ORR was 34% and 12.4% patients developed PD in N arm. The 3yrs DFS rate was 53.4% (A) vs 40.2% (N) with HR 0.52 (95% CI 0.30–0.91), p = 0.033. 5yrs DFS rate was 47.9% vs 29.9%, HR 0.42 (0.24–0.75), p = 0.005. Median DFS 4.8 vs 2.1 yrs with HR 0.69 (0.48–0.98), p = 0.036. 5yrs OS was 57.8% vs 42.1%, HR 0.48 (0.27–0.85), P = 0.0143. Median OS 7.1 vs 4.2 yrs, HR 0.73 (0.50–1.07), p = 0.104. For stage II and IIIa subgroup 3yrs DFS rate was 49.3% vs 33.3% with p = 0.031, HR 0.43 (0.21–0.87), p = 0.031. 5yrs OS was 49.7% vs 40.7%, HR 0.60 (0.30–1.19), p = 0.142. Median OS 5.2 vs 3.6 yrs, HR 0.83 (0.53–1.30) , p = 0.414. Recurrence model was similar between the two arms. 41.2% patients experienced grade 3-4 neutropenia. One chemotherapy related death in A arm.One patient died of perioperative pulmonary embolism in N arm. **Conclusions:** The 5-yrs DFS and OS of CSLC 0501 showed arm A was superior to arm N. Adjuvant chemotherapy or neoadjuvant with docetaxel plus carboplatin are feasible and safe in resectable clinical stage IB-IIIA NSCLC. Clinical trial information: NCT00321334.

8509 Poster Discussion Session; Displayed in Poster Session (Board #115), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Comparative efficacy and safety of pemetrexed or paclitaxel plus thoracic radiation therapy (TRT) in elderly patients with nonsquamous locally advanced NSCLC. *First Author: Ge Bai, Cancer Center, The First Affiliated Hospital of Xinjiang Medical University, Ürümqi, China*

Background: Concurrent chemoradiotherapy is the standard treatment of locally advanced NSCLC, which can significantly reduce the risk of death and prolong the survival of patients.As we focus on the tolerance and side effects of elderly patients with concurrent chemoradiotherapy.The purpose of this study is to compare the efficacy and safety of Pemetrexed versus Paclitaxel plus thoracic radiation therapy (TRT) in elderly patients with locally advanced nonsquamous NSCLC,to provide the basis for the choice of the best chemotherapy for elderly patients. **Methods:** Patients (66years-75years) with stage IIIA/B unresectable nonsquamous NSCLC in our single center , randomly received (1:1) pemetrexed 500 mg/m^2 d1 every 3 weeks plus concurrent TRT (arm PEM), or paclitaxel 45 mg/m^2 d1 every weeks plus concurrent TRT (arm PAC). TRT: 60~66 Gy/2 Gy/30~33f IMRT radiotherapy. **Results:** Eighty-two patients were eligible to enter the group and completed treatment (41 in arm PEM,41 in arm PAC).The objective remission rate (CR+PR) of PEM group was significantly higher than PAC group (72. 0% v 56. 0%;P = 0. 021);The 2 year overall survival rate of the PEM group was significantly higher than PAC group (49.6% v 30.7%;P = 0.037).The incidence of radioactive pneumonia PEM group was lower than PAC group (20.1% to 33.1%;P = 0.032);While, no statistically significant difference between bone marrow suppression and digestive tract reaction. **Conclusions:** Pemetrexed combined with TRT was superior to paclitaxel concurrent chemoradiotherapy for elderly nonsquamous LA-NSCLC.

8510 Poster Discussion Session; Displayed in Poster Session (Board #116), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety evaluation of nivolumab added concurrently to radiotherapy in a standard first line chemo-RT regimen in unresectable locally advanced NSCLC: The ETOP NICOLAS phase II trial. *First Author: Solange Peters, Oncology Department, Lausanne University Hospital, Lausanne, Switzerland*

Background: The feasibility of combined chemo-radiotherapy (chemo-RT) and concurrent PD-1 inhibition is of high scientific interest and has shown promising results in pre-clinical models. So far, concurrent immune-checkpoint inhibition and radical thoracic RT has never been assessed in a clinical trial. **Methods:** NICOLAS is a phase II trial evaluating the safety of the addition of nivolumab to first-line chemo-RT in stage III NSCLC. Efficacy will be evaluated if a safety conclusion has been achieved, based on a hierarchical design. Patients received 3 cycles of platinum-based chemotherapy (etoposide, vinorelbine or pemetrexed) and radical RT of 66 Gy. Nivolumab treatment (240 mg / Q4W) started concurrently to RT. The primary safety endpoint is defined as the rate of pneumonitis grade $\geq$3 at 6 months post RT. An interim analysis was scheduled when the first 21 patients reached 3 months follow-up after completion of RT, based on the assumption that 70% of the pneumonitis events occur within the first 3 months. An early positive safety conclusion is reached at interim analysis if there is no incidence of pneumonitis grade $\geq$3 in the initial 21 patients (exact group sequential design at one-sided significance level of 0.05 and power = 83%, testing a 6-month pneumonitis rate $\geq$33% versus $\leq$15%). **Results:** Up to December 14, 2017, 49 patients have been recruited with a median follow-up of 6.6 months [95% CI: 5.6, 7.8]. The median age is 63 years, with the majority of the patients being male (67.3%), former smokers (75.5%) and with tumor stage IIIb (65.3%). The most frequently observed adverse events (AEs) are fatigue and anemia. No unexpected AEs or increased safety risk were observed. For the first 21 patients, no pneumonitis grade $\geq$3 was observed by the end of the 3-month post RT follow-up period. The majority of these patients (18 patients) were on a concurrent chemo-RT schedule. **Conclusions:** This early interim safety analysis provides evidence that the addition of nivolumab to concurrent chemo-RT is safe and tolerable. In a next step, the 1-year progression-free survival will be evaluated according to the hierarchical design in an expanded patient cohort. Clinical trial information: NCT02434081.

8511 Poster Discussion Session; Displayed in Poster Session (Board #117), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Long-term survival comparison of stereotactic radiotherapy versus surgery for elderly patients with clinical stage T1-T2 non-small cell lung cancer. *First Author: Feng-Ming Spring Kong, Indiana University Department of Radiation Oncology, Indianapolis, IN*

Background: There are several matched-paired analysis reports of comparing the long-term outcome between Stereotactic Body Radiation Therapy (SBRT) and surgical resection. Most of them are small series. This study aimed to compare the long-term overall survival (OS) after SBRT and surgery from a single medical center with surgery performed with the same group of surgeons. **Methods:** We used our cancer registry of 2005-2015. Patients with clinical staged T1 and T2 N0 diseases treated with either primary surgery or SBRT . Only patients elder than 65 years. The log rank p-value was used for overall survival comparison between the groups. Cox regression was used for univariate test for age, gender, race, smoking history, alcohol use, primary site location, laterality, T stage, and histology grade. Variables with $p < 0.05$ from univariate analysis were then used for propensity score based matching to compare the effect of surgery or SBRT on overall survival. **Results:** A total 1244 patients with clinically staged T1-T2 N0 NSCLC, 774 patients were elder than 65 years and matched: 508 patients with surgery and 266 patients with SBRT. The median age was 73 years (range: 65-96 years), 50% were male, and 67% had T1 disease. Median follow-up was 60 months.Age ($p < 0.001$), gender (p = 0.007), primary lobar location, middle and lower lobe ($p < 0.001$), grade of 1, 2, 3, and 4 ($p < 0.001$) and treatment modality of surgery versus SBRT ($P < 0.001$) were all significantly associated with OS under univariate analysis. The median OS and survival rates at one-, three- and five years were 81 months (95%CI:66-92), 85%, 70% and 58% after surgery, and 37 months (95%CI:28-46), 83%, 50% and 29% after SBRT, respectively (log-rank $p < 0.001$). **Conclusions:** This matched analysis, representing the largest one in the literature, demonstrated that patients treated with surgery have significantly better long-term survival than that of SBRT in elderly patients. This result varies from some of previous reports showing similar survival between SBRT and surgery. Prospective randomized study is needed to determine whether SBRT can present as an alternative for operable patients.

8512 Poster Discussion Session; Displayed in Poster Session (Board #118), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group (JCOG0403)—Long term follow-up results. *First Author: Yasushi Nagata, Hiroshima Univ Hosp, Hiroshima, Japan*

Background: The purpose was to evaluate the safety and efficacy of stereotactic body radiation therapy (SBRT) in patients (pts) with both operable and inoperable T1N0M0 non-small cell lung cancer (NSCLC) (UICC 6th ed., 2002). The 3 and 5 year follow-up results were published in 2015. This is the updated report with a 10-year follow-up for the operable population. **Methods:** The eligibility criteria included NSCLC, clinical T1N0M0, operable pts assessed by thoracic surgeons. Operability was recategorized by the study coordinator after registration and before the primary analysis. The prescription was 48 Gy at the isocenter in 4 fractions over 4-8 days. The primary endpoint was the 3-year overall survival (OS) and the secondary endpoints included progression-free survival (PFS), local-progression free survival (LPFS), event-free survival (EFS) and toxicity. **Results:** Between July 2004 and May 2007, 65 operable pts were registered and 64 eligible pts were included in efficacy analysis. The pts characteristics were: male 45, female 20; median age 79 (range 50-91). All pts completed the protocol treatment. At the last follow-up in February 2017 (median follow-up is 5.2 years), 20 died with disease, 24 died with other disease, 1 with treatment-related death, 2 died with unknown reason and 17 alive. The median survival was 5.6 year (95% CI: 4.1 – 7.1 year).The 3, 5, 10-year survival were 76.5% (95% CI: 64.0% - 85.1%), 54.0% (95% CI: 41.0% - 65.4%) and 23.8% (95% CI: 13.7% - 35.5%). The 10-year PFS, LPFS, and EFS were 19.1% (95% CI: 9.8% - 30.7%), 20.9% (95% CI: 11.1% - 32.8%), 13.7% (95% CI: 6.0% - 24.6%). A total of 27 failures were observed including 9 with local failure, 11 with regional nodal failure and 11 with distant metastases. Grade 3 toxicity occurred in 6 pts: chest pain 1 (1.5%), dyspnea 4 (6.2%), hypoxia 1 (1.5%), and pneumonitis 2 (3.1%). No grade 4 or 5 toxicity occurred. **Conclusions:** Long term results confirmed the efficacy and safety of the previous result. SBRT has a potential to be an alternative to surgery and deserves a further evaluation. To further improve the tumor control, a randomized phase III study investigating higher dose is underway (JCOG1408). Clinical trial information: NCT00238875.

8513 Poster Discussion Session; Displayed in Poster Session (Board #119), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Effect of radiation dose escalation on outcomes in patients with N2 stage IIIA NSCLC undergoing induction therapy prior to surgical resection. *First Author: Greg Andrew Durm, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: For pts with resectable stage IIIA NSCLC, one accepted tx option is induction therapy with concurrent chemoradiation followed by surgical resection in selected pts. However, the appropriate dose of radiation (RT) has remained largely unanswered. Full dose RT has been reported to be safe and is often used in clinical practice. We conducted a National Cancer Database analysis to compare outcomes between dose escalation vs. conventional dose RT during induction therapy in patients with T1-T3, N2, M0 NSCLC tx with surgical resection. **Methods:** We queried the NCDB between 2006-2014 for pts with T1-T3, N2, M0 NSCLC undergoing curative surgery after induction therapy. We compared the short-term postoperative outcomes and long-term survival based on RT dose groups. Group 1: standard dose (45-50.4 Gy, 67%), Group 2: high dose ($>$ 50.4 Gy 33%). Statistical analysis was performed using SAS v9.4, and $p < 0.05$ was considered to be significant. **Results:** 2499 pts met inclusion criteria. High dose RT was significantly more common in academic centers, in later years, and left-sided tumors in the database, but not related to age, race, sex, Charlson Comorbidity Index (CCI) or type of surgery performed. Perioperative outcomes (length of stay, 30- and 90-day mortality) were not significantly affected by RT dose. Mediastinal sterilization ($<$ pN2 disease) increased significantly with dose escalation as did path CR rates, but median and 5-year survival did not (Table, with 95% CIs). In multivariate analysis, long-term OS was significantly higher in men, younger age, lower CCI and lobectomy, but not affected by RT dose (even if treated as a continuous variable). **Conclusions:** In pts with clinical stage IIIA NSCLC treated with induction concurrent chemoradiation, RT dose escalation resulted in increased mediastinal sterilization and pCR rates, but it did not change perioperative mortality or long-term OS.

2004-2014	N	5yr-OS (%)	Median OS (mo)	Mediastinal sterilization (%)	pCR (%)
45 to 50.4 Gy	1677	46.2 (43.4,49.1)	48.6 (42.6, 56.0)	51.1 (48.6,53.5)	13.3 (11.7,15.1)
Above 50.4 Gy	822	46.4 (41.7,50.9)	55.1 (42.8, 62.4)	61.0 (57.5,64.4)	18.5 (15.8,21.4)
p-value		.71		< 0.001	< 0.001

8514 Poster Discussion Session; Displayed in Poster Session (Board #120), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

SWOG S0905: A randomized phase II study of cediranib versus placebo in combination with cisplatin and pemetrexed in chemonaive patients with malignant pleural mesothelioma. *First Author: Anne S. Tsao, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Anti-angiogenic inhibitors combined with cisplatin-pemetrexed (CP) have shown efficacy in unresectable malignant pleural mesothelioma (MPM). Cediranib, a vascular endothelial growth factor receptor and platelet derived growth factor receptor inhibitor, showed preliminary efficacy in SWOG 0905 phase I. **Methods:** S0905 phase II randomized MPM patients to CP with cediranib/placebo followed by maintenance cediranib/placebo (CPC v CPP). Randomization was stratified by PS (0-1 vs 2) and histology [epithelioid (E) vs biphasic or sarcomatoid (B/S)].The primary endpoint was RECIST PFS. The trial was designed to detect a difference in PFS at the 1-sided 0.10 level, using a stratified log-rank test. **Results:** Ninety-two eligible patients were enrolled (2011-2016). Median age was 72, 85% men, 75% E and 25% B/S histology. The trial met its primary objective: PFS was significantly prolonged by CPC (HR 0.69, p = 0.096, median PFS 7.2 vs 5.6 months). CPC did not increase RECIST RR (26% vs 18%, p = 0.48), but did prolong the duration of response (median 6 vs 1.7 months). By modified RECIST, CPC increased RR (53% vs 20%, p = 0.01). CPC numerically improved OS (HR 0.84, p = 0.44; median OS 10 vs. 8.5 months). E patients had a markedly improved survival compared to B/S patients (median PFS 7.1 vs 3.4 months, HR 0.61, p = 0.047 and median OS 10.9 vs 6.4 months, HR 0.605, p = 0.045). B/S patients may derive less benefit from cediranib than E patients in terms of OS (HR 0.83 for E v HR 1.03 for B/S) despite a similar RECIST PFS (B/S HR 0.71 and E HR 0.72). Grade 3-4 toxicities were 64% versus 54% for CPC vs. CPP (p = 0.273). The most common toxicities (any grade) associated with CPC were diarrhea (46.7% vs. 17%) and hypertension (44% vs. 15%). **Conclusions:** The addition of cediranib to CP improves RECIST PFS in patients with MPM. E patients may benefit more with anti-angiogenic agents. Clinical trial information: NCT01064648.

Outcome	CPC (median in months)	CPP (median in months)	HR [95% CI], p-value
ITT PFS (RECIST)	7.2	5.6	0.69 [0.45-1.07], 0.096
ITT PFS (modified RECIST)	6.9	5.6	0.84 [0.55 – 1.23], 0.42
ITT OS	10	8.5	0.84 [0.54 – 1.32], 0.44
E PFS (RECIST)	7.4	6.1	0.72 [0.44-1.17], 0.18
B/S PFS (RECIST)	3.4	3	0.71 [0.29-1.7], 0.44

8515 Poster Discussion Session; Displayed in Poster Session (Board #121), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Phase 2, multicenter study of the EZH2 inhibitor tazemetostat as monotherapy in adults with relapsed or refractory (R/R) malignant mesothelioma (MM) with BAP1 inactivation. *First Author: Marjorie Glass Zauderer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: MM often presents at an advanced stage with a median survival of ~1 year. Treatments are limited; none clearly improve survival in second-line. In 40–60% of MM patients (pts) BRCA1 associated protein 1 (BAP1) is inactive and linked to a dependency on EZH2 (enhancer of zeste-homolog 2). EZH2 regulates gene expression to prevent differentiation of stem and progenitor cells, and aberrant EZH2 activity is implicated as an oncogenic driver. Tazemetostat, a potent, selective, oral EZH2 inhibitor demonstrated clinical activity in other malignancies; here we report preliminary data in inactive BAP1 MM. **Methods:** This is a phase 2, multicenter, open-label, single-arm study of tazemetostat (800 mg po BID) in pts with measurable R/R MM. PK and safety were assessed in a cohort of 13 pts. Efficacy was assessed via a 2-stage Green Dahlberg design in 61 pts with inactive BAP1 with a primary endpoint of 12-week disease control rate [DCR; CR or PR + SD]. Response was evaluated every 6 weeks with modified RECIST and/or RECIST 1.1. Secondary endpoints included ORR, PFS, OS, safety, population PK and response biomarkers (RNAseq, immunomodulation, exploratory prognostic indices). **Results:** Enrollment is complete (N = 74). Disease characteristics were typical of MM with the exception of a bias towards epithelioid histology (88%) that has a higher incidence of BAP1 inactivation. All pts had $\geq$1 prior systemic therapy. No pts discontinued due to AEs; however, 5 pts had dose reductions due to AEs. Fatigue (32%), decreased appetite (28%), dyspnea (28%), and nausea (27%) were the most frequently reported AEs of any grade regardless of attribution. In the efficacy portion of the study, the Stage 2 DCR criterion of $\geq$35% was surpassed, with 31 pts (51%) achieving disease control at 12 weeks and 15 pts (25%) sustained disease control at 24 weeks, 5 of whom are ongoing. Two of 61 patients had a confirmed partial response. **Conclusions:** Tazemetostat monotherapy shows promising antitumor activity, including confirmed responses and long-term disease control, with favorable safety/tolerability in pts with MM. These results support further evaluation of tazemetostat in pts with MM. Clinical trial information: NCT02860286.

8516 Poster Discussion Session; Displayed in Poster Session (Board #122), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

The TCGA malignant pleural mesothelioma (MPM) project: VISTA expression and delineation of a novel clinical-molecular subtype of MPM. *First Author: Marc Ladanyi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: To expand the understanding of MPM biology and pave the way for novel therapeutic strategies, The Cancer Genome Atlas (TCGA) Research Network conducted a comprehensive integrated genomic study of MPM. **Methods:** We performed whole exome, mRNA, miRNA, and non-coding RNA sequencing, copy number analysis, DNA methylation and reverse-phase protein array profiling on 74 rigorously reviewed and annotated MPM cases with no prior radio- or chemotherapy, followed by integrated data analyses. Findings were extended or validated using additional external datasets. **Results:** Three key findings emerged from the analyses of this comprehensive integrated genomic dataset. First, we defined a novel subtype of MPM characterized by extensive loss of heterozygosity, (genomic near-haploidization), and inactivating mutations in TP53 and SETDB1, which encodes a histone methyltransferase involved in epigenetic gene silencing. SETDB1 mutations appear specific to this novel subset of MPM, which accounts for approximately 3% of MPM patients, is more frequently found in younger and female patients and shows little or no linkage to asbestos exposure. Secondly, we detected strong expression of the immune checkpoint molecule VISTA [a.k.a. PD1-H (PD1 homolog) or B7-H5] in MPM, particularly in the more differentiated epithelioid subtype, where it is higher than in any other cancer type studied by TCGA. Immunohistochemistry confirmed that VISTA is present in epithelioid MPM tumor cells and in normal and reactive mesothelium, suggesting that its expression in epithelioid MPM may reflect retention of mesothelial cell antigen presenting properties. Thirdly, through the most comprehensive analysis of BAP1 status in MPM to date, we found the overall prevalence of BAP1 alterations to be 57%, and defined their downstream effects in terms of gene expression, transcriptional networks, and immune cell reactivity. **Conclusions:** Our findings highlight new avenues for further investigation of MPM biology and novel therapeutic options. In particular, our findings provide both a rationale and a biomarker for clinical trials of emerging anti-VISTA immunotherapies in this highly lethal cancer.

8517 Poster Discussion Session; Displayed in Poster Session (Board #123), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety and clinical activity of durvalumab in combination with tremelimumab in extensive disease small-cell lung cancer (ED-SCLC). *First Author: Daniel C. Cho, Perlmutter Cancer Center at NYU Langone Medical Center, New York, NY*

Background: Treatment options for ED-SCLC are limited, with standard first-line platinum and etoposide and second-line topotecan having limited clinical activity. Beyond these agents, no approved therapy prolongs survival. Dual checkpoint inhibition with the anti-PD-L1 durvalumab in combination with the anti-CTLA-4 tremelimumab has demonstrated a manageable safety profile and clinical activity in several solid tumor types. Here we present safety and clinical activity data for the combination in pretreated patients with ED-SCLC. **Methods:** In this phase 1 dose-exploration and expansion study, patients with ECOG PS 0–1 received durvalumab 20 mg/kg every 4 wks in combination with tremelimumab 1 mg/kg every 4 wks for 7 doses, then every 12 wks for 2 doses, followed by durvalumab 10 mg/kg every 2 wks for up to 12 mos, with retreatment permitted for progression after 12 mos of therapy. Antitumor activity was evaluated by investigator-assessed RECIST v1.1. **Results:** As of 20 Oct 2017, 30 patients (median age 63.5 y, 57% male, 70% ECOG PS 1) received treatment in the expansion phase. All patients had prior systemic therapy (median 2 prior therapies); 19 patients were platinum resistant/refractory. 20 patients (67%) reported $\geq$1 treatment-related AE (TRAE); the most common were fatigue (n = 7 [23%]) and pruritus (n = 7 [23%]). 7 patients (23%) had grade 3/4 TRAEs. No patients discontinued due to TRAEs and there were no treatment-related deaths. Confirmed ORR was 13.3% (2 CR, 2 PR; 95% CI 3.8–30.7), including 3 platinum resistant/refractory patients (1 CR with 2 prior therapies, 2 PR each with 1 prior treatment); median duration of response was 18.9 mos (95% CI 16.3–18.9). Disease control rate at 16 wks was 20.0% (95% CI 7.7–38.6). Median PFS was 1.8 mos (95% CI 1.0–1.9), median OS was 7.9 mos (95% CI 3.2–15.8), and 12-mo OS rate was 41.7% (95% CI 23.3–59.2). In addition, one patient with a brain metastasis was continuing in follow-up $>$ 2 years after starting treatment. **Conclusions:** Durvalumab in combination with tremelimumab had a tolerable safety profile and promising activity in pretreated ED-SCLC. Responses were durable and seen in both platinum-sensitive and platinum resistant/refractory patients. Clinical trial information: NCT02261220.

8518 Poster Discussion Session; Displayed in Poster Session (Board #124), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Safety and antitumor activity of durvalumab monotherapy in patients with pretreated extensive disease small-cell lung cancer (ED-SCLC). *First Author: Jonathan Wade Goldman, UCLA Medical Center, Los Angeles, CA*

Background: SCLC is an aggressive lung cancer with high rate of relapse following initial treatment; immunotherapy holds potential as a novel treatment option for this disease. The anti-PD-L1 antibody durvalumab has demonstrated clinical activity with manageable toxicity in several tumor types, including NSCLC. Here we report on the SCLC expansion cohort of a phase 1/2 study of durvalumab monotherapy. **Methods:** Patients with pretreated ED-SCLC, ECOG PS 0-1, regardless of PD-L1 expression, received durvalumab 10 mg/kg every 2 weeks for up to 12 months. The primary objective was to determine the safety profile; antitumor activity was evaluated using investigator-assessed RECIST v1.1. **Results:** As of 16 October 2017, 21 patients with ED-SCLC (median age 65.0 y, 62% male, 91% ECOG PS 1, 90% current/former smokers) were treated with durvalumab, median 3 cycles, median duration of follow-up 36.4 months (range 1.4–37.9). 20 patients (95.2%) received prior anti-cancer therapy (median, 2 lines). 7 patients (33.3%) had treatment-related AEs, all were grade 1 or 2; the most common were nausea, fatigue, and rash maculo-papular (each 9.5%). There were no treatment-related AEs leading to discontinuation and no treatment-related deaths. Confirmed ORR was 9.5% (2 PR; 95% CI 1.2–30.4) and DCR24 was 14.3% (95% CI 3.0–36.3). Duration of response was 14.6 months for one patient (treatment-naïve), and 29.5+ months for the other patient (platinum refractory with 3 prior lines of therapy), who continued to maintain response 25.5 months after completing protocol-defined initial treatment with durvalumab. Median PFS was 1.5 months (95% CI 0.9–1.8), median OS was 4.8 months (95% CI 1.3–10.4), and 12-month OS rate was 27.6% (95% CI 10.2–48.4). **Conclusions:** Consistent with studies in other tumor types and with other anti-PD-1/PD-L1 therapies, durvalumab monotherapy demonstrates durable clinical activity in certain patients with pretreated ED-SCLC with no new safety signals. Clinical trial information: NCT01693562.

8519 Poster Discussion Session; Displayed in Poster Session (Board #125), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 4:45 PM-6:00 PM

Efficacy of milciclib (PHA-848125AC), a pan-cyclin d-dependent kinase inhibitor, in two phase II studies with thymic carcinoma (TC) and B3 thymoma (B3T) patients. *First Author: Benjamin Besse, Gustave Roussy, Villejuif, France*

Background: Thymic carcinoma (TC) and B3 thymoma (B3T) are rare malignant tumors of the thymus. While TC, a highly aggressive and easily metastasizing cancer, has a very poor prognosis, B3T is a slow-growing cancer. Milciclib, a pan inhibitor of cyclin D-dependent kinases, Src and other kinases, exhibits antitumor activity against a number of solid tumors. Objectives of these studies were to evaluate efficacy and safety of oral treatment with milciclib in TC/B3T patients (pts). **Methods:** Two separate phase 2 multi-centered clinical trials (CDKO-125A-006: 72 pts, previously treated with one chemotherapy and CDKO-125A-007: 30 pts, previously treated with multiple chemotherapies) were conducted in the USA, France, and Italy. The proportion of patients with B3T and TC were 27.8% and 72.2% (CDKO-125a-006) and 56.7% and 43.3% (CDKO-125a-007), respectively. Milciclib was orally administered (150 mg daily; 1 cycle is 7d on/7d off) for multiple cycles. Progression-Free Survival rate at 3 months (PFS-3) was the primary endpoint. **Results:** Oral treatment with milciclib met PFS-3 as primary endpoint and OS as a secondary endpoint in both phase 2 trials. Five pts in CDKO-125A-006 and 2 in CDKO-125A-007 continued with treatment over 2 years and 2 of them over 5 years. 46.1% of pts in both studies experienced at least one AE. Common Grade 3-4 hematological and other toxicities were neutropenia (8.4%), creatinine, amylase, lipase increase (5.6%), nausea and asthenia (8.3%). The AEs leading to discontinuation were 12.7% for both studies. Clinical trial information: NCT01011439 and NCT01301391. **Conclusions:** Oral treatment with milciclib was safe and well-tolerated and met primary and secondary endpoints, achieving disease stabilization in a majority of TC/B3T patients.

	CDKO-125a-006		CDKO-125a-007	
	Primary endpoint: PFS-3 > 17% evaluable pts		Primary endpoint: PFS-3 > 40% evaluable pts	
Treatment Efficacy	Evaluable (n = 54)	Treated (N = 72)	Evaluable (N = 24)	Treated (N = 30)
PFS-3 (%)	44.4	41.7	54.2	46.7
Median PFS (mos)	6.83	5.78	9.76	5.65
Median OS (mos)	24.18	24.44	Not reached	21.03
Stable Disease (SD) ((%)	72.2	68.1	79.2	66.7
DCR (CR+PR+SD) (%)	75.9	72.2	83.3	70.0
ORR (%)	3.7	4.2	4.2	3.3

8520 Poster Session (Board #126), Sun, 8:00 AM-11:30 AM

The comparison of tumor mutational burden (TMB) in patients of early and late stage lung adenocarcinoma in China. *First Author: Kai Zhang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China*

Background: Although PD-L1 positivity improves immunotherapy efficacy, PD-L1 testing alone is insufficient for patient selection in most malignancies. High tumor mutational burden (TMB) is an emerging positive biomarker of immunotherapy in a growing number of malignancies. In this study, a method for TMB by cancer-gene panel (CGP) was set up, by which TMB from Chinese lung adenocarcinoma samples was measured to analyze the association between TMB and genes alterations in the implications for immunotherapy. **Methods:** The accuracy of TMB detection by our CGP was confirmed from data of TCGA and whole exome sequencing (WES) in our clinical samples. TMB detection method by CGP was further validated from sequencing accuracy, coefficient of variation, and the limit of detection of tumor purity. The level of TMB in Chinese lung adenocarcinoma samples and its correlation with genes alterations were then analyzed. **Results:** In our study, TMB measured by CGP has a high correlation with that measured by WES in 31 clinical tumor samples (R^2= 0.9111). Immunotherapy from the Rizvi cohort confirmed the accuracy of TMB detection by CGP. The mean level of TMB measured by CGP from 599 Chinese lung adenocarcinoma samples was similar with that from 389 TCGA lung adenocarcinoma samples (7.29 vs 7.6 mutations/Mb). We found that high level of TMB was significantly correlated with several genes alterations including TP53, KRAS and genes in DNA damage response pathway as BRCA1/2, ATR, CHEK2, POLE and MMR genes. However, low level of TMB was correlated with EGFR and ALK alteration obviously. Of note, we first discovered that the level of TMB was lower in the early stage lung adenocarcinoma compared with that in the late stage lung adenocarcinoma from Chinese clinical samples. **Conclusions:** TMB calculated by CGP and WES was highly correlated via analyzing data both from TCGA and our tumor samples. We found that the level of TMB was effected by several genes alterations in the analysis of our samples. We also found that the low level of TMB might imply a poor effect of mono-immunotherapy in the treatment of early stage lung adenocarcinoma. Of note, combining immunotherapy with DNA damaging agents could be a good way to improve efficacy.

8521 Poster Session (Board #127), Sun, 8:00 AM-11:30 AM

Neoadjuvant chemo/immunotherapy for the treatment of stages IIIA resectable non-small cell lung cancer (NSCLC): A phase II multicenter exploratory study—NADIM study-SLCG. *First Author: Mariano Provencio-Pulla, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain*

Background: The combination of chemotherapy and immunotherapy (CT-IO) has a high response rate and longer survival in unselected patients (pts) with metastatic non-small cell lung cancer (NSCLC). There are no data about this combination in the neoadjuvant setting. **Methods:** A Phase II, single-arm, open-label multicenter study of resectable stage IIIA N2-NSCLC adult patients with CT plus IO (nivolumab (NV)) followed by adjuvant treatment for 1 year. Neoadjuvant treatment: Three cycles of NV 360mg IV Q3W + paclitaxel 200mg/m^2 + carboplatin AUC 6 IV Q3W. After completing neoadjuvant therapy, tumor assessment is performed in patients prior to surgery. Surgery is performed in the 3rd or 4th week after day 21 of the third cycle of neoadjuvant treatment. Adjuvant treatment: nivolumab 240mg IV Q2W for 4 months and nivolumab 480mg IV Q4W for 8 months (total one year) after surgical resection. The study aims to recruit 46 pts. The primary endpoint is Progression-Free Survival (PFS) at 24 months. Efficacy is explored using objective pathologic response criteria. We present preliminary data on patients that completed 3 cycles and underwent surgical assessment. **Results:** At the time of submission, 30 pts had been included and 13 underwent surgery. CT-IO was well-tolerated and surgery was not delayed in any patient. None of the pts withdrew from the study preoperatively due to progression or toxicity. Thirteen surgeries had been performed and all tumors were deemed resectable. 9 cases (69.2%) achieved complete pathologic response (CPR) (CI 95% 38.6-90.9%), and 2 had a major pathologic response (MPR),defined as $<$ 10% viable tumor cells in the resection specimen. Considering both CPR and MPR, the overall response rate was 84.6% (95% CI 54.6-98.1%). **Conclusions:** This is the first multicentric study testing CT-IO in the neoadjuvant setting with promising antitumor activity. Neoadjuvant CT-IO with nivolumab in resectable IIIA NSCLC yields a complete pathologic response rate that has never been seen previously. The data will be updated at the time of the congress. EudraCT Number: 2016-003732-20 Clinical trial information: NCT03081689.

8522 Poster Session (Board #128), Sun, 8:00 AM-11:30 AM

Post-operative radiation therapy (PORT) in resected non-small cell lung cancer (NSCLC): An updated population based analysis. *First Author: Stephen Shamp, University Hospitals, Cleveland, OH*

Background: Post-operative radiation therapy (PORT) in resected NSCLC remains controversial. A previous Surveillance, Epidemiology, and End Results (SEER) analysis showed improved overall survival (OS) in subset with N2 disease, and detriment in N0-N1 (JCO, 2006). Reanalysis of the ANITA trial demonstrated overall detriment of PORT on OS, but improved OS in subset with N2 disease or N1 disease who did not receive chemotherapy (CT). Since SEER recently introduced chemotherapy information, we aim to analyze outcomes of PORT in conjunction with CT in these patient populations **Methods:** Patients with AJCC 6th stage II-III NSCLC diagnosed between 2004-2014 who underwent lobectomy or pneumonectomy were identified using the SEER 18 database. Patients who survived less than 4 months were excluded to account for perioperative mortality. Neoadjuvant RT was excluded. 15,644 patients met the criteria and were included, with a median followup of 31 months (range 5-120). Survival outcome was calculated using Kaplan-Meier analysis, with log-rank comparison. Multivariable analysis (MVA) was calculated using cox proportional hazard ratio **Results:** On Kaplan-Meier survival analysis, PORT was associated with inferior OS ($p < 0.0001$, 5-yr OS 40% vs 50%) whereas CT was associated with improved OS ($p < 0.0001$, 5-yr OS 46% vs 41%). Subset analysis demonstrated that PORT was associated with worse OS for patient with N0 and N1 disease both with and without CT, as well as N2 disease without CT ($p < 0.001$ for all). OS was similar with or without PORT for patients with N2 disease who received CT ($p = 0.41$). On MVA, receipt of PORT was associated with younger age, not receiving CT, advanced T and N stage, male sex, and receiving lobectomy. On MVA, improved OS was associated with younger age, receipt of CT, less advanced T and N stage, female sex, not receiving PORT, Asian race, and receiving lobectomy **Conclusions:** In a population based cohort, PORT use is associated with reduced OS, and CT is associated with improved OS. Subset analysis shows OS was similar with or without PORT for patients with N2 disease who received CT, but was associated with reduced OS in N2 without CT, as well as N0 and N1. Pneumonectomy was associated with reduced OS

8523 Poster Session (Board #129), Sun, 8:00 AM-11:30 AM

The population-based impact of adjuvant chemotherapy (CTx) on outcomes in AJCC6 stage IB non-small cell lung cancer (NSCLC). *First Author: Rahul Krishan Arora, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada*

Background: Adjuvant CTx is the standard of care in stage II and IIIA NSCLC, but its value in AJCC6 stage IB NSCLC (T2N0M0) is unclear. Guidelines suggest consideration of adjuvant CTx for stage IB patients at high recurrence risk, but CTx use is variable. Prior population-based studies lacked NSCLC-specific survival (CSS) and key covariates such as health insurance status. Using a Canadian cohort with universal health care coverage and CSS data, we aimed to identify predictors of use and assess the real-world benefit of adjuvant CTx in stage IB NSCLC. **Methods:** We examined all patients who underwent surgery for T2N0M0 NSCLC in a large Canadian province between 2004 and 2015 and categorized cases based on receipt of adjuvant CTx within 6 months of curative resection. We identified predictors of CTx receipt with logistic regression. We also identified correlates of overall survival (OS) and CSS using Kaplan-Meier methods and Cox regression. **Results:** 967 patients met eligibility criteria. Median age was 68 (IQR 61-74) years at diagnosis, 455 (47%) were men, and 164 (17%) received adjuvant CTx. Sex, topology, and laterality were similar in patients treated with or without CTx. Lower age at diagnosis, lower Charlson Comorbidity Index, large cell histology, and tumor size $\geq$ 4 cm were associated with higher likelihood of CTx receipt (all $p <$ 0.05). In the entire cohort and in the subset with $\geq$ 4 cm tumors, CTx improved OS but not DSS on univariate analysis. In both groups, CTx did not correlate with OS or DSS on multivariate analysis (Table). **Conclusions:** Adjuvant CTx does not improve survival in this real-world cohort of T2N0M0 NSCLC patients, even for patients with $\geq$ 4cm tumors, suggesting that it has a limited role in real-world practice.

Univariate and multivariate survival analysis for stage IB NSCLC patients based on receipt of CTx.

	All patients			≥ 4 cm tumors		
	CTx	No CTx	*P*	CTx	No CTx	*p*
mOS (months) [95% CI]	104 [67-114]	78 [69-86]	0.058	111 [85-137]	71 [55-87]	0.030
mCSS (months) [95% CI]	135 [NR]	NR	0.491	135 [NR]	NR	0.827
Adjusted HR for OS [95% CI]	0.93 [0.69-1.24]		0.598	0.73 [0.45-1.16]		0.177
Adjusted HR for CSS [95% CI]	1.20 [0.84-1.70]		0.316	0.92 [0.53-1.58]		0.754

m = median; HR = hazard ratio; NR = not reached.

8524 Poster Session (Board #130), Sun, 8:00 AM-11:30 AM

Evaluation of different treatment strategies between right-sided and left-sided pneumonectomy for stage I-IIIA non-small cell lung cancer patients. *First Author: Ziping Wang, Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: This study aimed to investigate the survival difference between right-sided and left-sided pneumonectomy in stage I-IIIA NSCLC patients, and to further develop the best treatment strategies. **Methods:** Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute across 18 cancer registry sites in the United States were used for the present study. To avoid the bias between groups, we used an innovative propensity score matching analysis. **Results:** Stage I-IIIA NSCLC patients with pneumonectomy from 2004 to 2014 were included in this study. Of all 2,683 patients who received pneumonectomy, Overall survival (OS) (HR = 0.875, 95%CI: 0.793 to 0.967, P = 0.008) and cancer-specific survival (HR = 0.863, 95%CI: 0.771 to 0.965, P = 0.010) were significantly longer with left-sided pneumonectomy over right-sided pneumonectomy. After propensity score matching analysis for 2,050 patients, OS (HR = 0.858, 95%CI: 0.768 to 0.959, P = 0.007) and cancer-specific survival (HR = 0.847, 95%CI: 0.745 to 0.963, P = 0.011) were also significantly superior of left-sided compared with opposite-sided pneumonectomy. After matching procedure, among left-sided pneumonectomy patients, adjuvant therapy significantly prolonged OS (46 versus 30 months, HR = 1.458, 95%CI: 1.239 to 1.715, P < 0.001) and cancer-specific survival (67 versus 51 months, HR = 1.314, 95%CI: 1.093 to 1.579, P = 0.004) while among right-sided pneumonectomy patients, adjuvant therapy was not associated with cancer-specific survival benefit (46 versus 42 months, HR = 1.112, 95%CI: 0.933 to 1.325, P = 0.236). Subgroup analysis showed that adjuvant chemotherapy could significantly improve OS and cancer-specific survival for both sided pneumonectomy patients. But patients with right-sided pneumonectomy who received radiotherapy were associated with worse survival. **Conclusions:** Right-sided pneumonectomy was associated with worse survival compared with left-sided pneumonectomy. Adjuvant chemotherapy contribute significant benefit to patients who received both sided pneumonectomy, but radiotherapy worsened prognosis for right-sided pneumonectomy.

8525 Poster Session (Board #131), Sun, 8:00 AM-11:30 AM

Population-based study predicting the probability of death resulting from non-small cell lung cancer (NSCLC) and other causes among NSCLC patients with surgery. *First Author: Bo Jia, Department of Thoracic Medical Oncology, Peking University Cancer Hospital & Institute, Beijing, China*

Background: This study aimed to predict the probability of death for non-small cell lung cancer (NSCLC) patients who received surgery and construct a comprehensive nomogram prognostic model to predict cumulative incidence of death resulting from NSCLC, other cancers, and non–cancer-related causes. **Methods:** Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute across 18 cancer registry sites in the United States were used for the present study. We estimated probabilities of death resulting from NSCLC, other cancers, and non-cancer causes for NSCLC patients who received surgery and analyzed relationships of patients' characteristics with probability of death. A nomogram prognostic model was used to predict the probability of death. **Results:** The entire cohort comprised 44,880 NSCLC patients who received surgery from 2004 to 2014. Male, race, tumor anatomic sites, histologic subtype, tumor differentiation, tumor size, tumor extent, lymph node involvement, examined lymph node, positive lymph node, type of surgery showed significant associations with probability of death ($P < 0.001$). Chemotherapy was associated with a significantly lower cumulative incidence of death ($P < 0.001$) while radiotherapy was associated with a significantly higher incidence of death ($P < 0.001$). The nomogram was constructed based on multivariate models with training data set. The probability of 5- or 10-year death can be calculated using this nomogram. In the validation cohort, the unadjusted C-index was 0.73 (95% CI, 0.72-0.74), 0.71 (95% CI, 0.66-0.75) and 0.69 (95% CI, 0.68-0.70) for lung cancer death, other cancer death and non-cancer death causes. **Conclusions:** A prognostic nomogram model was developed for predicting the probability of death for NSCLC patients who received surgery. This nomogram may be useful for clinicians to develop the best treatment strategies for NSCLC patients after surgery.

8526 Poster Session (Board #132), Sun, 8:00 AM-11:30 AM

Effects of comprehensive genomic testing in a large non-small cell cancer NSCLC cohort: Racial and survival impacts. *First Author: Fatemeh Ardeshir-Larijani, University Hospital Siedman Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: The clinical outcome of Non-Small Cell Cancer (NSCLC) has been advanced with molecular targeted therapy. To our knowledge, there is no data addressing targeted therapy outcomes based on race. Here, we focus on racial differences in response to targeted therapy in NSCLC. **Methods:** From a total of 1396 NSCLC patient between 2013 and 2017, 330 of them underwent targeted-exome sequencing. We conducted a matched study by propensity score generated using logistic regression with, sex, race, age, smoking, surgical resection, Immunotherapy and tumor stage as covariates. We used 258 genomic sequenced matched to 774 non-sequenced patients (1:3 match) to evaluate the outcomes (OS, PFS) of seven targeted gene therapies (*EGFR*, *ALK/EML*, *MET, BRAF, ROS1, ERBB2, RET*) using Kaplan-Meier method. **Results:** Of the 258 matched patients with genomic sequencing, 123 had at least one of the seven targeted gene mutations and 80 patients received targeted therapy (66% Caucasians, 24% African American (AA) , 10% others). The percentage of patients receiving targeted therapy for their tumors was 94% with *EGFR* (60/77), 35% with *MET* (6/17), 100% with *ALK/EML* (6/6), 0.05% with *BRAF* (1/19), 20% with *RET* (1/5), 50% with *ROS1* (1/2), and 62% with *ERBB2* (5/8) mutations. Independently from treatment types,those ones with genomic sequencing had significantly better OS (P = 0.002, 25.3 Vs. 14.6 months) and PFS (P = 0.008, 21.8 Vs. 12.3 Months) compared to non-sequenced matched control subjects. Patients who underwent targeted genomic therapy had both better OS (35.2 Vs. 28.3 m, P = 0.03) and PFS (29 Vs. 16.3 m, P = 0.01). There was no significant racial difference in baseline characteristics and driver mutation frequency (p = 0.47) except that *ALK/EML* had a higher mutation rate in AA (P = 0.019). No racial disparity in receiving targeted therapy (P = 0.45) was observed. Notably, Caucasian patients with mutant *EGFR* or *ALK* had significantly better OS (P = 0.01, 34.2 Vs. 14.9 m) and PFS (P = 0.02, 24.4 Vs.13.5) compared with AA patients. **Conclusions:** Genomic sequencing and targeted therapy increased survival outcomes in advanced NSCLC patients. Caucasians harboring *EGFR* or *ALK/EML* mutations had better survival compared to AAs.

8527 Poster Session (Board #133), Sun, 8:00 AM-11:30 AM

Definitive local therapy for oligo-recurrence in patients with completely resected non-small cell lung cancer. *First Author: Haruhisa Matsuguma, Division of Thoracic Surgery, Utsunomiya, Japan*

Background: The aim of this study was to elucidate a curable subgroup among patients with non-small cell lung cancer (NSCLC) who experienced post-operative recurrence. **Methods:** Between 1986 and 2012, among the 1,408 patients who underwent complete resection for NSCLC with anatomical lung resection at our institution, 420 experienced recurrence. After excluding 14 patients with insufficient information about recurrence, 406 patients were included in this retrospective study. We investigated the association between several clinicopathological factors and post-recurrence survival (PRS) and post-recurrence progression-free survival (PR-PFS). **Results:** The 5y-PRS and PR-PFS rates were 13.8% and 5.5%, respectively. By multivariate analysis, sex, disease-free interval (DFI), specific targeted therapy, time of recurrence, number of recurrent foci, and definitive-local therapy (DLT) were found to be independent prognostic factors for both PRS and PR-PFS. These 6 prognostic factors were classified into two types according to the 5 year PR-PFS rate difference. Among the 6 prognostic factors, Sex, DFI, and Specific targeted therapy were not associated with long term improvement of PR-PFS. **Conclusions:** We found that recent medical practice, a small number of recurrent foci (oligo-recurrence), and DLT treatment, were associated with cure of post-operative recurrence.

		Univariate		Multivariate	
	Variable	5y PR-PFS rate(%)	MST (months)	HR	P-value
Sex	Female/Male	3.0 / 7.1	6.8 / 5.5	1.33	0.018
DFI (months)	< 12 / ≥12	5.7 / 4.7	4.4 / 8.3	0.69	0.001
Time of recurrence	1987-1996 / 1997-2005 / 2006-	4.5 / 2.0 / 11.2	5.0 / 5.3 / 8.9	- / 0.95 / 0.71	- / 0.737 / 0.016
DLT	No / Yes	1.2 / 14.0	4.7 / 8.4	0.51	< 0.001
Specific targeted therapy	No / Yes	5.3 / 5.4	5.7 / 22.4	0.50	0.005
Number of recurrences	≥4 / 2 - 3 / 1	1.6 / 4.4 / 12.7	5.1 / 6.1 / 7.9	- / 0.82 / 0.64	- / 0.177 / 0.005

8528 Poster Session (Board #134), Sun, 8:00 AM-11:30 AM

A deep-learning radiomics model for predicting survival in early-stage non-small cell lung cancer. *First Author: Tafadzwa Lawrence Chaunzwa, Computational Imaging and Bioinformatics Laboratory, Harvard Medical School, Boston, MA*

Background: There is a growing body of evidence suggesting radiomic phenotypes can augment prognostic power, when used in combination with clinical features and tumor genomic profiles in lung cancer. In this study we present a deep-learning model that can act as a non-invasive prognostic biomarker in patients with Stage-I Non-Small Cell Lung Cancer (NSCLC). Our model would be able to assign patients to short term or long term survival groups, based on CT characteristics. **Methods:** Pretreatment CT studies were retrieved for 299 patients who underwent surgery for Stage-I NSCLC at MGH between 2004-2010. Image pre-processing included manual tumor identification, and isotropic rescaling of CT data. Further data curation resulted in a final cohort of 186 patients. Median follow-up from time of diagnosis was 2.9 years and 9.7% of patients were deceased at 2 years. To mitigate bias against a low probability event (mortality), data augmentation was performed yielding 242 50x50 pixel patches to feed into our model. A pre-trained 16 layer deep neural network (VGG-16) was used to perform visual recognition and data analysis. Fine-tuning of the last two convolutional blocks and a fully-connected classifier was performed with a training set of 144 labeled CT scans, matched to one of two groups based on 2 year survival. 34 samples were used for initial cross-validation. Data containing variations of imaging scanners and protocols were used in training to create a model that is robust for the variations. **Results:** Our model learned to classify patients with long term vs short term survival in an independent validation set of 64 samples with 75% accuracy and AUC = 0.798. In comparison, a multivariate linear regression model of conventional clinical prognostic factors (age, gender, tumor stage, histology, and smoking status) had a lower predictive performance (AUC = 0.665). Event rates were balanced between training and independent-validation groups. **Conclusions:** These findings suggest that Artificial Intelligence-enhanced radiomic feature extraction and predictive modeling can aid the clinician in assessing the benefits of treatment for patients with early-stage NSCLC.

8530 Poster Session (Board #136), Sun, 8:00 AM-11:30 AM

Carboplatin (CBDCA), S-1 and concurrent thoracic radiotherapy (TRT) for elderly patients with locally advanced non-small cell lung cancer (NSCLC): A phase II study. *First Author: Seiji Niho, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: S-1 is an oral anticancer agent containing a mixture of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, which has been shown to have a radiosensitizing effect in preclinical models. Recent phase II studies have shown that chemoradiotherapy using cisplatin and S-1 yields promising PFS durations of 15 to 20 months in non-elderly (less than 75 years old) patients with locally advanced NSCLC. We conducted a phase II study of CBDCA, S-1 and TRT for elderly patients with locally advanced NSCLC. **Methods:** The eligibility criteria included patients with unresectable stage III NSCLC, a chemotherapy-naïve status, PS 0 to 1, and age $\geq$ 71 years. Patients received CBDCA (AUC 3) on day 1 and S-1 (40mg/m^2 twice daily) on days 1 to 14, q4w, up to 4 cycles, plus concurrent TRT at a total dose of 60Gy. The primary endpoint was 1-year PFS rate. The sample size was set at 28 patients, with a one-sided alpha of 0.05, beta of 0.2, and expected and threshold values for primary endpoints of 50% and 30%. **Results:** Between Feb 2014 and Dec 2016, 28 patients were enrolled in this study. All 28 patients were eligible and assessable. Baseline characteristics as follows: median age (range) 77 (71-83) years; women, n = 3 (11%); ECOG PS of 0, n = 15 (54%); stage IIIB, n = 8 (29%); tumor histopathological type: adeno, n = 12 (43%), squamous, n = 13 (46%), and NSCLC-NOS, n = 3 (11%). All 4 cycles of CBDCA plus S-1 could be completed in 15 patients (54%). TRT at 60 Gy was completed in 26 patients (93%). Response rate was 71%. Grade 3-4 toxicities included neutropenia (7%), thrombocytopenia (21%), hypoalbuminemia (7%), hyponatremia (11%), anorexia (7%), fatigue (7%), and colitis (7%). Grade 3 radiation pneumonitis was observed in 5 patients (18%). No treatment-related death was observed. The 1-year PFS rate was 56% (90% CI, 40.0 to 71.7%), and the median PFS was 13.9 months (95%CI, 4.8 to 23.0 months) with a median follow-up period of 18.2 months in censored cases. **Conclusions:** Combination chemotherapy of CBDCA plus S-1 and concurrent TRT had promising efficacy in elderly patients with locally advanced NSCLC; however, radiation pneumonitis was frequently observed. Clinical trial information: UMIN000005794.

8531 Poster Session (Board #137), Sun, 8:00 AM-11:30 AM

Multimodal treatment in operable stage III non-small cell lung cancer using the new TNM staging classification version 8: Long term results of a pooled analysis of three SAKK trials. *First Author: Martin Frueh, Department of Oncology/Haematology, Cantonal Hospital St Gallen, St Gallen, Switzerland*

Background: The impact of the 8th edition of the TNM staging system on the optimal treatment choice and the best treatment strategy for stage III non-small cell lung cancer (NSCLC) is unclear. We applied the 8th version of the TNM classification to a pooled analysis of stage III NSCLC trials in order to test its validity and assess long term outcomes and prognostic factors. **Methods:** Individual patient data of 368 patients from three very similarly designed trials (SAKK 16/96, SAKK 16/00 and SAKK 16/01) were pooled. Patients with operable stage III NSCLC received preoperative radiotherapy following three cycles of induction cisplatin/docetaxel (tri-modal) or neoadjuvant cisplatin/docetaxel alone (bi-modal). Factors associated with improved 5-year overall survival (OS) were evaluated using a logistic regression model. **Results:** When applying the 8th TNM staging version*, 162 patients moved from stage IIIA to IIIB* and 5-and 10-year OS rates were 41% and 29% for stage IIIA and 35% and 27% for stage IIIB*. When using the 6th version 5- and 10-year OS rates were 38% and 28% for stage IIIA and 36% and 24% for stage IIIB. Factors associated with improved 5-year OS were age, R0 resection and pCR ($p = 0.043$, $p < 0.001$ and $p = 0.009$). There was no difference in the bi- vs. tri-modal group with regards to OS (median: 28 months [95% CI: 21-39 months] vs. 37 months [95% CI: 24-51 months], $p = 0.9$), event-free survival (median: 12 months [95% CI: 9-15 months] vs. 13 months [95% CI: 10-22 months], $p = 0.71$), local recurrence rate (48% vs 44%, $p = 0.61$), and pathologic complete remissions (pCR) rate (15% vs. 16% $p = 0.75$). R0 resection rates were lower in the bi-modal group (69% vs. 87%, $p < 0.001$). **Conclusions:** Similarly favourable long term outcomes were observed when the 8th vs. 6th TNM classification was applied. With the exception of the excluded patients with T4* due to multiple lesions in different lobes, multimodality treatment decisions in operable stage III NSCLC can be based on the 8th TNM version in upcoming trials. Tri-modal therapy resulted in higher R0 resection rates but did not improve OS. Younger age, R0 resection and pCR were associated with improved 5-year survival.

8532 Poster Session (Board #138), Sun, 8:00 AM-11:30 AM

Neoadjuvant atezolizumab + chemotherapy in resectable non-small cell lung cancer (NSCLC). *First Author: Catherine A. Shu, Columbia University Medical Center, New York, NY*

Background: Neoadjuvant chemotherapy is an accepted treatment approach for resectable NSCLC. Major pathologic response (mPR) defined as $\geq$ 90% tumor necrosis is seen in 20% of patients (pts) receiving neoadjuvant chemotherapy and portends a favorable survival. Combination anti-PD-(L)1 therapy and chemotherapy has demonstrated potential synergy in metastatic NSCLC. This ongoing phase II study explores the combination of neoadjuvant atezolizumab + chemotherapy. **Methods:** Pts with stage IB-IIIA resectable NSCLC receive 4 cycles of atezolizumab, nab-paclitaxel, and carboplatin prior to surgery. Never-smokers are excluded. Planned enrollment is 30 pts with a primary endpoint of mPR. Stage I trial evaluation after enrollment of 18 pts will be performed with pre-defined stoppage criteria for lack of efficacy (mPR in $\leq$ 4 pts). If $\geq$ 5/18 pts have mPR, an additional 12 pts will be treated in Stage II. The primary endpoint is met if $\geq$ 11/30 pts have mPR. **Results:** From 6/2016 to 1/2018, 14 evaluable pts were treated. Baseline characteristics: median age 71 years (range 49-83), 36% female, 57% adenocarcinoma, 85% stage IIIA, and 54% PD-L1 positive ($\geq$1%, 22C3). The most common toxicity was neutropenia (12/14 Grade 3-4), with 9/14 pts requiring chemotherapy dose reduction. 1 pt experienced G3 transaminase elevation, and another developed Type I diabetes (1 year after completion of treatment). 8/14 (57%) had radiologic PR, and the remainder had SD. 11/14 pts underwent resection successfully; 1 pt had post-operative complications unrelated to study drugs leading to death. The Stage I trial continuation criteria was met with 7/14 (50%) pts with mPR, including 3 with complete pathologic response (21%). mPR was seen in both PD-L1+ and PD-L1- pts. With a median follow-up of 8.6 months (95% CI 3.5, 17.8), there were 4 recurrent events: 2 were brain metastases. **Conclusions:** The combination of atezolizumab + chemotherapy demonstrated significant activity in the neoadjuvant setting. Treatment response was seen regardless of PD-L1 score. Correlative studies including multiplex IHC and tumor exome sequencing are ongoing. The data exceeded the futility boundary for mPR in Stage I and will proceed to Stage II. Clinical trial information: NCT02716038. Clinical trial information: NCT02716038.

8533 Poster Session (Board #139), Sun, 8:00 AM-11:30 AM

The effect of prior smoking history on the molecular profile of EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC). *First Author: Hadas Sorotsky, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Although *EGFR*m NSCLC occurs mainly in non-smoking patients, most series report 20%-35% of cases in current or previous smokers. Broad molecular profiling of *EGFR*m NSCLC in smokers has not been reported. **Methods:** Surgically resected primary *EGFR* exon 19 or 21 mutated NSCLC tumors from 108 patients were molecularly profiled by whole exome sequencing using the IIlumina HiSeq2000 platform. Alignment and variant discovery analysis was performed according to GATK best practices workflow; 87 sequenced to a mean coverage of 65.1x. Demographics and outcomes were compared for smokers and non-smokers (non-S), and by mutation profile. **Results:** Of the 63 non-smokers and 24 smokers (7 current/recent within 10 years), 71% were female, 53% were non-Asian, 64.5 years was the median age and 57.5% were EGFR exon 19. Of the 87 patients, 52% were stage I, 20.5% were stage II and 27.5% were stage III+. Smoking was associated with male sex ($p = 0.0028$) and non-Asian ethnicity ($p = 0.0006$) but not with age, stage or *EGFR* exon 19/21 subtype. Multiple "driver" mutations occurred in tumors of 25% smokers and 23.8% non-S. *TP53/EGFR* co-mutation occurred in 57.9% smokers and 46.2% non-S. Total non-synonymous mutation burden (TMB) was higher in smokers: median TMB in smokers 175.35 (84.93-388.24) compared to 155.31 (56.52-414.84) in non-S ($p = 0.096$). The strongest prognostic factor for OS and DFS was stage (I, II, III+) ($p < 0.001$ for each). In univariate analysis, there was a trend to shorter OS in smokers: HR 1.9 (CI 0.98-3.67, $p = 0.05$). Smoking within 10 years of NSCLC diagnosis was associated with shorter DFS HR 0.37(0.13-1.09) ($p = 0.06$) but not OS ($p = 0.34$). Neither *EGFR*m subtype nor *TP53/EGFR* co-mutation was associated with DFS or OS. High TMB was associated with shorter DFS: HR above *vs* below the median 1.96 (CI 1.06-3.62, $p = 0.028$), and OS HR 2.04 (CI 1.01-4.11, $p = 0.043$). TMB was still significant for DFS after adjusting for smoking status ($p = 0.033$), but not for OS ($p = 0.1$). **Conclusions:** *EGFR*m NSCLC in smokers is associated with a trend to higher non-synonymous TMB. Stage remains the strongest prognostic factor, but TMB appears to have a greater effect on survival outcomes than smoking status.

8534 Poster Session (Board #140), Sun, 8:00 AM-11:30 AM

Comparative evaluation of effectiveness of neoadjuvant chemoimmunotherapy (nPCIT) for non-small cell lung cancer (NSCLC). *First Author: Yuri Lazutin, Rostov Research Institute of Oncology, Rostov on Don, Russian Federation*

Background: The purpose of the study was to compare the results of neoadjuvant polychemoimmunotherapy (nPCIT) and conventional neoadjuvant polychemotherapy (nPCT) in patients with NSCLC. **Methods:** 64 pts with NSCLC were divided into 2 groups: main group – 32 pts, 2 nPCIT cycles (cisplatin 80 mg/m2 on day 1, gemcitabine 1200 mg/m2 on days 1 and 8 with i.v. infusions of the recombinant hybrid protein of tumor necrosis factor-alpha-thymosin-alpha1 100 000 IU on days 0, 3 and 6); control group – 32 pts, nPCT with the same cytostatics. Central cancer in 17(53.1%) pts of the main group (cT1NX-6.2%, cT2NX-37.5%, cT3NX-3.1%) and 20 (62.5%) (cT1NX-9.4%, cT2NX-40.6%) controls, peripheral cancer in 15(46.9%) (cT2b NX-9.4%, cT3> 7 NX-21.8%, cT3NX-18.7%, cT4NX-3.1%) and 12 (37.5%) (cT2b NX-12.5%, cT3NX-34.3%, cT4NX-3.1%), respectively. Squamous cell carcinoma in 17(53.2%) and 14(43.8%), adenocarcinoma in 7(21.8%) and 5(15.6%), non-small cell carcinoma in 8(25%) and 13(40.6%) pts, respectively. **Results:** CR in 3 (9.4%) and 2 (6.2%), PR - 14 (43.7%) and 13 (40.6%), SD - 13 (40.6%) and 14 (43.7%), PD - 2 (6.2%) and 3 (9.4%). Objective overall response rate was 53.1% in nPCIT vs 46.8% in nPCT, CR+PR+SD was 93.7% and 90.6%, respectively. 29 (90.6%) pts in each group received surgery. Extended lobectomy/bilobectomy in 14 (48.2%) pts in each group, extended pneumonectomy in 7 (24.1%) in nPCIT and 8 (27.5%) in nPCT. N2 disease in 10 (34.5%) and 13 (44.8%) pts, respectively. Post-surgical restaging: st. 0 – 10.3% vs 6.9%, st. I - 34.5% vs 31%, st. II - 20.7% vs 17.2%, st. IIIA - 34.5% vs 44.7%. Median survival in the main group - not reached, in controls – 23 months. OS was studied in pts with st. 0-II and st. IIIAN2 NSCLC; 3-year OS in early stages was 72% in the main group vs 49% in controls ($p = 0.0735$). **Conclusions:** The direct results were similar in nPCIT and nPCT, but 2-year EFS was 72% and 44%, respectively, with a tendency to improvement ($p = 0.05421$). 2-year OS in pts with st. IIIAN2 NSCLC improved to 55% in the main group vs 32% in controls ($p = 0.031777$).

8535 Poster Session (Board #141), Sun, 8:00 AM-11:30 AM

NanoPac inhalation treatment of NSCLC in a nude rat orthotopic lung cancer model. *First Author: Gere Dizerega, US Biotest, San Luis Obispo, CA*

Background: NanoPac is sub micronized paclitaxel in stable powder form without coating or carrier agents. In a previous PK study, healthy male rats inhaled a single exposure of nebulized NanoPac (0.37 mg/kg or 1.0 mg/kg) or IV Abraxane (5.0 mg/kg) with a final necropsy time-point at 14 days. $T_{1/2}$ of NanoPac and Abraxane were 56hrs and 20hrs with drug present at 14 days and not after 3 days, respectively. Tissue examined from the last time point were microscopically indistinguishable from non-treated controls. **Methods:** 120 nude rats were assigned to 6 groups and intratracheally instilled with Calu-3 lung tumor cells ($2x10^6$). Target doses and treatment schedules; Group 1 (Control: untreated), Group 2 (Abraxane: IV 5 mg/kg q1wx3), Group 3 (NanoPac: Inhaled (IH) 0.5 mg/kg q1wx4), Group 4 (NanoPac: IH 1.0 mg/kg q1wx4), Group 5 (NanoPac: IH 0.5 mg/kg q2wx4), Group 6 (NanoPac: IH 1.0 mg/kg q2wx4). Nebulized NanoPac (2μm Mass Median Aerodynamic Diameter) was delivered via nebulization into a nose-only exposure chamber; necropsy occurred (Group 2: 14 days), (Groups 3-6: 1 - 4 days) post final treatment. Histology was performed on sections of left lung stained with H&E from 10 animals in each group and scored using a 4-point grading scale. **Results:** Average lung/brain weight ratios for Group 2 (2.3) and Groups 3-6 (2.7) indicated a therapeutic effect vs Group 1 (3.2). Lung tumor burden decreased in combined Groups 3-6 as compared to Groups 1 and 2; characterized by the histological measures of tumor mass, primitive tumor cell population and tumor regression. Average primitive tumor cell population was significantly less ($p < 0.05$) for Groups 3-6 (0.3) compared to Group 1 (0.9) or Group 2 (1.0). Combined NanoPac Groups 3-6 (22/40) exhibited a significant ($p < 0.05$) incidence of tumor regression compared to Group 1 (0/10) and Group 2 (1/10). **Conclusions:** NanoPac treatment groups compared to Control and Abraxane groups demonstrated a therapeutic effect as measured by lower lung/brain weight ratio and lower overall lung tumor burden without apparent adverse events. Histological analysis of lung tumor burden treated with NanoPac IH showed a decrease in tumor mass, a decrease in primitive tumor cell population, and an increase in tumor regression.

8536 Poster Session (Board #142), Sun, 8:00 AM-11:30 AM

Concurrent chemotherapy and radiation versus chemotherapy alone for N3 stage IIIb NSCLC in elderly patients. *First Author: Angel Qin, University of Michigan, Ann Arbor, MI*

Background: The NCCN guidelines recommend treating stage IIIB NSCLC (non-small cell lung cancer) with concurrent chemotherapy and radiation (chemo-RT). There is data to suggest that N3 stage IIIB disease conveys worse prognosis, but this has not been explicitly interrogated. There is also concern regarding the safety of chemo-RT in patients ≥70 years old as they are under-represented in clinical trials, have worse overall survival, and experience increased toxicities. We therefore sought to interrogate the survival of N3 Stage IIIB NSCLC using the NCDB (National Cancer Database) with a focus on patients ≥70 years old. **Methods:** We conducted a retrospective analysis on data from the 2014 NCDB PUF (participant user file) of patients diagnosed with N3 stage IIIB NSCLC between 2010 and 2013. Kaplan-Meier method was used for median overall survival (OS) with log-rank tests. Multivariable Cox models were used for multivariable and subgroup analyses. **Results:** 9,769 patients were included in our analysis, 7,770 who received chemo-RT and 1,999 who received chemotherapy alone. A higher proportion of patients in the chemotherapy group were ≥70 years old compared to the chemo-RT group (46.6% and 34.5% respectively, $p < 0.0001$). The median OS for the chemo-RT group was 16.4 months compared to 12.7 months for the chemotherapy group ($p < 0.0001$). For patients ≥70 years old, the median OS was 15.0 months for those who received chemo-RT compared to 12.4 months for chemotherapy alone ($p < 0.0001$). In multivariable analyses, the benefit of chemo-RT was similar regardless of age. For age < 70, the hazards ratio (HR) was 0.73 with a 95% confidence interval (CI) of 0.67-0.79 and for age ≥70, HR = 0.77, 95% CI = 0.71-0.83 ($p = 0.43$). Subgroup analyses in patients ≥70 indicated a benefit to chemo-RT (HR < 1.0) across all patient and disease strata, including Charlson Comorbidity Index ($p < 0.05$ irrespective of score). **Conclusions:** There is a survival benefit to chemo-RT versus chemotherapy alone in N3 stage IIIB NSCLC in patients ≥70 years old, who represented 37% of all patients. Our findings suggest that age and comorbidity index alone should not preclude clinicians from recommending aggressive therapy to these patients.

8537 Poster Session (Board #143), Sun, 8:00 AM-11:30 AM

NORA trial (GECP 15/02): First efficacy results of the Spanish Lung Cancer Group (SLCG) phase II trial of concurrent chemo-radiotherapy (CT-RT) with cisplatin (P) plus metronomic oral vinorelbine (mOV) for unresectable locally advanced non-small cell lung cancer (LA-NSCLC). *First Author: Dolores Isla, Hospital Clínico Lozano Blesa, Zaragoza, Spain*

Background: CT-RT is the standard treatment for unresectable LA-NSCLC. P plus vinorelbine is widely used. Metronomic CT is a frequent administration of low doses of CT. mOV has shown good efficacy and improved safety, and could improve the RT effect. Our goal is to evaluate the efficacy and safety of P-mOV with radical RT in patients (pts) with LA-NSCLC. **Methods:** Pts aged 18-75 years with histologically proven untreated and unresectable LA-NSCLC, adequate bone marrow, hepatic & renal function, ECOG PS0-1, received P 80mg/m^2 D1 every 3 weeks combined with mOV 50mg/day on days D1, 3 & 5/weekly, 2 cycles (cy) as induction; patients without progression received 2 more cy of P at the same dose with mOV 30mg/day on D1, 3 & 5/weekly, concurrently with RT (66Gy in 6.5weeks). Primary endpoint was progression-free survival (PFS) by RECIST v1.1; secondary endpoints were: overall response rate (ORR), disease control rate (DCR), overall survival and safety profile. To guarantee an overall type-1 α error no greater than 0.05 and a type II (β) error 0.1 for PFS, a sample size of 67 pts was planned. **Results:** Sixty-seven pts were recruited in 17 Spanish sites from 04/2016 to 06/2017. One of them didn't meet all the inclusion criteria. We analyzed the first 57 pts included. Pt characteristics: Male 77.3%; median age 62 (range 33-75); PS 0/1 50/50%; smokers 45.5%; adenocarcinoma/squamous 34.8/43.9%; stage IIIA/B 43.9/56.1%. Only 29.8% of pts presented any grade 3-4 adverse event, including: neutropenia 22.8%; anemia 3.5%; febrile neutropenia 7%; esophagitis 1.8%; pneumonitis 1.8%. There were two deaths non-related to the treatment, during this period. Forty-four pts have completed the treatment. ORR: 66.7%. DCR: 79%. With a median follow-up of 11.2 months (range 1.1-21.7), the median PFS is 11.9 months (CI95%; 10.1-NR). **Conclusions:** mOV-P with RT is as effective as the standard administration of vinorelbine, improving its safety profile. EudraCT 2015-003312-21. Clinical trial information: EudraCT 2015-003312-21.

8538 Poster Session (Board #144), Sun, 8:00 AM-11:30 AM

Insurance disparity in cause-specific mortalities: A SEER study on early stage, non-elderly NSCLC cancer survivors. *First Author: Changchuan Jiang, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Lung cancer is the leading cause of cancer-related death in the US. Non-elderly, early stage (stage I&II) non-small cell lung cancer (NSCLC) patients have the most promising prognosis with appropriate treatments. Studies have shown uninsured and elderly patients on Medicaid being less likely to receive guideline-concordant therapy and thus with higher mortality. However, it remains unknown how insurance status influences cause-specific survival in non-elderly NSCLC patients, and whether disparity of care is improved in this cohort after ACA. **Methods:** Surveillance, Epidemiology, and End Results Program from 2007-2014 was used to identify NSCLC patients on stage I and II on diagnosis. Elderly patients ($>$ 65 years) were excluded. Demographic and lung cancer characteristics including age, gender, race, education, income, insurance status, tumor grade/stage and treatment were analyzed. Competing risk analysis was conducted using SAS9.4. **Results:** A total of 13,898 patients were included. After adjusting for socio-demographic factors, tumor grade and treatment, Medicaid and non-insured were associated with higher lung cancer mortality (HR: Medicaid 1.30 (1.17-1.44), non-insured 1.26 (1.05-1.50)). Patients with any Medicaid sustain the highest mortality for cardiovascular diseases(CVD) and non-cancer respiratory diseases(NCR) across different insurance status (CVD HR: Medicaid 2.17 (1.57-2.99), non-insured 1.37 (0.74-2.56); NCR HR: Medicaid 2.46 (1.76-3.43), non-insured 0.73 (0.30-1.81)). Diagnosis after ACA was associated with lower lung cancer specific mortality but not related to CVD or NCR mortality. No effect modification was found for diagnosis after ACA on any specific cause mortality. **Conclusions:** Despite ACA and Medicaid expansion in 2010, Medicaid and non-insured patients have higher cancer mortality compared with insured in early-stage NSCLC patients. Furthermore, non-elderly, early-stage NSCLC cancer survivors with Medicaid have remarkably higher CVD mortality compared to private insured survivors even without any insurance, which may reflect the disparity in health literacy, primary care, and cancer survivorship care access.

8539 Poster Session (Board #145), Sun, 8:00 AM-11:30 AM

Progression-free survival (PFS) and cardiac-toxicity-adjusted-PFS (CTA-PFS) as predictors of overall survival (OS) in locally advanced non-small cell lung cancers (LA-NSCLC) treated with concurrent chemoradiation (CCRT): A secondary analysis of NRG Oncology RTOG 0617. *First Author: Chen Hu, Johns Hopkins University, Baltimore, MD*

Background: OS is the gold standard for LA-NSCLC with CCRT, with complex relationships among RT dosimetry, systemic therapies, cardiopulmonary toxicity, progression (PD) and OS of growing scientific and clinical interest. **Methods:** RTOG 0617 (NCT00533949) randomized standard (SD, 60 Gy) versus high-dose (HD, 74 Gy) CCRT +/- cetuximab from 11/07-06/11. This analysis includes 469 patients (pts) given $\geq$50 Gy. A PFS event was defined as the first occurrence of local, regional, distant PD or death w/o documented PD. A CTA-PFS event was the first occurrence of grade 2+ treatment-related cardiac toxicity event or a PFS event. Landmark analyses at 6mo and 12mo were used to minimize the immortal time bias. Cox model with PD or CT/PD as a time-dependent covariate was used to evaluate their predictive roles. Median f/u time for surviving pts was 5.1 years. **Results:** As reported, pts treated with HD had significantly lower OS rates (HR = 1.28, 95%CI: 1.04-1.58, p = 0.018) and CTA-PFS rates (HR = 1.24, 95%CI: 1.02-1.51, p = 0.035), and marginally lower PFS rates (HR = 1.21, 95%CI: 0.99-1.47, p = 0.06) than pts treated with SD. Median survival time (MST) among pts having PD within 6mo versus not were 13.4mo (95%CI: 10.0-19.0) and 30.7mo (95%CI: 28.0-37.0) ($p < 0.001$). MST for pts having PD within 12mo versus not were 20.6mo (95%CI: 18.8-25.0) and 60mo (95%CI: 47.6-74.5)($p < 0.001$). Results are similar when using CTA-PFS with 6mo or 12mo cutoff ($p < 0.001$). RT dose was no longer significantly associated with OS (p = 0.08 or p = 0.15) when PD or CT/PD was included in multivariable analysis ($p < 0.001$), suggesting OS differences in HD/SD may be partially captured by PFS or CTA-PFS. **Conclusions:** RTOG 0617 survival results suggest that PFS (or CTA-PFS) status at 6mo or 12mo predicts long-term OS, and may potentially be considered as a surrogate endpoint of OS in clinical trials. Pts who were progression-free at 12mo had a MST of 5 years. Further validation on external datasets and in the modern era of immunotherapy are needed.

8540 Poster Session (Board #146), Sun, 8:00 AM-11:30 AM

Routine use of a modest next generation sequencing panel provides additional clinically useful data beyond single gene testing in non-small cell lung cancer and is fit for purpose as a clinical assay: Collated data from a single molecular diagnostic laboratory. *First Author: David Allan Moore, Sarah Cannon Molecular Diagnostics, London, United Kingdom*

Background: Testing of the EGFR gene for sensitising mutations is a critical part of patient stratification in non-small cell lung cancer. Analysis of a modest panel of relevant genes using a targeted Next Generation Sequencing (tNGS) has the potential to identify an extended range of actionable or trialable alterations compared with more limited technologies. There are additional analytical and technological advantages to this approach. Sarah Cannon Molecular Diagnostics has been delivering somatic variant analysis through Oncomine solid tumour panel since 2014. This project involved the collation of data from 3 years' worth of molecular diagnostic tNGS testing performed on non-small cell lung cancer specimens. **Methods:** The laboratory database was interrogated to identify all cases of non-small cell lung cancer submitted for testing from a 3 year period. Rate of rejection due to insufficient tumor, assay failure rate and turnaround time was calculated. For all cases successfully tested data was manually extracted for the relevant driver mutations and incidental evidence of gene amplification. **Results:** A total of 2796 NSCLC cases were submitted for multigene panel analysis over 3 years. 217 samples (7.8%) were rejected outright due to either low tumor content (189). Of 2579 accepted for testing, 'analysis failed' was reported in 131 (5.1%). Median turnaround time was 7 working days. 17% of cases reported were positive for a recognised EGFR driver mutation and 11% of EGFR-driven cancers also had a T790M mutation detected. 35% of those reported had evidence of a driver mutation in KRAS, 5.4% had other recognised driver mutations in BRAF, ERBB2, PIK3CA or NRAS and 3.5% of cases had no driver mutation but incidental evidence of amplification. **Conclusions:** A tNGS panel can be delivered as a diagnostic test for mutation analysis with an acceptable success rate and turnaround. Over 60% of patients have a driver event identified, providing additional relevant information beyond single gene testing.

8541 Poster Session (Board #147), Sun, 8:00 AM-11:30 AM

Neoadjuvant atezolizumab in resectable non-small cell lung cancer (NSCLC): Initial results from a multicenter study (LCMC3). *First Author: Valerie W. Rusch, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Platinum-based chemotherapy, before or after surgery, provides only a 5% benefit in 5yr. OS in locally advanced NSCLC. A recent pilot study (JCO 2017 35:15suppl, 8508) showed that preoperative immune checkpoint inhibitor therapy was well tolerated and yielded a clinically meaningful major pathologic response rate (MPR ≤10% residual viable tumor cells). This large multicenter trial tests the MPR rate and novel biomarkers of benefit using this novel neoadjuvant approach with atezolizumab (atezo) [NCT02927301]. **Methods:** Pts with stages IB -selected IIIB resectable NSCLC were to receive 2 cycles of atezo (1200 mg, days 1, 22) then undergo resection (day 40 +/- 10). Chest CT, PET obtained pre- and post atezo to assess clinical response. Primary tumor +/- node biopsies and blood samples were obtained before atezo and at surgery for biomarker studies. The primary endpoint was MPR. Secondary endpoints included safety, response by PD-L1, OS, and DFS. **Results:** For the prespecified initial safety analysis, the first 21 of 180 planned pts (67 pts currently on study) are reported: 13 males, median age 65 y, all ECOG 0-1; 4 current, 16 former smokers; 13 non-squamous NSCLC; clinical stages Ib/IIa/IIb/IIIa/IIIb = 4/2/6/5/4. Two pts received one dose of atezo due to treatment related AE (Gr 1 pyrexia, Gr 2 dyspnea) but underwent uncomplicated resection with MPR assessment. There were no Gr 5 AE, 5 Gr 3-4 AE (1 treatment related). By RECIST, 20 pts had SD, and 1 had PD. There were no major delays to surgery. 19 pts had MPR assessment: 1 pt discontinued atezo preop due to CNS mets and 1 pt had unresectable disease. MPR rate was 4/19 (21%, 95% CI 6-46). Excluding 2 pts who had known driver mutations (1 EGFR+, 1 ALK+), MPR rate was 4/17 (24%, 95% CI 7-50). 11/19 patients had ≤50% viable tumor. **Conclusions:** This first report of atezo in the neoadjuvant setting shows that preoperative treatment is feasible and well tolerated. MPR rate is encouraging. Clinical and pathological responses are often discordant. Safety and efficacy results from additional pts will be presented. Correlative analyses on pre- and post atezo tissues are ongoing. Preliminary correlative analyses in blood samples are included in a separate abstract. Clinical trial information: NCT02927301.

8542 Poster Session (Board #148), Sun, 8:00 AM-11:30 AM

Association between certain NSCLC driver mutations and sensitivity markers for chemotherapy or PD-(L)1 inhibition: A large-sample analysis. *First Author: Wenhua Liang, Department of Thoracic Surgery/Oncology, the First Affiliated Hospital of Guangzhou Medical University, China State Key Laboratory and National Clinical Research Center for Respiratory Disease, Guangzhou, China*

Background: Driver gene alterations play a pivotal role in NSCLC and are predictive markers for specific targeted therapy. However, few evidence has correlated certain mutation types with the sensitivity markers for different chemo-agents or immune-checkpoint inhibitors which are inevitable during the whole course of treatment. **Methods:** Specimens and clinical data were obtained from a consecutive cohort of resectable NSCLC patients from 2016-03 to 2017-11. Hybridization-capture sequencing (Ion Proton) of 8 important NSCLC-related drivers was conducted. The slides were tested for PD-L1 (SP142), ERCC1, RRM1, TS and β-tubulin3 by immunohistochemical staining. **Results:** Among a total of 785 patients, 498 (63.4%) patients had at least 1 driver alterations. The prevalence of each driver agreed with previous reports and their association with sensitivity markers were summarized as The overall percentage was used as a cut-off for each marker. *, representing good sensitivity to corresponding drugs. According to the results, preferable regimens might be indicated; the sensitivity indication was consistent with previous observations. For Kras+ patients, PD-(L)1 inhibition is an optimal option and platinum should be included when using chemo; for BRAF mutation where limited data presented, anti PD-(L)1 is optionable and taxanes might be the most sensitive chemo-agents. **Conclusions:** These results may aid in selecting optimal salvage regimen after targeted therapy failure, or adjuvant chemo-regimen where targeted therapy has not been a routine option. Further validation using true response data was warranted.

Type	Prevalence %	ERCC1 low %	RRM1 low %	TS low %	β-tubulin3 low %	PD-L1(+) %
Overall	100	11.70	66.30	72.00	57.00	27.60
Wide Type	36.56	**14.9** *	50.00	54.60	**61.8** *	**36.4** *
EGFR 19DEL	21.40	2.90	**76.8** *	**87.6** *	58.90	16.10
EGFR L859R	23.18	7.20	**81.2** *	**82.7** *	**60.3** *	18.90
EGFR rare	2.42	**16.7** *	**91.7** *	**100** *	**85.7** *	20.00
ALK	3.18	**22.7** *	**69.6** *	**95.7** *	39.10	25.00
HER2	0.25	0.00	**100** *	**100** *	0.00	-
RAS	9.81	**28.6** *	58.90	58.90	39.00	**44.9** *
RET	1.15	**14.3** *	50.00	57.10	28.60	0.00
ROS1	1.02	0.00	**66.7** *	66.70	14.30	**60** *
BRAF	0.64	0.00	20.00	40.00	**60** *	**60** *
MET (mut)	0.38	**33.3** *	**66.7** *	33.30	33.30	**66.7** *

8543 Poster Session (Board #149), Sun, 8:00 AM-11:30 AM

Association between hospital volume, treatment patterns, and overall survival (OS) of patients with stage 3A non-small cell lung cancer (NSCLC). *First Author: Sri Harsha Tella, University of South Carolina, Columbia, SC*

Background: There is significant heterogeneity in the treatment of stage IIIA NSCLC. We evaluated the therapeutic and survival disparities in IIIA NSCLC patients based on the hospital volume using National Cancer Data Base (NCDB). **Methods:** IIIA NSCLC patients diagnosed between 2004-2015 were included. We classified facilities by tertiles (T; mean patients with IIIA NSCLC treated/yr): T1: < 67.07; T2: 67.01 to 123.68 and T3: ≥123.68. We used SPSS to account for clustering of patients within centers (based on the volumes: lower, middle & higher 1/3rd of the cases) and Cox regression to determine the volume-outcome relationship, adjusting for patient demographics (age, sex, race), tumor characteristics (size, nodes and grade), insurance & therapy. Kaplan Meier estimates of OS were compared with log-rank test. **Results:** This analysis includes 101,110 patients treated at 1329 facilities. The median age at diagnosis was 68 yrs. The median annual facility volume was 91 patients/yr (range, 1- 798). Multivariable analysis showed that facility volume were independently associated with all-cause mortality ($p < .0001$). The unadjusted median OS by facility volume was: T1: 15 months (m), T2: 16 m, and T3: 19 m ($P < .0001$). Compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had significantly higher risk of death [T2 hazard ratio (HR), 1.09 (95% CI, 1.07-1.11); T1 HR, 1.11 (95% CI, 1.09 - 1.13)]. Patients treated at high volume centers were more likely to get surgery (27 vs 17%) and trimodality treatment (12% vs 9%) ($p = 0.01$). Chemo and radiation therapy patterns were similar among facilities. Receipt of surgical therapy was independently associated with prolonged OS. Compared to patients who received lobectomy, patients who received pneumonectomy had significantly higher risk of death HR, 1.32 (95% CI,1.3-1.4, $p < 0.0001$). **Conclusions:** Patients who were treated for stage IIIA NSCLC at T3 centers (> 123 cases/yr) had a significant improvement in survival and are more likely to receive trimodality therapy.

	Therapy (%)				Survival (%)		
	Surgery	Chemo	Radiation	Trimodality	1 yr	3yr	5 yr
T1 (33%)	17	69	68	9	57	26	17
T2 (34%)	20	70	68	10	59	28	19
T3 (33%)	27	70	65	12	64	33	23

8544 Poster Session (Board #150), Sun, 8:00 AM-11:30 AM

The ASCENT trial: A phase II study of neoadjuvant afatinib, chemoradiation and surgery for stage III EGFR mutation-positive NSCLC. *First Author: Lecia V. Sequist, Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA*

Background: The stage III NSCLC paradigm now includes immunotherapy (IO), but advanced EGFR-mutant (EGFR+) pts typically don't respond to IO. In 2011 we began a phase II trial of neoadjuvant afatinib (NeoAfat) and standard of care (SOC) curative intent treatment for EGFR+ stage III NSCLC, NCT01553942. We present an interim analysis given the evolving SOC landscape. **Methods:** EGFR+ stage III pts amenable to curative-intent chemoradiation (CRT) ± surgery were treated with NeoAfat 40mg po QD x2mo, then concurrent CRT: cisplatin 75mg/m2 + pemetrexed 500mg/m2 IV q3wk up to 4 cycles and 3D conformal RT or IMRT personalized to tumor size, site, operability. Surgery and adjuvant afatinib (AdjAfat) x2yr were optional. Primary outcome was objective response rate (ORR) to NeoAfat. **Results:** 13 pts were treated (10F/3M); med age 56 (range 34-75). EGFR mutations: del19 (n = 9); L858R (n = 4). Stage: operable IIIA (n = 7); inoperable IIIA/B (n = 6). NeoAfat ORR = 69% (95% CI 39-91); 5 (38%) pts dose reduced NeoAfat. All pts proceeded to CRT with pre-op med RT dose of 54 Gy (range 45-66; n = 7), definitive med dose of 65 Gy (range 63-72; n = 6). 5 (71%) of the 7 surgical pts had major (4) or complete (1) pathologic response. 7 (54%) pts started AdjAfat at med dose of 30mg QD; 4 completed 2yr, 2 aborted early, 1 ongoing . Key grade 3/4 toxicities: rash 5), diarrhea (5), esophagitis (3), nausea (3), pneumonitis (2 gr 3) and febrile neutropenia (1); no treatment-related deaths. With med follow-up of 24.1 mo (range 5.0-64.2), 6 (46%) pts have recurred; including 4/6 inoperable pts, 2/7 who had surgery, 1/5 with major path response (CNS-only recurrence). Med PFS is 34.6 mo (95% CI 12.6-NR). 2-yr OS is 85% (95% CI 33-98). **Conclusions:** Neoadjuvant afatinib achieves high ORR and major surgical path responses, and doesn't impair receipt of SOC, curative CRT ± surgery in EGFR+ stage III NSCLC. Feasibility of NeoAfat exceeds AdjAfat in stage III setting. The prolonged PFS compares favorably to PACIFIC IO arm; more data is needed about optimal strategy for stage III EGFR+ pts. ASCENT is still ongoing, but it and similar randomized RTOG 1306 have accrued slowly, highlighting the challenge of studying curative approaches in genotype-defined subgroups. Clinical trial information: NCT01553942.

8545 Poster Session (Board #151), Sun, 8:00 AM-11:30 AM

Using deep-learning radiomics to predict lung cancer histology. *First Author: Tafadzwa Lawrence Chaunzwa, Computational Imaging and Bioinformatics Laboratory, Harvard Medical School, Boston, MA*

Background: Histologic phenotype is an important predictor of clinical outcomes in lung cancer. Tissue diagnosis is the most definitive approach to categorization, however, this is often technically challenging for thoracic lesions. In this study, we explore Deep-Learning Radiomics methods for non-invasive histology classification in early-stage Non-Small Cell Lung Cancer (NSCLC). **Methods:** A cohort of 157 patients with Stage I NSCLC identified as either adenocarcinoma or squamous cell carcinoma on pathology was used. All patients were surgical candidates at Massachusetts General Hospital between 2004-2010. Deep feature extraction from pretreatment CT images was conducted using a pre-trained VGG-16 convolutional neural network (CNN). In addition to appending fully-connected classifying layers to the network, a transfer learning approach was also employed using different classifiers. Three machine-learning classification models were independently evaluated on the extracted features: K-Nearest Neighbors (kNN), Random Forest Classifier (RF), and Least Absolute Shrinkage and Selection Operator (LASSO). Principal component analysis was employed in selecting features corresponding to 90% cumulative explained variance. A LASSO method was then used to select the best features. Models were trained on 100 patients and cross-validated on an independent test-set of 57 patients. **Results:** All models were able to perform binary classification of tumor histology (adenocarcinoma vs squamous cell carcinoma). The fully-connected CNN had the highest performance (AUC = 0.751). Other classifiers also showed significant predictive power after dimension reduction of the feature space (from 512 to 46), with AUC = 0.712 for LASSO ($\alpha = 0.1$), and AUC = 0.689 for kNN (k = 5). RF had the lowest predictive performance (AUC = 0.533). 73% of the study group had adenocarcinoma vs 27% with squamous cell carcinoma, and ratios were balanced between training and validation sets. **Conclusions:** Deep-Learning Radiomics is a promising approach to non-invasive lung cancer histology classification. These methods can potentially augment other emerging techniques, such as liquid biopsy; offering complementary information to help in clinical decision making.

8547 Poster Session (Board #153), Sun, 8:00 AM-11:30 AM

Clinical relevance of intratumoural immune cell composition in non-small cell lung cancer. *First Author: Xuetao Li, Guangdong Lung Cancer Institute, Guangdong General Hospital affiliated to South China University of Technology & Guangdong Academy of Medical Sciences, Guangdong Key Laboratory of Lung Cancer Translational Medicine, Guangzhou 510080, China, Guangzhou, China*

Background: While the understanding of immune landscape of NSCLC has been greatly improved, it is largely unknown how local repertoire of tumor infiltrating leukocytes differs in context of tumor genomics and impacts on prognosis and response to immunotherapy. The aim of this study was to deconvolve immune cell fractions from bulk tissue gene expression profiles (GEPs), and to determine the distinct immune cell composition in molecular subgroups of NSCLC. **Methods:** Bulk GEPs of 1692 tumor samples of NSCLC patients with known clinical information were obtained from GEO. CIBERSORT algorithm was used to infer the relative proportions of 22 human leukocyte subsets in each tumor. The common and specific immune infiltrating patterns were established for histological and genomic subgroups of NSCLC defined by driver gene mutations. The correlation between intratumoural immune profiles and overall survival (OS) was assessed using multivariable Cox regression model. **Results:** An increased fraction of regulatory T cells ($p < 0.001$) and a decreased fraction of plasma cells (PCs) ($p < 0.003$) were found in advanced NSCLC. With respect to histology, macrophages (Ms) were significant differential cellular component between adenocarcinoma and squamous cell carcinoma. Nevertheless, the high fraction of PCs had longer median OS (8.4 vs 4.4 years, HR 0.59, p = 1e-05) than the low fraction of PCs. The median OS for the low fraction of neutrophils was 7.9 years vs 5.6 years for the high fraction of neutrophils (HR 1.64, p = 0.00072). We found that EGFR-mutant NSCLC was characterized by enriched CD4+ memory resting (CD4mr) ($p < 0.0001$) and dendritic resting ($p < 0.0001$) cells, as well as lacking of Ms ($p < 0.001$). Strikingly, ALK-mutant NSCLC showed a similar intratumoural immune profile with KRAS-mutant NSCLC, illustrated by a low fraction of CD4mr cells and enriched Ms in both molecular subgroups. **Conclusions:** Our results pointed out the complex relationship between the heterogeneity of intratumoural immune infiltrates, tumor genomics, and patient prognosis across subtypes of NSCLC. Further research is warranted to validate the relation in independent patient cohorts and to explore the impact of immune landscape on immunotherapeutic response.

8548 Poster Session (Board #154), Sun, 8:00 AM-11:30 AM

Evaluating PD-L1 status and its correlation with clinical features in surgically resected lung adenocarcinoma patients: Comparison of tissue microarrays and whole tissue section. *First Author: Hsu-Ching Huang, Chest Department, Taipei Veterans General Hospital, Taipei, Taiwan*

Background: PD-1/PD-L1 has been a novel therapeutic target in non-small-cell lung cancer (NSCLC). PD-L1 immunohistochemical staining is the most commonly used test for therapeutic guide. Although PD-L1 expression heterogeneity is well acknowledged, data are limited in PD-L1 staining results between small biopsied sample and whole tissue section (WTS) obtained from the same specimen. Current study aimed to compare PD-L1 staining between tissue microarray (TMA) and WTS and correlate it with clinical features. **Methods:** Two hundred and nineteen lung adenocarcinomas from patients who underwent surgical resection in Taipei Veterans General Hospital during Sep. 2002 and Aug. 2006 were used to construct TMA. Among them, the correspondent WTS was available in 173 specimens. Tumor PD-L1 staining on TMA and WTS were evaluated by SP142 (Spring Bioscience) on Leica autostainer. Positive PD-L1 expression was defined as membranous staining in $\geq$ 1% of tumor cells. Correlations between TMA and WTS PD-L1 expression were performed. Patients' demographic characteristics, survival and histology subtypes were investigated and correlated with PD-L1 expression on WTS. **Results:** 25 (14.5%) and 58 (33.5%) specimens were PD-L1 positive in TMA and WTS, respectively. Thirty-three (19.1%) specimens were PD-L1 negative in TMA but positive in WTS. The expression level was 1% in 8, 2-5% in 7; 6-49% in 14, and $\geq$ 50% in 4 specimens. Discordancy was more common in larger tumor size (p = 0.025), wild type EGFR (p = 0.044), and advanced stage (p = 0.01). Tumors with lepidic predominant histology ($p < 0.001$), EGFR wild-type (p = 0.002) and early disease stage (p = 0.006) were more likely to be PD-L1 negative. Kaplan-Meier survival analysis showed longer recurrence-free survival ($p < 0.001$) among patients with negative PD-L1 expression. **Conclusions:** PD-L1 IHC readout discordancy between small and large samples were not uncommon in NSCLC and it seemed related to tumor size and stage. Patients with negative PD-L1 expression tended to have longer recurrence-free survival.

8549 Poster Session (Board #155), Sun, 8:00 AM-11:30 AM

Impact of somatic mutations on recurrence free survival (RFS) and overall survival (OS) for resected non-small cell lung cancer (NSCLC): results from the Japan Molecular Epidemiology for lung cancer study (JME). *First Author: Akihiro Tamiya, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan*

Background: We previously reported molecular profiling as a primary endpoint in a prospective multicenter molecular epidemiology study, collecting 876 surgically resected NSCLC and examining 72-gene somatic mutation status using the next-generation sequencing (JME study; Kawaguchi T, J Clin Oncol 2016). The secondary endpoint was OS and RFS analysis (UMIN 000008177). Here, we report follow-up data and clinical outcomes in the JME study and the impact of somatic mutations on RFS and OS. **Methods:** All the patients were enrolled from July 2012 to December 2013, and clinical and prognostic data were obtained until the end of November 2017. Cox proportional hazards model were applied to assess the impact of the gene mutations on RFS and OS, considering gender, smoking history, age, stage, histology, history of adjuvant chemotherapy, EGFR, KRAS, TP53, and number of coexisting mutations. **Results:** Median follow up time was 48.4 months, and 876 patients were analyzed: 419 were men; 734 were non-squamous carcinoma; 441 had smoking history; 450 were $\geq$70 years; 618/131/127 were stage I/II/III-IV, 309 received the adjuvant chemotherapy. Among these, 141 had $\geq$ two somatic mutations. Multivariate analysis showed the number of coexisting mutations ($\geq$2 vs. 0 or 1, HR = 1.643, 95%CI: 1.126-2.373), age ($\geq$70 vs. $<$ 70, HR = 1.561, 95%CI: 1.201-2.035) and pathological stage (II vs. I, HR = 3.103, 95%CI: 2.217-4.304; $\geq$III vs. I, HR = 6.382, 95%CI: 4.641-8.758) were significantly associated with RFS, while in OS, *EGFR* mutations (yes vs. no, HR = 0.450, 95%CI: 0.277-0.715), adjuvant chemotherapy (yes vs. no, HR = 0.493, 95%CI: 1.406-2.967), age ($\geq$70 vs. $<$ 70, HR = 1.694, 95%CI: 1.201-2.415) and pathological stage (II vs. I, HR = 2.448, 95%CI: 1.581-3.723; $\geq$III vs. I, HR = 6.601, 95% CI: 4.498-9.665) were also significant prognostic factors. **Conclusions:** Our prospective study showed less number of coexisting mutations, earlier stage and younger age were associated with longer RFS, while in OS, *EGFR* mutation and adjuvant chemotherapy were significantly associated with improved OS as well as earlier stage and younger age in resected NSCLC.

8550 Poster Session (Board #156), Sun, 8:00 AM-11:30 AM

Circulating tumor DNA (ctDNA) as a marker of minimal residual disease (MRD) in localized non-small cell lung carcinoma (NSCLC). *First Author: Nicholas I. Simon, Northwestern University, Chicago, IL*

Background: ctDNA has been used to identify driver genomic alterations during treatment of metastatic NSCLC. Recent studies have also demonstrated ctDNA being used as a way to monitor response to therapy. Here we performed an analysis on a cohort of NSCLC patients (pts) with localized disease who underwent ctDNA testing after definitive treatments to determine whether ctDNA can be used as a marker of MRD. **Methods:** Between 2015-2018, 51 pts with localized NSCLC received ctDNA testing. ctDNA testing was done using the next generation sequencing (NGS) panel of 73 genes via digital sequencing technology (Guardant360). Statistical analysis was performed to determine which factors were associated with ctDNA levels and recurrence free survival (RFS). **Results:** Of the 51 pts analyzed, 23 pts had ctDNA testing performed after definitive treatment. Median duration of follow up was 10 months (range: 1 to 23). 30% (n = 7) had Stage I disease, 30% (n = 7) had Stage II disease, and 40% (n = 9) had stage III disease. 74% (n = 17) were adenocarcinoma while 26% (n = 6) were squamous cell carcinoma. 52% (n = 12) had no recurrence during our observation time, while 48% (n = 11) experienced progression. For definitive treatments, 35% (n = 8) underwent surgery alone, 43% (n = 10) underwent surgery with adjuvant chemotherapy, 4% (n = 1) underwent radiation alone, and 17% (n = 4) underwent chemoradiation therapy prior to their ctDNA levels [variant allele frequency (VAF)] being drawn. Of these, 13% (n = 3) tested negative for any ctDNA, while 87% (n = 20) were positive. None of the pts with undetectable levels of ctDNA experienced recurrence of cancer. Nine among 20 pts with detectable ctDNA had recurrence. Kaplan-Meir survival analysis revealed a trend toward significant association between the presence of detectable ctDNA and RFS (p = 0.055). Among pts with detectable ctDNA, there were no differences in RFS between pts with high vs. low ctDNA levels (cut off at 1% VAF). Presence of ctDNA was not associated with sex, smoking history, histology, stage, nor modality of definitive treatment. **Conclusions:** Our analysis demonstrates that ctDNA could potentially be used as a marker of MRD following definitive treatment for localized NSCLC.

8551 Poster Session (Board #157), Sun, 8:00 AM-11:30 AM

Microwave ablation plus recombinant human endostatin (endostar) versus microwave ablation alone in inoperable stage I non small cell lung cancer. *First Author: Min Meng, Shandong Provincial Hospital Affliated to Shandong University, Jinan, China*

Background: Previous studies showed that inoperable stage I non small cell lung cancer (NSCLC) benefited from microwave ablation (MWA) alone. This prospective, randomized, control, single-center clinical trial aimed to determining the survival benefit of MWA plus recombinant human endostatin (endostar) compared with MWA alone. **Methods:** Patients with untreated, inoperable, stage I NSCLC were recruited. They were divided into MWA/ endostar group and MWA group, the former received MWA in the primary tumor sites, followed by 2 to 4 cycles of endostar and the latter treated with MWA only. The primary endpoint was overall survival (OS), the second endpoint included disease-free survival (DFS) , and adverse events (AE). **Results:** A total of 183 patients were enrolled, involved 92 cases in the MWA/ endostar group and 91 cases in the MWA group. Up to the latest follow-up , there were 24 cases of disease progression and 6 deaths in the MWA/ endostar group, versus 49 cases of disease progression and 9 deaths in the MWA group. DFS in the MWA/ endostar group (30.0 months, 95% CI, 27.1-32.9) was significantly better than MWA group (21.3 months, 95% CI, 19.5-23.1, p = 0.000). But there was no significant difference (p = 0.471) in OS between the MWA/ endostar group (31.6 months ,95% CI, 28.3-35.0) and MWA group (30.0 months, 95% CI, 27.2-36.5). The 1, 2 and 3 year survival rates in the MWA/ endostar group were 94%, 82% and 82%, respectively, while those in the MWA group were 94%, 89% and 89%, respectively. There was no significant difference between the two groups (p = 0.982, p = 0.924, p = 0.924). AEs of MWA were observed in 63.7 % patients. Endostar -associated AEs were not observed in the MWA/ endostar group. **Conclusions:** MWA was a safe and effective alternative treatment for patients with inoperable stage I non small cell lung cancer. MWA combined with endostar significantly improved DFS compared to MWA alone, while not increased the MWA-related complications.

8552 Poster Session (Board #158), Sun, 8:00 AM-11:30 AM

Long-term results of a phase I/II trial of nelfinavir with concurrent chemoradiotherapy for locally advanced non-small cell lung cancer. *First Author: Ramesh Rengan, Department of Radiation Oncology, University of Washington, Seattle, WA*

Background: The objective of this Phase I/II trial was to determine the response rate and overall survival (OS) of concurrent chemoradiotherapy (CT-RT) in combination with the radiosensitizer Nelfinavir in locally advanced non-small cell lung cancer (LA-NSCLC) compared to historical controls. **Methods:** Nelfinavir (Dose Level (DL) 1: 625mg PO BID, DL2:1250mg PO BID) was administered for 7 to 14 days prior to and during concurrent CT-RT to patients (pts) with biopsy confirmed unresectable IIIA and IIIB NSCLC. 23 pts (65.7%) had stage IIIA disease; 11 pts (31.4%) had stage IIIB disease; 1 pt (2.9%) had N2 recurrence after surgery. Median age was 60 years for all pts. 19 pts (54.2%) were male, 16 (45.7%) were female. Patients were treated with concurrent CT-RT to a dose of 66.6/1.8Gy and cisplatinum and VP-16. DLTs were defined as any treatment related Grade 4 hematologic toxicity requiring a break in therapy or non-hematologic Grade $\geq$ 3 toxicity except esophagitis and pneumonitis. Protocol specified criteria for compliance included receiving greater than 80% of the prescribed RT treatments and 70% of the prescribed Nelfinavir doses. **Results:** Thirty-five pts were enrolled and met protocol-specified criteria for compliance, 5 at DL1 and 30 at DL2. No DLTs were observed. The recommended phase II dose of Nelfinavir was 1250 mg PO BID. Median follow-up for all pts was 6.8 years and minimum follow-up for survivors was 5 years. 33 of the 35 pts had evaluable post-treatment CT with RECIST response rate of 94% and (31/33) stable disease rate of 6% (2/33). The cumulative incidence of local failure as site of first failure was 20%, with the median time to failure not reached (NR). The cumulative incidence of distant failure as site of first failure was 51%, with the median time to distant failure of 15.8 months. The median progression-free survival was 12 months. The median OS for all pts was 40 months; 5 year OS was 37 %. **Conclusions:** Nelfinavir administered with concurrent CT-RT is associated with acceptable toxicity and very promising local control, overall response rate, and survival in unresectable LA-NSCLC. These data suggest that Nelfinavir may enhance the efficacy of chemo-RT in this disease. Clinical trial information: NCT00589056.

8553 Poster Session (Board #159), Sun, 8:00 AM-11:30 AM

Significance of aromatase-estrogen receptor axis in EGFR status of lung adenocarcinoma. *First Author: Kazumi Tanaka, Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Japan*

Background: Aromatase alongside with estrogen receptor beta (ERβ) is a potential target for novel therapeutic strategy in lung adenocarcinoma (AC). The purpose of this study is to examine the correlations of expressions of aromatase and ERβ with other prognostic factors including epidermal growth factor receptor (*EGFR*) in lung AC. **Methods:** We analyzed 186 consecutive patients with lung AC who underwent surgical resection at Gunma University Hospital between Dec. 2003 and Feb. 2010. The clinicopathological characteristics and survivals of patients were subclassified based on the expressions of aromatase, ERα, ERβ, and progesterone receptor (PR) as determined by immunohistochemical staining. Gene alterations of *EGFR* and *KRAS* were evaluated with SmartAmp2. Multivariate analysis using Cox regression model was carried out to evaluate the effect of aromatase expression. In vitro experiment was performed with shRNA transduced aromatase-depleted lung AC cells. **Results:** Expressions of aromatase, ERα, ERβ, and PR were detected in 86.6%, 1.6%, 78.5%, 2.7% of all patients, respectively. In all patients, the expression of aromatase is an independent prognostic factor in OS (Hazard Ratio [HR] = 2.1; 95% confidential interval [CI], 1.2-3.6; *P*= .008) and RFS (HR = 1.8; 95%CI, 1.1-2.8; *P*= .022), while that of ERβ is not statistically significant. In patients with wild-type *EGFR*, high aromatase expression is also an independent prognostic factor in OS (HR = 2.4; 95%CI, 1.2-4.6; *P*= .009) and RFS (HR = 2.5; 95%CI, 1.3-4.7; *P*= .006). Interestingly, high aromatase expression is significantly correlated with poor survival only in women (OS, *P*= .019; RFS, *P*= 0.033) in patients with wild-type *EGFR*, while no prognostic significance is observed in patients with *EGFR* mutations. In line with this, depletion by shRNA of aromatase suppressed oncogenic activity in soft agar assays. **Conclusions:** Aromatase expression is independent negative prognostic factor in especially *EGFR* wild-type adenocarcinoma. We further showed that in patients with wild-type *EGFR*, high aromatase expression is a significant correlated with poor survival only in women. Aromatase-depleted lung AC cells transduced shRNA, demonstrate decreased tumorigenicity.

8554 Poster Session (Board #160), Sun, 8:00 AM-11:30 AM

Long-term outcomes after sublobar resection for clinical stage IA lung adenocarcinoma meeting node-negative criteria defined by HRCT and FDG-PET/CT. *First Author: Yasuhiro Tsutani, Hiroshima University, Hiroshima, Japan*

Background: The purpose of this study is to evaluate long-term outcomes after sublobar resection for patients with clinical stage IA lung adenocarcinoma meeting our proposed node-negative (N0) criteria: solid component size of less than 0.8 cm on HRCT or SUVmax of less than 1.5 on FDG-PET/CT. **Methods:** Between April 2006 and December 2010, 347 patients with clinical stage IA lung adenocarcinoma underwent complete resection after preoperative HRCT and FDG-PET/CT in Kanagawa Cancer Center and Hiroshima University. Long-term outcomes of patients who met the N0 criteria after sublobar resection were evaluated. **Results:** Two-hundred one (57.9%) patients met the N0 criteria. Patients who met the N0 criteria were significantly associated with low grade adenocarcinoma subtype (adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic adenocarcinoma; $P < 0.001$), negative lymphatic invasion ($P < 0.001$), negative vascular invasion ($P < 0.001$), and negative pleural invasion ($P < 0.001$). One of 201 (0.5%) patients had lymph node metastasis. The median follow-up period was 86.1 months. There was significant difference in overall survival (OS) between patients who met the N0 criteria (5-year OS rate, 93.9%; 10-year OS rate, 90.3%) and those who did not meet the N0 criteria (5-year OS rate, 81.5%; 10-year OS rate, 64.3%; $P < 0.001$). In patients who met the N0 criteria, there was no significant difference in OS between patients who underwent lobectomy (5-year OS rate, 94.3%; 10-year OS rate, 92.6%) and those who underwent sublobar resection (5-year OS rate, 93.8%; 10-year OS rate, 89.3%; $P = 0.640$). **Conclusions:** Sublobar resection is feasible for clinical stage IA lung adenocarcinoma meeting N0 criteria defined by HRCT and FDG-PET/CT with excellent long-term survival.

8555 Poster Session (Board #161), Sun, 8:00 AM-11:30 AM

A phase I study of neoadjuvant cisplatin (C), docetaxel (D) and nintedanib (N) for resectable non-small cell lung cancer (NSCLC). *First Author: Tina Cascone, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Major pathologic response (mPR) in resected NSCLC following neoadjuvant chemotherapy correlates with long-term survival. This phase 1 study assessed the safety and efficacy of N added to neoadjuvant C and D, using mPR as primary surrogate of efficacy endpoint. **Methods:** Eligible patients (pts) had stage IB (≥4 cm) to IIIA (single station N2) resectable NSCLC (AJCC 7^{th}). The study included an expansion phase of N 200 mg p.o. bid priming monotherapy for 28 days, followed by 3 cycles of C 75 mg/m^2, D 75 mg/m^2 every 21 days, and N 200 mg p.o. bid, and surgery (after a run-in phase in 6 pts determined safety of escalating N doses). With 33 pts, the study had 90% power to detect an increase in mPR from 15% (historical controls) to 35%, with a 10% type I error rate. Based on the Simon's two-stage design, the protocol called for discontinuation of the trial if there were < 4 responders in the first 19 pts treated at N 200 dose level (NCT02225405). **Results:** From July 2015 to May 2017, 21 pts (15 female, 1/8/12 stages I/II/III) were treated (6 with N 150 mg bid, 15 with N 200 mg bid). Only 1/15 pts treated with N 200 mg bid achieved a mPR (6.7%, 95% CI 0.2% - 32.0%). An interim analysis demonstrated that the probability of observing ≥4 mPRs if accrual were to continue to 19 pts was only 5.4%, assuming the prior of p beta(0.35, 0.65). Hence, the study was discontinued for futility. The best objective response rate by RECIST 1.1 in all 21 pts was 33.3%. No patients responded to N priming monotherapy. With a median follow up time of 11 months, the 12-month RFS in the whole cohort was 71% (95% CI 49%, 100%). The most frequent treatment-related grade 3-4 toxicities in all pts were: transaminitis (14.3%); nausea (9.5%) and electrolyte abnormalities (14.3%). No unexpected perioperative complications were observed. **Conclusions:** Although tolerable, neoadjuvant N, C, and D did not increase the mPR rate compared to historical controls of induction chemotherapy alone. Additional studies of the combination in this setting are not recommended. Our trial design, utilizing mPR as an intermediary endpoint, may serve as a framework to rapidly screen novel compounds that should be investigated further as neoadjuvant therapies for resectable NSCLC. Clinical trial information: NCT02225405.

8556 Poster Session (Board #162), Sun, 8:00 AM-11:30 AM

A comparative safety analysis for durvalumab in patients with locally advanced, unresectable NSCLC: PACIFIC versus pooled durvalumab monotherapy studies. *First Author: Scott Joseph Antonia, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: In PACIFIC, durvalumab significantly extended PFS compared with placebo (HR 0.52; P<0.0001) for pts with locally advanced, unresectable NSCLC who had previously received concurrent chemoradiotherapy (cCRT). The safety profile of durvalumab in this study was similar to placebo. Here we report a safety analysis of a descriptive comparison of PACIFIC with a pooled dataset of durvalumab monotherapy studies. **Methods:** Data were pooled for pts treated with durvalumab monotherapy (10 mg/kg IV Q2W) from three trials (N=1,889), the Phase III PACIFIC (n=475), Phase II ATLANTIC (n=444 advanced NSCLC pts), and Phase I/II 1108 (n=970 solid tumor pts, including 304 NSCLC pts) studies. The incidences of all-causality AEs (as of Feb 13, 2017, data cutoff for the PACIFIC analysis) were graded using CTCAE v4.03 and summarized descriptively for comparison between PACIFIC and the pooled dataset. **Results:** Compared with the pooled dataset (Table), PACIFIC had lower incidences of grade 3/4 AEs and SAEs, but a higher rate of AEs leading to discontinuation (15.4% [durvalumab] vs. 9.8% [placebo] compared with 9.4% [pooled dataset]). In a separate comparison excluding PACIFIC from the pooled dataset (N=1,414), any-grade (grade 3/4) pneumonitis/radiation pneumonitis occurred in 33.9% (3.4%) of pts on durvalumab and 24.8% (3.0%) on placebo in PACIFIC (with similar grade 3/4 incidences for both) and 2.3% (0.5%) of pts in the reduced pooled dataset. **Conclusions:** Durvalumab monotherapy has a well-defined and acceptable safety profile. Differences observed in the rates of AEs with durvalumab on the PACIFIC regimen may be attributable to the pt population or prior cCRT.

	PACIFIC		
Demographics	**Pooled monotherapy dataset (N=1,889)**	**Durvalumab (n=475)**	**Placebo (n=234)**
Median age (range), years	63.0 (19–96)	64.0 (31–84)	63.5 (23–90)
Age ≥75 years, %	10.0	7.6	7.7
Male, %	59.8	70.1	69.7
Overview of AEs			
Exposure-adjusted grade 3/4 AEs,* n	94.0	47.5	46.8
Exposure-adjusted SAEs,* n	79.5	42.5	38.2
Any AE leading to discontinuation, %	9.4	15.4	9.8
Any AE with outcome of death, %	5.4	4.4	6.0
Any AESI, %	55.5	65.5	48.7
Any imAE, %	15.6	24.2	8.1

*Reported as events per 100 pt-years

8557 Poster Session (Board #163), Sun, 8:00 AM-11:30 AM

Geriatric assessment to predict toxicity in elderly patients with unresectable locally advanced non-small-cell lung cancer treated with concurrent chemoradiotherapy. *First Author: Ernest Nadal, Department of Medical Oncology, Catalan Institute of Oncology, Hospitalet (Barcelona), Spain*

Background: There is no consensus on the treatment of elderly patients with unresectable locally advanced non-small-cell lung cancer (LA-NSCLC). We aimed to determine whether the comprehensive geriatric assessment (CGA) as well as other screening tools were able to predict toxicity in this clinical setting. **Methods:** Elderly patients (≥ 75y) with LA-NSCLC underwent CGA, the Vulnerable Elders Survey (VES-13) screening tool and the Cancer and Aging Research Group (CARG) toxicity predictive tool. Based on CGA, fit and medium-fit patients were deemed candidates for platinum-based chemotherapy concurrent with thoracic radiation therapy (cCRT) and unfit patients received best supportive care. The ability of CGA, CARG and VES-13 to predict grade 3–4 (G3-4) toxicity was assessed by logistic regression. **Results:** 85 elderly patients with LA-NSCLC were assessed by CGA and classified into fit 37%, medium fit 48% and unfit 15%. Based on VES-13, 56% were considered vulnerable. Fifty-four fit and medium-fit patients received cCRT and 42 (78%) patients completed the scheduled treatment. No differences in treatment completion were seen among both CGA groups. Reasons for not completing cCRT were toxicity (10%), cancer recurrence (4%), patient decision (4%) or aggravation of comorbidities (4%). The median OS (mOS) in fit and medium-fit patients receiving cCRT was 21.1 months (95% CI 16.2 – 26.0). Most common G3-4 adverse events were neutropenia (20%), febrile neutropenia (7.5%), asthenia/fatigue (11%), respiratory infection (13%) and radiation pneumonitis (13%). CARG toxicity tool classified fit and medium-fit patients into high 10%, medium 52% and low risk 38%. GGA groups were not predictive of G3-4 toxicity. Medium and high risk patients based on CARG were more likely to have G3-4 toxicity ($p = 0.086$).Vulnerable patients defined by VES-13 had significantly higher risk of grade 3-4 toxicity (OR = 3.99, 95% CI 1.28-12.37, $p = 0.017$). **Conclusions:** CGA is helpful in selecting elderly patients with unresectable LA-NSCLC that may benefit from cCRT. VES-13 was significantly associated with higher risk of G3-4 toxicity in this clinical setting.

8558 Poster Session (Board #164), Sun, 8:00 AM-11:30 AM

Long-term survival after salvage SBRT for recurrent or secondary non-small cell lung cancer after prior surgery or radiation therapy. *First Author: Chunyu He, Indiana University Department of Radiation Oncology, Department of Thoracic Radiation Oncology, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China*

Background: Patients with locally recurrent or newly diagnosed NSCLC after previous definitive radiotherapy (RT) or surgery pose a challenge in management. SBRT has been attempted as option of salvage treatment. The objective of this study is to report long-term outcome of SBRT in patients with recurrent or second primary NSCLC after previous local treatment. **Methods:** This single-institution retrospective study included patients with NSCLC who received thoracic SBRT for newly diagnosed or recurrent NSCLC. The primary and second endpoints were overall survival and radiation pneumonitis, respectively. Clinical factors analyzed included age, gender, race, tobacco history, respiratory/cardiovascular comorbidity, histology, modality of previous treatment, T stage, gross tumor volume (GTV), planning target volume (PTV), and prescription dose. Radiation pneumonitis was graded consistently per RTOG1106. **Results:** A total of 326 patients met the inclusion criteria, including 43, 40 and 243 patients with prior RT, surgery, and no prior treatment, respectively. The median follow-up was 59 (95% CI 48-68) months. The median survival were 23 (95% CI 15-31), 50 (95% CI 35-65), and 32 (95% CI 25-40) months, and the 5-year survival rates were 26.2%, 42.4%, and 24.7%, respectively (P= 0.077). In those treated with previous RT, there were no significant differences in overall survival between conventionally fractionated radiation therapy and SBRT (median survival 25.0 vs 13.4month, P= 0.280). In those treated with prior surgery, there was no significant difference in overall survival between pneumonectomy and lobectomy (56.0 vs 50.0 months, P= 0.576). The were significant differences in rates of grade 1+ (44.2%, 30.0%, 21.5%, P= 0.007), and 2+ RP (18.6%, 12.5%, 7.0%, P= 0.039), but no statistically significant differences in grade 3+ pneumonitis among these three groups. **Conclusions:** Salvage SBRT after previous radiation or surgery provides a chance of cure, with 5-year survival not significantly different from that of SBRT for newly diagnosed NSCLC, with significantly increased but acceptable risk of radiation pneumonitis.

8560 Poster Session (Board #166), Sun, 8:00 AM-11:30 AM

Long-term survival following trimodality therapy vs. medical management of malignant pleural mesothelioma. *First Author: Frédéric Larose, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada*

Background: Medical management based on palliative chemotherapy is currently the standard of care in malignant pleural mesothelioma (MPM). Median survival of 12-16 months has been reported with modern chemotherapy regimens. Multimodality therapy incorporating radical surgery, systemic chemotherapy and radiotherapy has recently evolved. The MARS feasibility study suggested that extrapleural pneumonectomy might be detrimental, but recent publications suggested that pleurectomy/decortication (P/D) may lead to better outcomes with overall median survival of 30-35 months in selected patients. Retrospective studies comparing trimodality therapy vs. medical management conducted in centers where surgery is offered are obviously limited by selection bias. Our objective was to compare overall survival in patients offered trimodality therapy at a single institution to the one of patients treated at another institution where the management of MPM is exclusively medical. **Methods:** Retrospective analysis of two databases: 106 consecutive patients (cohort 1) treated by a single team in London (UK) from 2009 to 2016 and 98 consecutive patients (cohort 2) exclusively treated medically at the Quebec Heart and Lung Institute (Canada) during the same period were included. **Results:** In cohort 1, all patients had P/D with hyperthermic pleural lavage with povidone-iodine, prophylactic chest wall radiotherapy and systemic chemotherapy. In cohort 2, 51% received palliative care only; 31% were treated with chemotherapy. Median survival was 32 months vs 10 months in cohort 1 and 2, respectively (hazard ratio with age, gender, pathology and TNM staging as covariates: 3.81; 95% CI: 2.66 – 5.45; $p < 0.0001$). **Conclusions:** Aggressive therapy of MPM using cancer-directed surgery, systemic chemotherapy and prophylactic radiotherapy may provide a significant survival benefit in selected patients.

	Trimodality therapy (n = 106)	Medical therapy (n = 98)	P
Age (mean ± SD)	64 ± 2	70 ± 5	< 0.0001
Gender (n, % male)	83 (78%)	73 (74%)	0.16
Pathology (n, %)			< 0.0001
Epithelioid	73 (69%)	57 (58%)	
Sarcomatoid	2 (2%)	15 (15%)	
Biphasic	31 (29%)	21 (21%)	
Unknown	0	5 (5%)	
Staging (n, %)			0.0005
1 -2	22 (21%)	43 (44%)	
3 – 4	84 (79%)	55 (56%)	

8561 Poster Session (Board #167), Sun, 8:00 AM-11:30 AM

Uncommon ALK fusion partners in advanced ALK-positive non-small-cell lung cancer. *First Author: Jin Kang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: The variants affect the efficacy of crizotinib in echinoderm microtubule protein-like-4 (*EML4*)- anaplastic lymphoma kinase (*ALK*) fusion-positive non–small-cell lung cancers (NSCLCs). Non–EML4-ALK fusions were detected and may have biologic and clinical implications differently. However, few studies focused on the effects of non–EML4-ALK fusions on the efficacy of crizotinib. **Methods:** Among 182 ALK-positive patients whose ALK rearrangement were confirmed by fluorescence in situ hybridization developing resistance to crizotinib as the initial ALK-TKI between October 2010 and December 2017, 41 patients with sufficient tumor specimens could be evaluated for *ALK* variants by next-generation sequencing (NGS). Uncommon *ALK* fusion partners include non-EML4 or EML4-based variants. We retrospectively investigated progression-free survival (PFS), objective response rate (ORR) and overall survival (OS) between the patients with uncommon *ALK* fusion partners and those with EML4-ALK variants. **Results:** The frequency of uncommon ALK fusion partners was 34.1% (14/41). Among the 14 patients , there are 9 patients only harboring with one kind of non-EML4 partners. The ALK fusion partners of the other 5 patients included non-EML4 and EML4. The median PFS was longer in patients with uncommon ALK fusion partners than in those with EML4 variants (10.5 months VS 3.7 months [95% CI, 0.85 to 3.06 months], respectively; P = 0.142). The ORR between two groups were 64.3% and 77.8% in the two groups respectively. The median OS was 34.2 months and 21.0 months in the two groups respectively (95% CI, 1.21 to 4.65 months ; P = 0.012) . Four patients harbored with uncommon *ALK* fusion partners developed primary resistance to crizotinib and these fusions included DTNB-ALK, NR_110271-ALK, ZC3H8-ALK and STED2-ALK. A emerging FSHR-ALK fusion was found in a patient who had dynamic plasma to be monitored during the treatment of crizotinib. **Conclusions:** The *ALK* fusion partners have a profound impact on the efficacy of ALK TKIs. Some partners led to primary resistance to crizotinib and some partners might produce better efficacy of ALK TKIs than *EML4* in advanced *ALK*-positive NSCLCs. The *ALK* fusion partners should be detected by NGS beforehand.

8562 Poster Session (Board #168), Sun, 8:00 AM-11:30 AM

***PBRM1* genomic alterations in mesothelioma: Potential predictor of immunotherapy efficacy.** *First Author: Jeffrey S. Ross, SUNY Upstate Medical University, Syracuse, NY*

Background: PBRM1, of the SWI/SNF family, modulates chromatin remodeling. *PBRM1* genomic alterations (GA) are enriched in renal cell carcinoma and mesothelioma (MS). Recent evidence suggests that *PBRM1* GA are strongly associated with neoantigen production and responsiveness to immune checkpoint inhibitors (ICPI). **Methods:** Comprehensive genomic profiling (CGP) was performed on 50 ng of DNA for 783 FFPE mesothelioma (MS) samples using a hybrid-capture, adaptor ligation-based next-generation sequencing assay to a median coverage depth of > 600X. The results were analyzed for all classes of GA and tumor mutational burden (TMB), determined on up to 1.2 Mb of DNA. Microsatellite instability (MSI) status was evaluated by principal component analysis of optimal homopolymer loci. GA were counted as relevant if known to disrupt *PBRM1* or homozygous in the tumor. **Results:** Of 783 relapsed/refractory MS, 8 (1%) were pericardial (PCDMS), 187 (24%) peritoneal (PERMS), and 588 (75%) pleural (PLRMS) tumors (Table). Median ages were similar, but specimens from males were more common (72%) in PLRMS and females (56%) in PERMS. The *PBRM1* GA frequency was 11% overall, from 7.7% (PLRMS) to 20.3% (PERMS). *BAP1* GA were found in 84.1% of *PBRM1*-altered MS and *NF2* GA in 28%. In *PBRM1* wild type MS, *BAP1* GA were in 43.7% and *NF2* GA in 31.2%. The median TMB was low and TMB > 20 mut/Mb were very uncommon. There were very few instances of MS with high MSI. MS patients with *PBRM1* GA responding to ICPI treatment will be presented. **Conclusions:** Immunotherapy strategies for the treatment of MS have recently emerged. *PBRM1* GA are seen in 11% of MS and represent a potential predictive biomarker for therapy selection in this typically devastating disease. Further study of PBRM1 status in the ICPI treatment of MS in the clinical trial setting appears warranted.

	Total MS	PCDMS	PERMS	PLRMS
Cases	783	8	187	588
Median Age	67	66	59	66
Gender	F 33%	F 57%	F 56%	F 28%
***PBRM1* GA Frequency**	82 (10.5%)	1 (14.3%)	38 (20.3%)	43 (7.7%)
BAP1 (PBRM1 Mut; WT)	69 (84.1%); 306 (43.7%)	0 (0%); 2 (28.6%)	33 (86.8%); 69 (46.3%)	36 (83.7%); 235 (43.1%)
NF2	23 (28.0%); 219 (31.2%)	1 (100%)	10 (26.3%); 35 (23.5%)	12 (27.8%); 185 (26.4%)
Median TMB (mut/Mb)	1.7	2.4	1.7	1.2
TMB ≥ 20 mut/Mb	1%	0%	2%	1%
MSI-High	< 1%	0%	2%	0%

8563 Poster Session (Board #169), Sun, 8:00 AM-11:30 AM

Phase 1b study of avelumab in advanced previously treated mesothelioma: long-term follow-up from JAVELIN Solid Tumor. *First Author: Raffit Hassan, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, Bethesda, MD*

Background: Avelumab, a human anti-PD-L1 IgG1 antibody, is approved for treatment of metastatic Merkel cell carcinoma in various countries and advanced urothelial carcinoma progressed on platinum therapy in the US. We report updated results with avelumab in a phase 1b cohort of patients (pts) with mesothelioma. **Methods:** Pts with unresectable pleural or peritoneal mesothelioma progressed after platinum and pemetrexed therapy received avelumab 10 mg/kg IV Q2W until progression, unacceptable toxicity, or withdrawal. Endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs). A post-hoc landmark analysis was performed using a Cox regression model. **Results:** At data cutoff on Dec 31, 2016, 53 pts were treated and followed for a median of 24.8 mo (range 16.8–27.8). Pts had received a median of 2 prior lines of therapy (range 1–8). Confirmed ORR was 9.4% (95% CI 3.1–20.7) including complete response (CR) in 1.9% and partial response (PR) in 7.5%. Median duration of response was 15.2 mo (95% CI 11.1–not estimable). 26 pts (49.1%) had stable disease (SD) as best response and the disease control rate was 58.5%. Median PFS was 4.1 mo (95% CI 1.4–6.2) and the 6-mo PFS rate was 38.0% (95% CI 24.2–51.7). Median OS was 10.9 mo (95% CI 7.5–21.0) and the 12-mo OS rate was 45.9% (95% CI 31.9–58.8). In a landmark analysis of pts still on treatment at 3 mo, duration of OS beyond 3 mo was longer in patients who had achieved CR/PR (HR $<$ 0.01; 95% CI 0–inf.) or SD (HR 0.43; 95% CI 0.20–0.89) vs other pts. In evaluable pts with PD-L1+ (n = 16) or PD-L1− (n = 27) tumors ($\geq$5% tumor cell cutoff), ORR was 18.8% (95% CI 4.0–45.6) and 7.4% (95% CI 0.9–24.3), respectively. Treatment-related (TR)AEs occurred in 43 pts (81.1%), including infusion-related reaction (35.8%; all grade 1/2), chills (15.1%), fatigue (15.1%), and pyrexia (11.3%) in $>$ 10%. 5 pts (9.4%) had a grade $\geq$3 TRAE. 12 pts (22.6%) had an immune-related TRAE, which was grade $\geq$3 in 3 pts (5.7%; pneumonitis, colitis, and type 1 diabetes mellitus). No treatment-related deaths occurred. **Conclusions:** Updated data confirm the clinical activity and acceptable safety of avelumab in pts with previously treated mesothelioma. Clinical trial information: NCT01772004.

8564 Poster Session (Board #170), Sun, 8:00 AM-11:30 AM

Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *First Author: Vasiliki Panou, Department of Respiratory Diseases & Department of Clinical Medicine & Clinical Cancer Research Center & Research Unit of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Aalborg, Denmark*

Background: Malignant mesothelioma (MM) is thought to be largely due to asbestos exposure, but the prevalence and the causative role of germline cancer susceptibility gene mutations in MM is unknown. **Methods:** Targeted genomic capture and next generation sequencing of 85 cancer susceptibility genes was performed on DNA extracted from peripheral blood or saliva from 198 patients with pleural, peritoneal, or tunica vaginalis MM presenting to The University of Chicago Mesothelioma Clinic. **Results:** The patient population fit usual MM demographics: the majority were male (n = 136, 69%), had pleural disease (n = 148, 75%), epithelioid histology (n = 157, 79%), and a history of occupational asbestos exposure (n = 129, 65%). The median age at MM diagnosis was 67 years (range 24-88). We identified 24 pathogenic germline mutations in 13 genes in 23/198 (12%) MM patients. *BAP1* mutations were the most common (n = 6, 25%). The remaining were in genes involved in cell cycle and DNA repair (n = 14), oxygen sensing (n = 2), endosome trafficking (n = 1), and cell growth (n = 1). Pleural site (OR 0.23; 95% CI 0.10-0.58), asbestos exposure (OR 0.28; 95% CI 0.11-0.72), and older age (OR 0.95, 95% CI 0.92-0.99) were associated with decreased odds of carrying a germline mutation while having a second cancer diagnosis (OR 3.33; 95% CI 1.22-9.07) significantly increased the odds. The odds of carrying a mutation in *BAP1* (OR 1658; 95% CI 199-76224), *BRCA2* (OR 5; 95% CI 1.0-14.7), *CDKN2A* (OR 53; 95% CI 6-249), *TMEM127* (OR 88; 95% CI 1.7-1105), and *VHL* (OR 50; 95% CI 1.1-453) were significantly higher in MM cases than in a non-cancer control population. Tumor sequencing identified mutations in a homologous recombination (HR) DNA repair pathway gene in 52% (n = 29/54), including *BAP1* (n = 27), *FANCA* (n = 2), *ATM* (n = 1), *ATR* (n = 1), *BRCA2* (n = 1), and *CHEK2* (n = 1). **Conclusions:** A significant proportion of MM patients carry germline pathogenic mutations in cancer susceptibility genes, especially those with peritoneal MM, minimal asbestos exposure, young age, and a second cancer diagnosis. These data support clinical germline genetic testing for MM patients and provide rationale for a further investigation of the HR pathway in MM.

8565 Poster Session (Board #171), Sun, 8:00 AM-11:30 AM

Phase II trial of pembrolizumab (P) in patients (pts) with previously-treated mesothelioma (MM). *First Author: Arpita Desai, University of Chicago, Chicago, IL*

Background: We conducted a phase II trial (NCT02399371) of P in previously treated MM to characterize activity in a non-selected population and determine a PD-L1 expression threshold **Methods:** Eligible pts had histologically confirmed MM, PS 0-1, disease progression, 1-2 prior regimens. P 200 mg was given Q21 days; CT scans Q9 weeks. 1^0 endpoints determine 1) objective response rate (RR) in an unselected and a PD-L1 positive population 2) optimal threshold for PD-L1 expression (22C3 IHC tumor cell/tumor proportion score (TPS) assay). Part A required $\geq$3 responses in 35 PD-L1 unselected pts. Part B PD-L1 preselects if a threshold is found in Part A. We previously reported (WCLC 2016) 7 responses in Part A; as no PD-L1 threshold was found (ROC 0.62), Part B enrolled 30 pts with no biomarker enrichment. **Results:** 65 pts enrolled 5/15-2/18; 1 withdrew. Median age: 68 (range 26-85); PS 0: 53%; male: 77%; epithelioid/biphasic/sarcomatoid: 76.6%/15.6%/7.8%; pleural/peritoneal: 87.5%/12.5%; 1 prior regimen: 61%. Mean cycles: 9 (range 1-34). Partial response: 12 (19%), stable disease: 29 (47%). Median progression-free survival (PFS): 4.5 months (mo) (95% CI: 2.3, 6.2). Median overall survival: 11.5 mo (95% CI: 7.6, 14). Grade $^3/_4$ toxicity: adrenal insufficiency 3%, pneumonitis 3%, rash 3%, colitis 1.6%, confusion 1.6%, hepatitis 1.6%, hyperglycemia 1.6%. Grade 5: hepatitis 1.6%, unknown 1.6%. PD-L1 expression by TPS (N = 62): none ($<$ 1%) 45%; low (1-49%) 32%; high ($\geq$50%) 23%. RR by TPS: none 7%, low 26%, high 31%. RR by histology: epithelioid 16%, biphasic 10%, sarcomatoid 40%. RR by site: pleural 20%, peritoneal 12.5%. PD-L1 did not correlate with RR as a continuous metric (ROC area 0.65; 95% CI: 0.48, 0.82); there was a trend to higher RR in PD-L1 $\geq$1% (28%) vs. PD-L1 $<$ 1% (7%). Median/1-year PFS by TPS: none 3.1 mo/7%; low 6.2 mo/7%; high 6.1 mo/31%. **Conclusions:** P has clinically meaningful single-agent activity in PD-L1 unselected, previously treated MM, yielding a 19% RR, a 66% disease control rate, and manageable toxicity. Though an optimal PD-L1 threshold could not be established, there was a trend to higher RR and more durable PFS with increasing PD-L1 expression. Responses were more frequent in pleural and sarcomatoid MM. Funded by MARF. Clinical trial information: NCT02399371.

8566 Poster Session (Board #172), Sun, 8:00 AM-11:30 AM

Tumor burden (TB) and treatment exposure (TE) in patients (pts) with malignant pleural mesothelioma (MPM) receiving nintedanib (N)/placebo (P) in combination with first-line pemetrexed/cisplatin (PEM/CIS) in phase II of the LUME-Meso study. *First Author: Sanjay Popat, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom*

Background: In the double-blind, placebo-controlled phase II/III LUME-Meso trial, N was combined with up to 6 cycles of PEM/CIS, followed by N monotherapy until progression or toxicity. The primary analysis of phase II showed improved progression-free survival (primary endpoint) with N vs P (hazard ratio (HR) = 0.56; 95% confidence interval (CI): 0.34–0.91; p = 0.017); for overall survival HR = 0.77; 95% CI 0.46–1.29. We evaluated outcomes in the combination and monotherapy phases to understand better the overall study results. **Methods:** Pts with unresectable MPM (ECOG PS 0–1), stratified by histology, were randomized 1:1 to receive $\leq$6 cycles PEM (500 mg/m^2)/CIS (75 mg/m^2) Day 1 + N or P; 200 mg bid, Days 2–21), followed by N or P monotherapy maintenance. TE was analyzed for PEM/CIS, N and P. TB, measured using sum of diameter by modified RECIST 1.0, was analyzed over time, using a mixed-effects model in pts with at least two imaging datapoints. **Results:** 87 pts were randomized: 85 pts (N: 44, P: 41) were treated; 61 pts (N: 34, P: 27) received maintenance; median follow-up was 29 months. Both groups received a median of 6 cycles of PEM/CIS. In the combination phase, greater and longer reduction in TB was seen with N. Average TB reduction from baseline to nadir was 46% greater for N vs P (33.1 vs 22.6 mm). The nadir occurred at 4.1 vs 2.3 months for N vs P. In the monotherapy phase, treatment with N vs P showed markedly slower tumor regrowth from nadir (e.g. +46% vs +112% at 12 months). Median TE (N vs P) was 7.8 vs 5.3 months over the full treatment period. In the monotherapy phase, TE was 5.3 vs 2.8 months. The proportion of pts with serious AEs (N vs P) was similar between treatment groups during combination (34% vs 32%); during monotherapy the rate was 15% vs 26%. **Conclusions:** Pts receiving N had greater, more sustained reduction in TB than those receiving P and remained on active therapy for longer. AEs were manageable in both phases of the trial. Together with the primary study results, these analyses show that combination of N + PEM/CIS followed by N maintenance delivers clinical benefit to pts with MPM. Clinical trial information: NCT01907100.

8567 Poster Session (Board #173), Sun, 8:00 AM-11:30 AM

Long-term survival outcomes of a placebo-controlled phase 3 trial with NGR-hTNF in combination with best investigator choice in relapsed malignant pleural mesothelioma (MPM). *First Author: Vanesa Gregorc, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy*

Background: NGR-hTNF is a vascular-targeting agent able to increase intratumoral chemotherapy penetration and T-cell infiltration by modifying tumor microenvironment. MPM patients failing first-line therapy have limited treatment options. **Methods:** In the phase 3 trial NGR015 (ASCO 2015; abs 7501), 400 patients received single-agent gemcitabine, vinorelbine or doxorubicin ± NGR-hTNF as second-line therapy. By ITT analysis, overall survival (OS) did not differ between arms (median follow-up 18.7 months; data maturity 75%). In subgroup analyses, there was a significant interaction only between treatment and treatment-free interval (TFI) after first-line therapy. NGR-hTNF improved OS and PFS in the short TFI subset (< median: 4.8 months; n = 198). We assessed long-term outcomes in patients with short TFI and prognostic TFI value after adjusting for baseline covariates (age, sex, PS, histology, EORTC score, NLR, response to prior therapy and selected chemotherapy). **Results:** At a median follow-up of 33.8 months (data maturity 86%), a treatment-by-TFI interaction for OS persisted in univariate (p = 0.004) and multivariable models (p = 0.002). In the short TFI subset, median OS was 9.2 months (95% CI 6.6-11.8) for NGR-hTNF vs 6.3 months (5.7-7.0) for placebo (HR 0.67; 0.48-0.93; p = 0.02; adjusted HR 0.64; 0.45-0.89; p = 0.008). Survival rates were 39% (29-50) vs 24% (16-32) at 1 year and 18% (9-26) vs 9% (3-15) at 2 years. The 25% survival rate occurred 7 months later with NGR-hTNF than with placebo (17.3 months vs 10.2 months). NGR-hTNF treatment was associated also with improved PFS (median 3.4 vs 1.9 months; HR 0.66; 0.48-0.91; p = 0.01; adjusted HR 0.65; 0.47-0.90; p = 0.009). In sensitivity analyses, consistent results were found using a 6-month TFI cutoff. The prognostic TFI value was assessed in the control group to avoid confounding effects of experimental treatment. A short TFI independently correlated with worse OS (HR 1.79; 1.29-2.50; p = 0.0006). **Conclusions:** Benefit with NGR-hTNF treatment in the short TFI subgroup was maintained after a 3-year follow-up, deserving a confirmatory randomized trial as these MPM patients have a poor prognosis. Clinical trial information: NCT01098266.

8568 Poster Session (Board #174), Sun, 8:00 AM-11:30 AM

Association between progression-free survival (PFS) rate (PFSR) and overall survival (OS) in LUME-Meso, a study of nintedanib (N) vs. placebo (P) in combination with first-line pemetrexed/cisplatin (PEM/CIS) in patients (pts) with malignant pleural mesothelioma (MPM). *First Author: Nick Pavlakis, Northern Cancer Institute, St Leonards, Sydney, Australia*

Background: We evaluated the relationship between PFSR and OS in the Phase II part of LUME-Meso, a double-blind, placebo-controlled study that showed improved PFS (primary endpoint; hazard ratio [HR] = 0.56; 95% confidence interval [CI]: 0.34–0.91; p = 0.017), for N vs P; for OS HR = 0.77; 95% CI 0.46–1.29. **Methods:** Pts with unresectable MPM (ECOG PS 0–1), stratified by histology (epithelioid/biphasic), were randomized 1:1 to receive ≤6 cycles PEM (500 mg/m^2)/CIS (75 mg/m^2) on Day 1 + N or P (200 mg bid on Days 2–21), followed by N or P monotherapy maintenance. PFSR was defined as the proportion of pts who did not meet criteria for progressive disease (PD) at the specified time point (a 'landmark analysis'). PFSR was assessed at 6 (PFSR6) and 8 (PFSR8) months. The association with OS was then evaluated based on the progression status at the landmark. Pts who died prior to the landmark were excluded from analysis. **Results:** 87 pts were randomized (N: 44; P: 43). The PFSR6 analysis included 71 pts (28 with PD and 43 without PD); subsequently there were 52 deaths. The PFSR8 analysis included 63 pts (32 with PD and 31 without PD); subsequently there were 45 deaths. There were more pts treated with N vs P who had not progressed at 6 (63% vs 37%) and 8 (71% vs 29%) months. Both PFSR6 and PFSR8 predicted OS (HR for PFSR6: 0.19; 95% CI: 0.11–0.35; HR for PFSR8: 0.18; 95% CI: 0.09–0.37). In the PFSR6 analysis, median OS was 22.8 months (95% CI: 15.6–28.4) in pts without PD prior to the landmark vs 6.1 months (95% CI: 3.3–7.0) in pts with PD prior to the landmark. In the PFSR8 analysis, median OS was 23.9 months (95% CI: 15.6–28.4) in pts without PD prior to the landmark vs 5.0 months (95% CI: 3.9–11.6) in pts with PD prior to the landmark. PFSR also predicted OS in pts with epithelioid histology at 6 months (n = 63; HR = 0.19; 95% CI: 0.10–0.36) and at 8 months (n = 57; HR = 0.20; 95% CI: 0.09–0.40). **Conclusions:** In our study in pts with MPM, landmark PFSR at 6 and 8 months predicts OS. These data are consistent with previously published findings. Phase III of LUME-Meso is ongoing (NCT01907100). Clinical trial information: NCT01907100.

8569 Poster Session (Board #175), Sun, 8:00 AM-11:30 AM

A real-world experience of nivolumab in advanced malignant mesothelioma (MM). *First Author: Hussein Hamad, Baylor College of medicine, Houston, TX*

Background: Nivolumab showed promising results in phase II clinical trials for advanced MM patients with good performance status (PS). Limited data exists for poor PS patients treated outside of clinical trial. We report the efficacy and safety in patients enrolled in a Nivolumab expanded-access program (EAP). **Methods:** 27 advanced MM patients were enrolled in EAP and treated from 12/2015 - 12/2017 at Mesothelioma Treatment Center at Baylor College of Medicine. Nivolumab 3 mg/kg was administered every 2 weeks until disease progression. Blinded radiologist assessed responses using RECIST 1.1 criteria. Baseline tumor volumes (BTV) were measured. PD-L-1 expression on tumor samples was quantified by PD-L1 IHC 28-8 pharmDx assay. **Results:** 25 patients were evaluable (2 patients expired before evaluation for response). Median age was 67 years (range 38-89). 72% were male, 56% had PS ≥ 2; epithelioid/ biphasic histologies: 76%/ 24%. Median follow up time was 6 months (range 2-23). 72% received Nivolumab as second line or later therapy. Median progression free survival was 5 months. Response rate was 24% (3 CR, 3 PR); 9 stable disease (SD), disease control rate (DCR) was 60% (CR+PR+SD). Median duration of response 6 months (range 2-24). For patients with PS ≥ 2, DCR was 50%. For patients treated as first line, DCR was 42%. 20 patients had PDL-1 expression evaluated; DCR was 55% in patients (45%) with PDL1 < 1%, and 63% in those with PD L 1 > 1%. Median BTV was 251 cm^3, DCR was 50% for patients with BTV > median and 75% for patients with BTV < median. At 6 months, 52% of patients were alive. Grade 1/2 adverse events (AE) include skin rash (1), body aches/arthritis (2) and enteritis/diarrhea (2). No grade 3/4 AE or treatment related death occurred. **Conclusions:** Nivolumab is effective and safe for MM patients with poor PS. Durable responses were achieved in a subset of patients. Our limited data showed responses regardless of tumor PD-L1 expression. Smaller BTV may predict response but validation of this observation is warranted.

8570 Poster Session (Board #176), Sun, 8:00 AM-11:30 AM

Efficacy and safety of lurbinectedin (PM1183) in small cell lung cancer (SCLC): Results from a phase 2 study. *First Author: Jose Manuel Trigo Perez, Hospital Virgen de la Victoria, Malaga, Spain*

Background: SCLC is a deadly cancer and despite initial 80% response, almost all patients (pts) will relapse and die of this disease. Limited options exist after failure of first line, with a median time to progression (TTP) of around 3.5 months. New therapeutic agents are needed. Lurbinectedin (L) is a new anticancer drug that blocks transcription and induces DNA double-strand breaks, leading to apoptosis. **Methods:** A multicenter phase 2 basket trial to assess the efficacy and safety of L in several types of advanced solid tumors, including SCLC, is ongoing. In the SCLC cohort, 15 adult patients without brain metastases, who had received one prior chemotherapy line, were recruited. If at least one confirmed response was observed, recruitment would be increased to 100 patients. The study intervention comprised L 3.2 mg/m^2 in a 1-hour infusion every 3 weeks. **Results:** 50 pts were treated and evaluable for efficacy. Median age was 60 years (range, 40-83) and 29 (58%) were males. 45 (80%) had an ECOG of 0/1. 34 pts (68%) had metastatic disease at study entry. 25 (50%) pts had a chemotherapy free interval (CTFI) ≥ 90 days and 22 (44%) had a CTFI < 90 days (unknown in 3). Pts received a median of 5 cycles of therapy (range, 1-18) and a median total dose of 15.9 mg/m^2 (range, 2.9-58.2). Nineteen pts (38%) had a partial response (PR); among pts with CTFI ≥ 90 days, 52% (13/25) had a PR. Twenty pts (40%) had disease stabilization, 6 of them for > 4 months. Median response duration was (K-M) 5.3 (CI 95% 2.8-8.8) and median progression free survival (PFS) was 4.2 months (CI 95% 2.8-6.3). Median PFS for pts with CTFI ≥ 90 days was 4.7 months 95% CI (3.1-7.4). Myelosuppression was the most common adverse event: 44% neutropenia grade (G) 3/4, 12% febrile neutropenia, and 8% thrombocytopenia G 3/4; 8 pts had dose delay due to neutropenia G2-4, and 10 pts had dose reduced because of neutropenia G4. G-CSF was given to 9 pts. There was one protocol-defined withdrawal due to neutropenia. **Conclusions:** Lurbinectedin as a single agent shows compelling activity as second line treatment in SCLC, with an acceptable tolerability and manageable safety profile. No unexpected or grade 5 toxicity occurred. Updated results will be presented. Clinical trial information: NCT02454972.

8571 Poster Session (Board #177), Sun, 8:00 AM-11:30 AM

Safety and efficacy of combination olaparib (O) and temozolomide (T) in small cell lung cancer (SCLC). *First Author: Anna F. Farago, Massachusetts General Hospital, Boston, MA*

Background: SCLC is a high-grade neuroendocrine malignancy with overall response rates (ORR) to second-line chemotherapy generally ranging from 10-30%. The poly(ADP-ribose) polymerase (PARP) inhibitor O has activity in SCLC in preclinical studies and may synergize with the alkylating agent T. **Methods:** We performed a single-arm phase 1/2 study of combination O/T in adults with SCLC. Eligibility criteria included histologically/cytologically confirmed incurable SCLC which had progressed following ≥ 1 platinum-based chemotherapy. O (tablet formulation) and T were administered orally on days 1-7 of 21-day cycles at escalating doses using a 3+3 design in the phase 1 portion, followed by a phase 2 expansion at the recommended phase 2 dose (RP2D). Response assessments were performed every 6 weeks. The primary endpoint of the phase 2 portion was ORR. We present data at a planned interim analysis after enrollment of 20 patients at the RP2D. Patient-derived xenografts (PDXs) were generated from a subset of patients prior to O/T and at progression. O/T activity was assessed *in vivo* in PDXs in a co-clinical trial. **Results:** 13 patients were enrolled to 4 escalating dose levels in the phase 1 portion, and 17 additional patients were enrolled at the RP2D, O 200 mg BID and T 75 mg/m2 QD. The median (m) age was 62.0 years (range 39.2-85.2) and m prior lines of therapy was 2 (range 1-7). The most common treatment emergent adverse events (AEs) related to study drugs across dose levels were thrombocytopenia (67%; 23% grade (g) 3-4), anemia (63%; 23% g 3-4), and neutropenia (50%; 47% g 3-4). There was one related g 5 AE due to pneumonia and neutropenia. Among 29 evaluable patients at all dose levels, ORR was 41.4% (95% CI 23.5-59.3), with responses seen in 10/19 and 2/9 platinum-sensitive and -resistant patients, respectively. The mPFS was 87 days (95% CI 48-159), the mOS was 220 days (95% CI 140-308), and the mDOR was 103 days. In PDX models, responses to O/T mirrored those in donor patients, and basal total PARylation was a strong predictive biomarker for sensitivity. **Conclusions:** O/T shows promising clinical activity in SCLC. Further exploration of dosing strategies and biomarkers in patients and PDXs is underway. Clinical trial information: NCT02446704.

8572 Poster Session (Board #178), Sun, 8:00 AM-11:30 AM

Large-scale nationwide genomic screening system for small cell lung cancer in Japan (LC-SCRUM-Japan). *First Author: Yukari Ogawa, Kyorin University Hospital, Mitaka, Japan*

Background: Recent genomic analyses of small-cell lung cancer (SCLC) have provided insights into novel therapeutic targets such as the PI3K pathway. Thus, we prospectively analyzed clinical samples of SCLC using a large-scale nationwide genomic screening project in Japan (LC-SCRUM-Japan) to identify the patients harboring targetable genomic alterations. **Methods:** Submitted tumor samples were subjected to a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay, enabling the simultaneous analysis of 143 (ver.1) or 161 (ver.3) cancer-related genes. **Results:** From July 2015 to January 2018, 544 patients had been enrolled. The median age was 68 years. 76% were male and 95% were smokers. Among 468 samples completed analysis, we identified high prevalence of inactivating TP53/RB1 mutations in 341 (73%) /148 (32%) of cases, respectively. MYC/MYCL1/MYCN amplifications were detected in 18 (4%) /23 (5%) /7 (2%) of cases, respectively. The NGS analysis also showed that 30 (6%) of cases had activating alterations in receptor tyrosine kinase genes: 7 EGFR mutations, 8 KRAS mutations and 15 FGFR1 copy number gains. Mutations in the PI3K pathway were detected in 35 (7%) of the tumors: 13 PIK3CA mutations, 17 PTEN inactivating mutations, 1 AKT mutation and 4 TSC2 inactivating mutations. Among them, 6 cases harboring mutations in the PI3K pathway enrolled in the investigator-initiated phase II study of gedatolisib (UMIN 000020585). Survival data was available in 244 patients receiving platinum-based chemotherapy. Multivariate analysis revealed that the presence of MYC/MYCN amplification or KRAS mutation were significantly associated with poor progression free survival of the first-line chemotherapy (HR, 3.07; 95% CI 1.81 – 5.20; $p < 0.001$) and unfavorable survival (HR; 2.31; 95% CI 1.26 – 4.22; p = 0.007). **Conclusions:** To our knowledge, this is the world's largest prospective genomic screening project for SCLC. This nationwide screening system is helpful for identifying biologically relevant genomic alterations and prognostic prediction in SCLC. This screening program is currently ongoing to screen 800 SCLCs as a final goal. Updated screening results will be presented at the 2018 ASCO Annual Meeting.

8573 Poster Session (Board #179), Sun, 8:00 AM-11:30 AM

Outcomes of EGFR-mutant lung adenocarcinomas (AC) that transform to small cell lung cancer (SCLC). *First Author: Nicolas Marcoux, Massachusetts General Hospital, Boston, MA*

Background: 5-10% of EGFR-mutant ACs undergo SCLC/neuroendocrine transformation (SCLC-T) but the clinical course of such pts is poorly characterized. **Methods:** We identified 50 pts with EGFR-mutant SCLC-T seen at our institutions. Medical records were reviewed retrospectively after IRB approval. Demographics, disease features and outcomes were analyzed. **Results:** Among 50 pts (27F/23M), median (med) age was 55. At diagnosis, 44 had AC histology; 5 had *de novo* SCLC or mixed AC/SCLC. All but the 5 cases with baseline SCLC received ≥1 EGFR TKI prior to SCLC-T; 93% were on a TKI at the time of SCLC-T (24 erlotinib/gefitinib, 5 afatinib, 9 osimertinib, 4 other). Med time from original diagnosis to SCLC-T was 17.8 mo (95% CI 13.0-25.9). 44/50 cases had tissue genotyping at first evidence of SCLC (albeit with varied assays); all maintained their founder EGFR mutation; among 16 with prior T790M-positivity, 13 lost T790M at SCLC-T, 3 were T790M-pos at SCLC-T. Other recurrent mutations included TP53 (24/33, 73%), Rb1 (13/21, 62%) and PIK3CA (10/36, 28%). The most common therapy given upon SCLC-T was platinum-etoposide (n = 35); this regimen had a clinical response rate (cRR) of 51% and med PFS of 2.8 mo (95% CI 2.1-4.8). 20 pts received taxane-based therapy at some point after SCLC-T: cRR = 50%, med PFS = 3.1 mo (95% CI 0.9-3.2). None of 15 pts receiving immunotherapy (including 6 ipi/nivo) for SCLC-T responded. Med OS from stage IV cancer diagnosis was 36.8 mo (95% CI 25.0-41.5) and med OS from time of SCLC diagnosis was 10.9 mo (95% CI 7.3-13.8). **Conclusions:** EGFR-mutant AC with SCLC-T is a rare but recurrent phenomenon, often characterized by Rb1, TP53 and PIK3CA mutations. The SCLC-T subclone is typically distinct from the T790M subclone in pts with serial biopsies. The med OS of 10.9 mo after SCLC-T is similar to newly diagnosed, EGFR wild-type advanced SCLC. Responses to platinum-etoposide and taxanes were frequent but transient, while no responses were seen with immunotherapy. Interestingly, med OS from initial diagnosis was similar to that of pts that never transform to SCLC at 36.8 mo. Further investigation is needed to better elucidate optimal strategies for this group.

8574 Poster Session (Board #180), Sun, 8:00 AM-11:30 AM

Identifying treatment options for SCLC patients with multiplexed clinical proteomic testing. *First Author: Eunkyung An, NantOmics, LLC, Rockville, MD*

Background: Even with standard platinum doublet therapy, most patients with small-cell lung cancer (SCLC) survive < 1 year. For those with refractory or relapsed disease, second-line, single-agent chemotherapy is recommended. Pre-treated SCLC patients can opt for clinical trials of agents such as temozolomide, fluorouracil (5FU), and antibody-drug conjugates (ADC) targeting the proteins DLL3, CD56, or TROP2. Some of these therapies have produced responses in untreated SCLC. To assess the proportions of patients who would be likely to respond to these therapies, we profiled protein targets in clinical tumor biopsies of SCLC using quantitative mass spectrometry. **Methods:** Archived tumor samples from 88 SCLC patients were microdissected and solubilized for proteomic quantification of 58 therapeutically relevant biomarkers. In each sample, quantities of tumor protein were compared with pre-defined thresholds based on evidence from clinical studies or on quantification limits of proteomic assays. Prevalences and protein expression levels in SCLC were compared with those of other cancer indications analyzed in the same clinical laboratory. **Results:** 15 of 83 (18%) SCLC tumors had low or absent MGMT protein expression (< 200 attomoles per microgram [amol/ug]), indicating likely response to temozolomide. 14 of 88 (15%) overexpressed TYMP protein (> 1335 amol/ug), suggesting likely response to 5FU. Except for one patient, likely responders to temozolomide or 5FU were mutually exclusive. Prevalences of quantifiable levels of the ADC markers DLL3, TROP2, and CD56 were 43%, 49% and 97%, respectively. The SCLC tumors expressed a wide range of DLL3 protein (range: 101 – 1201 amol/ug); median expression in SCLC was 2 times higher than in pediatric neurological cancers, while median expression of TROP2 was lower in SCLC than in other indications. CD56 protein levels in SCLC were similar to other indications, but with higher prevalences in SCLC. **Conclusions:** In patients with SCLC, clinical proteomics identified protein targets of multiple approved and investigational therapies.

8575 Poster Session (Board #181), Sun, 8:00 AM-11:30 AM

A phase II study of pembrolizumab and paclitaxel in refractory extensive disease small cell lung cancer. *First Author: YuJung Kim, Seoul National University, Seongnam-si, Korea South*

Background: Patients with platinum refractory extensive disease (ED) small cell lung cancer (SCLC) have a poor prognosis and a little progress have been made. We aimed to investigate the efficacy and safety of pembrolizumab and paclitaxel in these patients. **Methods:** In this phase II, open-label, multicenter study, 26 patients who progressed after etoposide/platinum chemotherapy were enrolled. The patients received paclitaxel 175mg/m2 every 3 weeks for up to 6 cycles. Pembrolizumab 200mg was added from the second cycle and continued until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), safety, and biomarker analysis including programmed death-ligand 1 (PD-L1) expression, next-generation sequencing (NGS), and flow cytometric analysis of peripheral blood immune cells. **Results:** The median age was 68.5 years, and 88% were male. Of the 26 evaluable patients, the ORR was 23.1% (complete response: 3.8%, confirmed partial response [PR]: 19.2%, stable disease: 57.7%, progressive disease 7.7%, not evaluable 11.5%). Including unconfirmed PR, 38.4% responded, and disease control rate was 80.7%. The median PFS and OS were 5.0 months (95% CI, 2.7-6.7) and 9.2 months (95% CI, 6.6-15.1), respectively. Grade 3 or 4 adverse events included febrile neutropenia (8%), neutropenia (8%), asthenia (8%), hyponatremia (8%) and type I diabetes (4%). Four patients showed PD-L1 positivity and no significant difference in PFS was observed according to PD-L1 positivity (5.0 *vs.* 3.9 months, $P = 0.897$). NGS was performed in 12 tumor samples, and we could not find significant differences in mutational load or specific genetic alteration, except for the *MET* copy number gain (PFS 10.5 *vs.* 3.4 months, $P = 0.019$). According to flow cytometric analysis, NK cell activity was significantly lower in responders after 2 cycles of treatment ($P = 0.022$). **Conclusions:** Pembrolizumab and paclitaxel combination therapy showed a moderate activity with an acceptable toxicity in refractory ED SCLC. Further studies are warranted to define a subset of patients who may benefit from the addition of pembrolizumab. Clinical trial information: NCT02551432.

8576 Poster Session (Board #182), Sun, 8:00 AM-11:30 AM

Genomic evolutions in the progression from lung preneoplasia to adenocarcinoma. *First Author: Xin Hu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Carcinogenesis may result from accumulation of genomic and epigenomic aberrations. It has been postulated that atypical adenomatous hyperplasia (AAH), the only recognized pre-neoplasia to lung adenocarcinoma (ADC) may progress to adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and further to frankly invasive ADC. Yet the pathological definition and management of these lesions remain controversial due to lack of sufficient molecular evidences. This aim of this study is to delineate the temporal molecular carcinogenetic events and evolutionary process during the evolution from pre-neoplastic lesions to early-stage adenocarcinoma. **Methods:** We performed multi-regional (2-5 spatially separated regions per lesion) whole exome sequencing and reduced representation bisulfite sequencing to AAH (N = 22), AIS (N = 27), MIA (N = 54) and ADC (N = 13) from 53 patients including 39 patients presenting with multifocal disease and 23 patients carrying more than two different types of lesions. **Results:** Mutation burden progressively increases from AAH to AIS, then to MIA and ADC, with evidence of positive selection of non-silent mutations. APOBEC signature also progressively increases with APOBEC enrichment scores of 0.94 in AAH, 0.99 in AIS, 1.04 in MIA and 1.28 in ADC, ($p = 0.011$). In addition, genomic heterogeneity becomes more complex with neoplastic evolution with tumor allelic frequency-derived median Shannon index. Interestingly, aneuploidy was a common phenomenon in AIS, MIA and ADC, but not in AAH, while allelic imbalance (AI) only became prevalent in MIA and ADC, followed by structural rearrangements in ADC. Phylogenetic analysis revealed varying evolutional processes in different lesions highlighting the substantial heterogeneity even at the preneoplastic states. **Conclusions:** We provide molecular evidence supporting the pathological model of early lung carcinogenesis from AAH, to AIS, MIA and ADC, suggesting progressive genomic evolution at the single nucleotide level during carcinogenesis of lung ADC with macro-evolution at the transition from AAH to AIS and AIS to MIA, possibly driven by ploidy change and allelic imbalance (AI), respectively.

8577 Poster Session (Board #183), Sun, 8:00 AM-11:30 AM

Early assessment of therapy response in small cell lung cancer via longitudinal ctDNA analysis. *First Author: John F. Palma, Roche, Pleasanton, CA*

Background: From the prospective, observational German Lung Cancer Multi-Marker Study we selected the first 72 consecutive small-cell lung cancer (SCLC) patients, UICC-stage IIIB/IV, where plasma samples were available prior to start of therapy, and prior to the second cycle of chemotherapy, and prior to third cycle. We hypothesized that assessment of the level of ctDNA after starting therapy relates to treatment effect and prognosis. **Methods:** We employed AVENIO ctDNA Surveillance Kit, a 197-gene NGS assay, which allowed us to perform longitudinal ctDNA analysis and measure the mutant molecules per milliliter-of-plasma (MMPM), which quantifies ctDNA over all variants of all sequenced genomic regions. All extracted cfDNA samples were processed and sequenced in order of date of blood draw. **Results:** At baseline (b0), we identified variants in all (72/72) subjects to enable ctDNA monitoring. Using serial liquid biopsies from each subject, the mean MMPM at post-first treatment cycle (p1) and the mean MMPM at post-second treatment cycle (p2) were analyzed. We tested a Continuous Responder algorithm, defined by a continuous drop in ctDNA levels represented by mean MMPM reduction over time ($p2 < p1 < b0$), to a mean MMPM below 20 at p2. As a result, continuous responders 26/72 were associated with a better therapy response OS HR = 1.9 (95% CI 1.1 – 3.2, log-rank P = 0.015). The continuous responders demonstrated a median survival benefit of 4.4 months over the poor responders. Neither gender, nor age, nor ECOG, nor stage were predictors of response in the models. **Conclusions:** An early assessment of treatment effect can be measured by mutant molecule counts in the plasma. A decrease in post-treatment ctDNA levels was associated with better prognosis in advanced SCLC.

8578 Poster Session (Board #184), Sun, 8:00 AM-11:30 AM

Association of the high expressions of SOX2 and IGF-1R signaling molecules in thymic epithelial tumors with shorter overall survival. *First Author: Guk Jin Lee, Catholic University of Korea, Bucheon, Korea, Republic of (South)*

Background: Thymic epithelial tumors (TET) are consisted of thymoma(TM) and thymic carcinoma(TC). They are rare heterogeneous tumors with a broad spectrum of clinical characteristics. Although the investigations for potential markers provided some insights into the molecular biology of TET, still there is no established target and biomarker. **Methods:** We performed the gene microarray related to Insulin-like growth factor-1 receptor (IGF-1R) pathway in the fresh tissues (6 TMs and 5 TCs), and validated the analyzed data of expression profile with quantitative measurement of IGF1, IGF2, IGF1R, INSR, SOX2, and OCT-4 mRNA transcripts using RT-PCR. With the tumor tissues collected from 140 TET patients, we constructed the tissue microarray and did immunohistochemistry (IHC) for IGF-1R signaling-related molecules including SOX2, IGF1R, IGF-1, and pAKT. **Results:** The mRNA expressions of SOX2 (216 folds) and IGF-1 (5.2 folds) were notably higher in fresh tumor tissue from TC patients than TM, but no significant differences of IGF-1R, Oct-4, and INSR were found between two tumors. Among 140 TET cases, 111 cases were TM, and 29 cases were TC. The expression level of SOX2 (HR 7.57, $P = 0.001$) and IGF-1 (HR = 9.43, $P = 0.001$) were significantly higher in TC than TM. With analyzing intermolecular correlation between each molecule, there was statistically significant implications between SOX2 and IGF-1, SOX2 and pAKT ($P = 0.021$, $P = 0.026$). In univariate analysis, LDH, clinical TNM staging, WHO classification, SOX2, IGF-1R, IGF-1, and pAKT expression were significantly correlated with overall survival (OS). By multivariate analysis using forward-selection procedure, not only clinical N staging and M staging, but also positive expression of SOX2 and IGF-1 (HR 4.48, $P = 0.001$) were strongly correlated with OS. **Conclusions:** Taken together, our study shows that there are great differences between SOX2 and IGF-1 expressions between thymoma and thymic carcinoma. In thymic epithelial tumors, the expression of SOX2 has a strong relation to IGF-1 expression and their higher expressions are significantly associated with shorter overall survival and more aggressive tumor behavior.

8579 Poster Session (Board #185), Sun, 8:00 AM-11:30 AM

A phase II study of regorafenib in patients with thymic epithelial tumours previously treated with chemotherapy. *First Author: Matteo Perrino, Department of Oncology, Humanitas Research Hospital - Humanitas Cancer Center, Rozzano, Italy*

Background: Angiogenesis has an important role in thymic epithelial tumours (TETs); VEGF, PDGF and PDGFRα are overexpressed in TETs, and VEGF expression and microvessel density are associated with invasiveness and stage. Regorafenib potently inhibits VEGFR1, 2, and 3, TIE2, FGFR and PDGFR-β. The aim of this study is to determine the activity of Regorafenib as monotherapy in patients (pts) with advanced/metatstatic Thymoma (type B2 – B3) (T) and Thymic Carcinoma (TC) previously treated with cisplatin-based chemotherapy. **Methods:** Pts with progressive disease were prospectively enrolled in single arm, phase II trial to receive oral Regorafenib 160 mg once daily 3 weeks on/1 week off until documented disease progression, unacceptable toxicity, or pt refusal. Tumour assessment and safety were asessed every six and three weeks, respectively. This Fleming phase II trial was designed to reject the null hypothesis of a progression free survival (PFS) rate ≤25% with a type I error of 0.10 and a statistical power of 80% at the alternative hypothesis of a PFS rate of ≥50%. The drug should be recommended for further study if 8 or more of the 19 total evaluable pts would be progression free at 2 months. Clinical trial information: NCT02307500. **Results:** Results of the 19 enrolled pts are presented. Pt characteristics are as follow: median age 54 years (range 40;75), male/female 11/8 (58%/42%); T/TC 7/12 (37%/63%), and number of previous lines (1line/≥2lines) of chemotherapy 9/10 (47%/53%). Two pts were not evaluable for response (10.6%). According to RECIST criteria, we observed partial response (PR) in 1 pt (T) (5.3%), stable disease (SD) in 14 pts (9T/5TC) (73.5%), and progressive disease (PD) in 2 pts (1T/1TC) (10.6%), with a disease control rate of 78.8%. Response evaluation with Choi criteria is planned. With a median follow up of 6.4 months (0.9-39.3 months), median PFS was 8.9 months, while median OS was not reached. Thirteen patients were progression free at 2 months. The 1-year PFS rate and 1-year OS rate were 17.9% and 94.4%, respectively. **Conclusions:** The primary end-point of this study was reached. On the basis of PFS and OS results, the efficacy of Regorafenib should be better evaluated in subsequent larger trials. Clinical trial information: NCT02307500.

TPS8580 Poster Session (Board #186a), Sun, 8:00 AM-11:30 AM

Phase II randomized clinical trial comparing immunotherapy plus stereotactic ablative radiotherapy (I-SABR) versus SABR alone for stage I, selected stage IIa or isolated lung parenchymal recurrent non-small cell lung cancer: I-SABR. *First Author: Joe Y. Chang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Stereotactic ablative radiotherapy (SABR), which delivers high biologically effective radiation doses, can kill cancer cells, release tumor-associated antigens, and activate tumor-specific T cells, thereby functioning as a cancer-specific vaccine in situ. The combination of the immune-triggering effects of ionizing radiation with immune check point PD-1inhibitor may leverage the effects of radiotherapy, transforming what was once considered a local therapy to a novel systemic treatment. Further, the combined effects of local control plus systemic control may improve cure rate in early stage NSCLC. **Methods:** This is a randomized phase II trial (NCT03110978) designed to study SABR (biological effective dose > 100 Gy) with or without concurrent and adjuvant Nivolumab for total of 7 doses in early stage or isolated recurrent NSCLC. Inclusion criteria: stage I disease (tumor≤5cm, N0M0) OR selected cases of stage IIa disease (tumor > 5cm but≤7cm, N0M0), including multiple primary tumors, OR isolated lung-parenchymal recurrent or persistent NSCLC suitable for SABR. Tumor tissue / blood/stool samples will be collected before/during/after treatment and at the time of recurrence. Primary endpoints: Event-free survival , secondary malignancy and death; Secondary endpoints: overall survival; toxicity; exploratory analyses of potential predictive markers and immunologic mechanisms of action. Statistical design: It is considered significant with a decrease of the 4-year cumulative event rate from 46% to 23%. Assuming a one-sided type I error rate of 0.05, an accrual rate of 3.5 patients per month, and an additional 20 months of follow-up, a study with 70 patients in each arm will have 85% power to detect an improvement of 23% in 4-year EFS rate. One interim analysis will be done to allow early termination of the trial should evidence at that time reveal that I-SABR is superior to SABR-only or that no difference is found between the two treatment arms. Up to January 2018, 20 of planned 140 patients have been enrolled, met with anticipated enrollment rate. Clinical trial information: NCT03110978.

TPS8581 Poster Session (Board #186b), Sun, 8:00 AM-11:30 AM

EA5142 adjuvant nivolumab in resected lung cancers (ANVIL). *First Author: Jamie E. Chaft, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There have been no advances in the systemic treatment of resected lung cancers in the last decade. In contrast, targeted therapies and immunotherapies have demonstrated benefit in advanced disease. Furthermore, adjuvant immunotherapy after concurrent chemoradiation in locally advanced non-small cell lung cancer (NSCLC) has demonstrated improvement in progression free survival. The role of adjuvant immunotherapy after surgery remains unknown. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) is a National Cancer Institute sponsored National Clinical Trials Network initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of NSCLC. EA5142 is the arm of the ALCHEMIST investigating adjuvant nivolumab in patients not eligible for the *EGFR* or *ALK* directed trials. **Methods:** ALCHEMIST is a clinical trial platform that consists of integrated protocols: ALCHEMIST Screening (A151216; NCT02194738), ALCHEMIST-EGFR (A081105; NCT02193282), ALCHEMIST-ALK (E4512; NCT02201992), and ALCHEMIST-nivo (EA5142; NCT02595944; ANVIL). In ALCHEMIST-Screening, up to 8,000 patients with pathologically confirmed stage IB (≥ 4 cm)-IIIA NSCLC will be enrolled after surgical resection. Tumors that are non-squamous histology will be centrally genotyped for *EGFR* mutations and *ALK* rearrangements. Patients with *EGFR* or *ALK*-positive tumors are offered enrollment in trials evaluating adjuvant erlotinib or crizotinib, respectively. In the ~80% of patients enrolled with tumors that have wildtype *EGFR* and *ALK* or those with squamous histology, central testing will be performed for PD-L1 by immunohistochemistry (DAKO 28-8). Adjuvant chemotherapy and/or radiotherapy is allowed but not required. Patients are randomized to nivolumab versus standard of care observation, stratified by stage, histology, prior adjuvant treatment, and PD-L1 status (≥1% or < 1%). ANVIL is active at over 600 US sites and is actively enrolling. The study statistical plan is to detect co-primary endpoints of a 30% improvement in overall survival and/or a 33% improvement in disease free survival favoring nivolumab. EA5142 design changes under review at CTEP will be presented. Clinical trial information: NCT02595944.

TPS8582 Poster Session (Board #187a), Sun, 8:00 AM-11:30 AM

Nivolumab plus cisplatin/pemetrexed or cisplatin/gemcitabine as induction in resectable NSCLC. *First Author: Nathaniel R. Evans, Thomas Jefferson University, Philadelphia, PA*

Background: For patients (pts) with stage IB (≥4cm)-IIIA Non-small-cell lung cancer (NSCLC), multi-modality therapy yields a modest improvement in 5 year post-surgical overall survival (OS), with comparable benefit for induction and postoperative adjuvant chemotherapy (chemo). Induction can speed the discovery of promising regimens by using pathologic response as a surrogate for OS. About 20% of pts treated with induction chemo have major pathologic response (MPR) (< 10% viable tumor) at primary and lymph nodes while pathologic complete responses (pCR) average 4%. MPR was strongly associated with improved OS (Hellmann MD, Lancet, 2014). PD-1 checkpoint inhibitors (CI), nivolumab (nivo), pembrolizumab (pembro), and the PD-L1 CI, atezolizumab, are established in advanced NSCLC as 2nd line therapy, and pembro is approved as a single agent as 1st line treatment of pts with PD-L1 high expressing tumors. In a phase III 1st line NSCLC study, pts with high mutational burden tumors had superior OS with nivo plus ipilimumab compared to doublet chemo. Pembro plus carboplatin with pemetrexed (P) was approved as 1st line therapy based on a randomized phase II study in advanced NSQ NSCLC showing improved clinical response and PFS compared to chemo alone with no increase in grade III toxicity. We therefore hypothesize that the addition of nivo to induction cisplatin (C) P or C gemcitabine (G) will increase the MPR rate over induction chemo alone compared to historical controls. **Methods:** This is an investigator initiated trial for pts with newly diagnosed clinical stage I-IIIA (stage I ≥ 4cm) SQ and NSQ NSCLC. Induction is C 75mg/m2 IV q 3w x 3 plus either P 500 mg/m2 IV q 3wks x 3 or G 1250mg/m2 IV d1, d8 q 3 wks x 3 plus nivo 360mg IV q 3w x 3. Surgery is planned 3 wks after the last dose. The primary outcome is MPR. Secondary outcomes include safety, pCR, overall clinical response rate, clinical CR, 1 year PFS, OS and exploratory outcomes assessing markers of immune bias. Enrollment will be 34 pts. Clinical trial information: NCT03366766.

TPS8583 Poster Session (Board #187b), Sun, 8:00 AM-11:30 AM

Randomized, double-blind phase 3 study evaluating neoadjuvant platinum-based chemotherapy with perioperative pembrolizumab or placebo in resectable stage IIB or IIIA NSCLC: KEYNOTE-671. *First Author: Hiran C. Fernando, Department of Surgery and Department of Thoracic Oncology, INOVA Fairfax Medical Campus, Falls Church, VA*

Background: Robust and durable antitumor activity was previously demonstrated with pembrolizumab in patients with advanced NSCLC, both as a monotherapy in the first- and second-line settings (in patients with PD-L1 tumor proportion score [TPS] ≥50% and ≥1%, respectively) and when combined with pemetrexed-carboplatin (in patients with nonsquamous histology). KEYNOTE-671 (NCT03425643) is a phase 3 study that evaluates standard neoadjuvant chemotherapy with perioperative pembrolizumab or placebo in early-stage NSCLC. **Methods:** This international double-blind phase 3 trial enrolls patients aged ≥18 years with previously untreated, resectable stage IIB/IIIA NSCLC, ECOG PS 0–1, and tumor samples for evaluation of PD-L1 expression. Patients are randomized 1:1 to neoadjuvant chemotherapy (cisplatin 75 mg/m^2 with gemcitabine 1000 mg/m^2 [days 1 and 8; squamous histology] or pemetrexed 500 mg/m^2 [nonsquamous histology]) combined with either pembrolizumab 200 mg or placebo Q3W for 4 cycles, followed by surgery, then adjuvant pembrolizumab 200 mg or placebo Q3W for 13 cycles. Randomization is stratified by disease stage, PD-L1 TPS < 50% vs ≥50%, squamous vs nonsquamous, and East Asia vs non-East Asia. Radiographic response is assessed 3 weeks after cycles 2 and 4, and every 12 weeks from adjuvant cycle 1 (RECIST v1.1, blinded independent central review). Disease recurrence/progression is confirmed by biopsy. Adverse events are graded per CTCAE v4.0 or later. Primary endpoints are event-free survival (time from randomization to first of disease/local progression, unresectable tumor, local/distant recurrence, or death) and overall survival (time from randomization to all-cause death). Secondary endpoints are major pathological response (≤10% viable tumor cells in resected primary tumor/lymph nodes), pathological complete response (no residual invasive cancer on H&E stained slides of resected lung specimen/lymph nodes post–neoadjuvant therapy), safety, and patient-reported outcomes. An estimated 786 patients will be enrolled, beginning March 9, 2018. Clinical trial information: NCT03425643.

TPS8584 Poster Session (Board #188a), Sun, 8:00 AM-11:30 AM

SAKK 16/14: Anti-PD-L1 antibody durvalumab (MEDI4736) in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC)—A multicenter single-arm phase II trial. *First Author: Sacha Rothschild, University Hospital Basel, Basel, Switzerland*

Background: Improving the outcome of locally advanced non-small cell lung cancer (NSCLC) is one of the major challenges in thoracic oncology. Based on previous trials from the Swiss Group for Clinical Cancer Research (SAKK) neoadjuvant chemotherapy with 3 cycles of cisplatin/docetaxel is an accepted standard of care. Recently, the PACIFIC trial showed significantly improved progression-free survival (PFS) for durvalumab as consolidation therapy after definitive chemoradiotherapy in unresectable stage III NSCLC. Here, we give an update on the ongoing trial and present results from a predefined safety evaluation focusing on 30-day post-operative mortality rate. **Methods:** This is a single-arm phase II clinical trial evaluating the addition of perioperative immunotherapy with durvalumab to the previously established standard of care for stage IIIA(N2) patients. Eligible patients must have pathologically proven NSCLC stage IIIA(N2) (T1-3 N2 M0) according to the 7th edition of the TNM classification, irrespective of histological subtype, genomic aberrations or PD-L1 expression status. Tumor tissue has to be available for the mandatory translational research. Patients whose tumor is deemed resectable at diagnosis receive 3 cycles of chemotherapy with cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 every three weeks followed by two cycles of durvalumab 750 mg every two weeks. Following surgery, patients will be treated with durvalumab 750 mg every two weeks for 12 months. The primary endpoint of the trial is event-free survival at 12 months. Secondary endpoints include OS, objective response, nodal down-staging, complete resection, pattern of recurrence and toxicity. Additionally, a large translation research program accompanies the trial investigating potential predictive biomarkers of anti-PD-L1 therapy. Based on the protocol, a first safety evaluation has been done after the first 25 operated patients. This analysis demonstrated a 30-day post-operative mortality of less than 10%. According to the decision rule described in the protocol the trial thus shall continue as per protocol. Clinical trial information: NCT02572843.

TPS8585 Poster Session (Board #188b), Sun, 8:00 AM-11:30 AM

Phase II trial of atezolizumab before and after definitive chemoradiation for unresectable stage III NSCLC. *First Author: Helen J. Ross, Mayo Clinic, Scottsdale, AZ*

Background: Over 40,000 patients in the US/year are diagnosed with stage III NSCLC, but only ~25% will be cured by standard chemoradiation (CRT). Combining checkpoint inhibition through PD-L1 blockade with CRT may attenuate tumor related immunosuppression via depletion of Tregs and clonal expansion of effector T-cells, thereby improving tumor immunogenicity. Responses to immunotherapy seem to be higher in patients with significant cytoreduction, such as with radiation (RT). Further, CRT may reveal otherwise hidden antigens that can present additional targets to the reconstituting immune system. Whether anti-PD-L1 therapy before CRT will further improve outcomes in this setting is unknown. **Methods:** This phase II single arm Alliance Foundation Trials study (AFT-16, NCT03102242) will evaluate safety and efficacy of atezolizumab before and after definitive CRT. 63 patients with stage III NSCLC, PS 0-1, no active autoimmune disease and no underlying organ dysfunction will be enrolled at 15 US Alliance sites. Treatment consists of 4 cycles of neoadjuvant atezolizumab 1200 mg IV q 21 days with restaging after cycles 2 and 4. Non-progressing patients undergo carboplatin and paclitaxel (C/P) weekly with 60 Gy RT followed by 2 cycles of C/P consolidation followed by atezolizumab to complete one year of therapy. The primary endpoint of this pilot study is disease control rate (CR +PR+SD) after neoadjuvant atezolizumab. Secondary endpoints include ORR, PFS and OS, safety and QoL assessed by the EORTC QLQ-30. Correlatives include the role of PD-L1 and tumor mutation burden as predictive biomarkers. Tumor tissue will be obtained at study entry, and plasma and immune cells will be isolated at study entry, post neoadjuvant atezolizumab, post CRT, during adjuvant atezolizumab and at study end. Additional potential predictive biomarkers will be to define how atezolizumab affects the proportions of immunologic subtypes and immune activation using flow cytometry and T cell receptor immunophenotyping, multiplex immunohistochemistry and cytokine analysis. The trial was activated on 11/1/17. As of 2/13/18, the trial has been opened at 4 centers and 8 patients have been enrolled. Clinical trial information: NCT03102242.

TPS8586 Poster Session (Board #189a), Sun, 8:00 AM-11:30 AM

CONFIRM: A phase III randomized trial to evaluate the efficacy of nivolumab versus placebo in relapsed mesothelioma. *First Author: Dean Anthony Fennell, University Hospitals of Leicester, Leicester, United Kingdom*

Background: Mesothelioma, an incurable, apoptosis-resistant cancer, represents a growing health burden but remains under-researched, with limited treatment options. Despite a significant number of clinical studies in the second line setting, no randomized study has been positive. Early promising signals of activity relating to both PD-L1 and PD-1 targeted treatment in mesothelioma warrant a randomized phase III trial to evaluate the efficacy of nivolumab. **Methods:** CONFIRM is the first ever placebo controlled, randomized phase III trial of a PD-1/PD-L1 immune checkpoint inhibitor in mesothelioma. The primary objective is to determine if nivolumab increases overall survival (OS). Secondary endpoints include progression-free survival; response rate; safety/tolerability; quality of life and cost per QALY. A translational study will determine if sensitivity to nivolumab differs according to PD-L1 expression (subgroups < 1%, 1-49%, ≥50%); and the correlation between OS and mutational burden, estimated by genome-wide analysis of CNAs, and immunotranscriptomic profile. The trial is coordinated by the CRUK Southampton Clinical Trials Unit, within the Centre for Cancer Immunotherapy, UK. The trial aims to recruit 336 patients with pleural or peritoneal mesothelioma who have received at least two prior lines of therapy, from UK sites between March 2017-2021. Current enrolment at 01 Feb 2018 was 63. Patients will be randomized 2:1 (treatment: control), stratified according to epithelioid vs. non-epithelioid, to receive 240mg nivolumab (anti PD-1 antibody) monotherapy or saline placebo as a 30 minute intravenous infusion. Allocation will be double blind. Treatment will be every 14 days until disease progression for max. 12 months. Trial follow up will continue for 6 months after the last participant has progressed, or completed or discontinued treatment. The trial is powered (80% with 2-sided 4% significance level) to detect a hazard ratio of 0.7 using an adjusted Cox regression model (time to event) and will be analyzed using intention-to-treat. This trial is funded by Cancer Research UK (C16728/A21400) and Bristol Myers Squibb (CA 209-841). Trial registrations: NCT03063450, ISRCTN79814141. Clinical trial information: NCT03063450.

TPS8587 Poster Session (Board #189b), Sun, 8:00 AM-11:30 AM

ATLANTIS: Global, randomized phase III study of lurbinectedin (L) with doxorubicin (DOX) vs. CAV or topotecan (T) in small-cell lung cancer after platinum therapy. *First Author: Anna F. Farago, Massachusetts General Hospital, Boston, MA*

Background: Lurbinectedin (L), a synthetic analog of marine-based tetrahydroisoquinolone, blocks active transcription, produces DNA breaks and apoptosis, and affects the inflammatory microenvironment. L showed promising activity in combination with DOX in a phase I cohort of relapsed small cell lung cancer (SCLC) patients (pts) (overall response rate (ORR) = 67%, n = 21, ASCO 2015, abstract 7509). Most common toxicities were hematologic. Lower dose improved safety and confirmed activity in an expanded cohort (ORR = 37%, n = 27 SCLC pts). **Methods:** We present an ongoing multinational (20 countries), multicenter (154 sites), open-label, randomized phase III study of L/DOX *vs.* control arm (investigator choice of either cyclophosphamide, DOX and vincristine (CAV) or topotecan (T)). 600 pts will be randomized (1:1) and stratified according to ECOG performance status (PS), central nervous system (CNS) involvement, previous treatment with antiPD1/antiPD-L1, chemotherapy-free interval, and investigator´s choice of control arm. Interim safety analysis by an independent data monitoring committee (IDMC) is planned when the first 150 pts are randomized. The most relevant inclusion criteria are: age $\geq$18 years; confirmed SCLC diagnosis (if primary site unknown, Ki-67 expression $>$ 50%); previous platinum-containing line (additional immunotherapy allowed); ECOG PS 0-2; adequate major organ function (including LVEF $>$ 50%). Main exclusion criteria include chemotherapy-free interval $<$ 30 days; prior treatment with L DOX or T; symptomatic or steroids-requiring CNS involvement. The primary objective is to determine a difference in progression-free survival (RECIST v.1.1) by independent review committee. Secondary endpoints include overall survival, survival rates at 12/18/24 months, antitumor response, duration of response, quality of life, safety, and pharmacokinetics. The first patient was randomized in August 2016. The pre-planned interim safety analysis was done on November 2017 and the IDMC recommended to continue the trial unmodified. Trial recruitment is expected to be completed in Q2 2018. Clinical trial information: NCT02566993.

TPS8588 Poster Session (Board #190a), Sun, 8:00 AM-11:30 AM

A two-part, open-label, randomized, phase 2/3 study of dinutuximab and irinotecan versus irinotecan for second-line treatment of subjects with relapsed or refractory small cell lung cancer. *First Author: Martin J. Edelman, Fox Chase Cancer Center, Philadelphia, PA*

Background: Small cell lung cancer (SCLC) is characterized by rapid growth and early dissemination to distant sites. Although highly responsive to initial chemotherapy and radiotherapy, most patients relapse within one year of starting treatment (Tx). The outcome for patients with SCLC who relapse or are refractory (RR) to first-line Tx is poor. Topotecan (T) is the only FDA-approved agent for second-line (SL) Tx of platinum-sensitive patients with SCLC. Irinotecan (I) is listed by the National Comprehensive Cancer Network as an alternative agent for second and subsequent lines of therapy. Dinutuximab (D) is a chimeric monoclonal antibody that binds cell surface glycolipid disialoganglioside GD2 and induces tumor cell lysis through antibody-dependent cell-mediated and complement-dependent cytotoxicity. GD2 is expressed in a variety of neuroectoderm-derived tumors, including SCLCs. The potential for combination D and I to improve upon outcomes currently seen with single-agent SL Tx (I or T) in RR SCLC warrants exploration. **Methods:** A two-part, multicenter, open-label, randomized study of D and I versus I alone in subjects with RR SCLC is underway (NCT03098030). Inclusion criteria include documented progressive disease during or RR disease after first-line platinum-based Tx and an Eastern Cooperative Oncology Group performance status of 0 or 1. Subjects who are candidates for re-Tx with original platinum-based regimen as SL Tx will be excluded. Part 1 of the study involved intrasubject (n = 12) dose escalation to evaluate the safety and tolerability of D in combination with I. Part 1 results are to be presented (Edelman et al., European Lung Cancer Congress, 11-14 April 2018). Part 2 of the study is currently enrolling and is designed to determine whether combination D and I prolongs overall survival compared with I alone. Subjects will be randomized 2:2:1 to: I, D and I, or T. Randomization will be stratified by duration of response to prior platinum Tx (relapse-free period $<$ 3 or $\geq$3 months). It is anticipated first data monitoring committee review will occur in April 2018. Clinical trial information: NCT03098030.

TPS8589 Poster Session (Board #190b), Sun, 8:00 AM-11:30 AM

Phase I/II trial of anti-PD-1 checkpoint inhibitor nivolumab and ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate for patients with extensive-stage small cell lung cancer. *First Author: Chul Kim, Georgetown University, Washington, DC*

Background: Small cell lung cancer (SCLC) accounts up to 15% of all new cases of lung cancer. 60% of patients with SCLC present with extensive-stage SCLC (ES-SCLC). Despite initial sensitivity to chemotherapy, patients with ES-SCLC relapse quickly. Studies have shown that somatostatin receptors are expressed in SCLC. ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera) is a ^{177}Lutetium-labeled somatostatin analog that can target somatostatin receptor positive cancer cells. Mounting evidence suggests that radiation therapy can augment the immunogenic response. Based on these findings, we hypothesize that Lutathera and nivolumab, an anti-PD-1 therapy, may have synergistic effects on the generation of anticancer immunity and this combination given as maintenance treatment may delay progression in patients with ES-SCLC. **Methods:** This is a multicenter phase I/II trial of Lutathera and nivolumab in patients with ES-SCLC (NCT03325816). Patients with tracer uptake on gallium-68 dotatate PET scan (NETSPOT) will be eligible. In the phase I part, we aim to determine the recommended phase II dose of Lutathera and nivolumab in patients with relapsed or refractory ES-SCLC, non-progressing ES-SCLC after first-line chemotherapy, or advanced grade I-II pulmonary neuroendocrine tumors. In the phase II part, patients with ES-SCLC are randomly assigned to either maintenance treatment with Lutathera and nivolumab or observation, after completion of front-line chemotherapy. The primary endpoint for the phase II part is progression-free survival (PFS). Crossover is allowed at progression for those in the observation group. Assuming a median PFS of 2 months following first-line platinum-based chemotherapy for ES-SCLC in the observation group, and an expected median PFS of 5 months for the maintenance therapy group (hazard ratio 0.4), a total of 52 patients are required to have 80% power at a two-tailed alpha of 0.05. Seven cancer centers will participate in the trial: Georgetown University, Hackensack University Medical Center, Walter Reed National Military Medical Center, Memorial Sloan Kettering Cancer Center, Vanderbilt University, UCLA, and UCSF. Clinical trial information: NCT03325816.

LBA9000 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. *First Author: Robert M. Jotte, Rocky Mountain Cancer Centers, Denver, CO*

The full, final text of this abstract will be available at abstracts.asco.org at 7:30 a.m. ET on Saturday, June 2, 2018, and in the Annual Meeting Proceedings online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On site at the Meeting, this abstract will be printed in the Monday edition of *ASCO Daily News*.

9001 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Nivolumab (Nivo) + platinum-doublet chemotherapy (Chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumor PD-L1 expression: Results from CheckMate 227. *First Author: Hossein Borghaei, Fox Chase Cancer Center, Philadelphia, PA*

Background: CheckMate 227 (NCT02477826), a phase 3 study of 1L nivo + ipilimumab (ipi), nivo, or nivo + chemo vs chemo in advanced NSCLC, met its co-primary endpoint of prolonged progression-free survival (PFS) with nivo + ipi vs chemo in patients (pts) with tumor mutational burden ≥10 mutations/Mb. Identifying effective tx for pts without known predictive biomarkers remains an unmet need. Prior studies suggest addition of chemo to anti–PD-(L)1 tx can improve outcomes in an unselected pt population, although benefit is most pronounced in pts with higher tumor PD-L1 expression. We report results for nivo + chemo vs chemo in pts with < 1% tumor PD-L1 expression. **Methods:** Pts (n = 550) with chemo-naive, stage IV/recurrent NSCLC, no known sensitizing *EGFR/ALK* mutations, and < 1% tumor PD-L1 expression were stratified by tumor histology and randomized 1:1:1 to nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W, nivo 360 mg Q3W + chemo, or chemo (optional pemetrexed maintenance after chemo for nonsquamous [non-SQ] NSCLC). Pts were treated up to 2 yr. A descriptive analysis was performed for the secondary endpoint of PFS for nivo + chemo vs chemo in pts with < 1% tumor PD-L1 expression. No alpha was allocated for this analysis. **Results:** Baseline characteristics were balanced between nivo + chemo (n = 177) and chemo (n = 186) arms. PFS was improved with nivo + chemo vs chemo (HR = 0.74 [95% CI: 0.58, 0.94]; minimum follow-up 11.2 mo; descriptive comparison). PFS benefit with nivo + chemo was observed across most subgroups. Among histologic subgroups, benefit was more pronounced in non-SQ (HR = 0.68) relative to SQ NSCLC (HR = 0.92). Rates of any grade tx-related adverse events leading to discontinuation were 13% with nivo + chemo and 14% with chemo. **Conclusions:** 1L nivo + chemo improved PFS vs chemo in pts with advanced NSCLC and < 1% tumor PD-L1 expression, and was well tolerated. Results are encouraging in this analysis, which includes only pts with < 1% PD-L1. CheckMate 227 Part 2 (ongoing) is evaluating nivo + chemo vs chemo irrespective of PD-L1 expression and will further inform benefit from this combination across different subgroups of NSCLC. Clinical trial information: NCT02477826.

9002 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. *First Author: Mark A. Socinski, Florida Hospital Cancer Institute, Orlando, FL*

Background: Atezo (anti–PD-L1) inhibits PD-L1 to restore anticancer immunity; bev may enhance atezo efficacy by inhibiting VEGF immunosuppression and promoting T-cell tumor infiltration. IMpower150 is the first randomized Ph 3 trial evaluating atezo + chemo (carboplatin [C] + paclitaxel [P]) ± bev vs CP + bev in 1L NSQ NSCLC. PFS benefit was observed with atezo + CP + bev vs CP + bev regardless of PD-L1 expression. Here we present the IMpower150 interim OS results. **Methods:** 1202 patients (pts) received atezo 1200 mg + C AUC 6 + P 200 mg/m^2 (Arm A) or atezo + CP + bev 15 mg/kg (Arm B) vs CP + bev (Arm C) IV q3w for 4 or 6 cycles per investigator (INV); then maintenance atezo, atezo + bev, or bev, respectively. Co-primary endpoints were INV-assessed PFS in the ITT-WT (*EGFR/ALK* WT) and in WT pts with expression of a tumor T-effector gene signature (Teff-high WT) and OS in the ITT-WT. Data cutoff: 1/22/2018. **Results:** 349, 359, and 337 ITT-WT pts were enrolled in Arms A, B, and C, respectively, with median age 63 y, 62% male, 85% current/previous smokers, and 42% ECOG PS 0. With 13.5 mo min FU, OS was improved in Arm B vs C (HR, 0.78 [95% CI: 0.64, 0.96]; $P = 0.016$) in the ITT-WT; populations of interest are shown in the Table. Arm A vs C OS HR was 0.88 (95% CI: 0.72, 1.08; $P = 0.204$). In all treated patients, Gr 3-4 treatment-related AEs occurred in 43%, 57%, and 49% of pts in Arms A, B, and C, respectively. **Conclusions:** IMpower150 showed a significant OS benefit with atezo + CP + bev vs CP + bev in 1L NSQ NSCLC, and no new safety signals were seen. Clinical trial information: NCT02366143. IC, tumor-infiltrating immune cells; NE, not estimable; TC, tumor cells. [a] WT excludes pts with *EGFR* or *ALK* genomic alterations. [b] Present at baseline. TC1/2/3 or IC1/2/3 = PD-L1+ ≥ 1% of TC or IC; TC0 and IC0 = PD-L1+ < 1% of TC and IC

Arm B vs C OS in populations of interest.

			mOS, mo	
Population	**No. of Pts**	**HR (95% CI)**	**Arm B**	**Arm C**
ITT-WT[a]	696	0.78 (0.64, 0.96)	19.2	14.7
ITT	800	0.76 (0.63, 0.93)	19.8	14.9
***EGFR/ALK*+**	104	0.54 (0.29, 1.03)	NE	17.5
Liver metastases[b]	94	0.54 (0.33, 0.88)	13.2	9.1
Subgroups in ITT-WT				
TC1/2/3 or IC1/2/3	357	0.77 (0.58, 1.04)	22.5	16.4
TC0 and IC0	339	0.82 (0.62, 1.08)	17.1	14.1
Teff-high	285	0.83 (0.59, 1.17)	25.0	16.7
Teff-low	377	0.78 (0.60, 1.02)	17.6	14.3

9003 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Deleterious effect of baseline steroids on efficacy of PD-(L)1 blockade in patients with NSCLC. *First Author: Kathryn Cecilia Arbour, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Treatment with PD-(L)1 inhibitors is now standard therapy for patients with lung cancer. The immunosuppressive effect of steroids may reduce efficacy of PD-(L)1 blockade. On-treatment steroids for treatment of irAEs do not appear to affect efficacy, but the potential impact of baseline steroids at time of treatment initiation is unknown. Clinical trials typically excluded patients receiving baseline corticosteroids leading us to use real-world data to examine the effect of steroids at treatment initiation. **Methods:** We identified 640 PD-(L)1 naïve patients with advanced NSCLC from two institutions (Memorial Sloan Kettering Cancer Center [MSKCC] and Gustave Roussy Cancer Center [GRCC]) treated with single agent PD-(L)1 blockade. Clinical and pharmacy records were reviewed to identify IV or PO steroid use at the time of beginning PD-(L)1 and stratified into two groups: ≥10mg qd prednisone equivalents vs < 10mg/no steroids on Day 1 of PD-(L)1 therapy. Response was evaluated according to RECIST 1.1. Progression free survival (PFS) and overall survival (OS) comparisons were made using log-rank test. Multivariate analyses were performed using Cox proportional hazards model and logistic regression. **Results:** 14% (90/640) received ≥10mg/qd steroids at the start of PD-(L)1 blockade. Common indications for steroids were dyspnea (33%), fatigue (21%), and brain metastases (19%). In both independent cohorts (MSKCC and GRCC), baseline steroids were associated with decreased ORR, PFS, and OS with PD-(L)1 blockade (Table). In the pooled population, after adjusting for smoking history, performance status, and history of brain metastases, baseline steroids remained significantly associated with decreased ORR ($p = 0.05$), PFS ($p = 0.03$), and OS ($p < 0.001$). **Conclusions:** Baseline steroid use of ≥10mg of prednisone was associated with poorer outcome in NSCLC patients treated with PD-(L)1 blockade. Prudent use of steroids at the time of initiating PD-(L)1 blockade is recommended.

	Progression Free Survival		**Overall Survival**		**Best Overall Response**		
Institution	**HR**	**p-value**	**HR**	**p-value**	**+steroids**	**No/low steroids**	**p-value**
MSKCC	1.9	< 0.01	2.7	< 0.01	6%	19%	0.02
GRCC	1.6	0.04	2.5	< 0.01	8%	18%	0.2

9004 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Dacomitinib (daco) versus gefitinib (gef) for first-line treatment of advanced NSCLC (ARCHER 1050): Final overall survival (OS) analysis. *First Author: Tony Mok, State Key Laboratory of South China, Department of Clinical Oncology, Chinese University of Hong Kong, Hong Kong, China*

Background: In the ongoing phase 3 ARCHER 1050 study, first-line treatment with daco significantly improved the primary endpoint of progression-free survival, duration of response, and time to treatment failure vs gef in patients (pts) with epidermal growth factor receptor (*EGFR*) mutation-positive advanced non-small cell lung cancer (NSCLC) (Wu et al, *Lancet Oncol*, 2017). Here, we present the OS results. **Methods:** Pts with newly diagnosed stage IIIB/IV or recurrent NSCLC harboring an *EGFR* mutation (exon 19 del or exon 21 L858R ± exon 20 T790M) and without central nervous system metastasis were randomized 1:1 to oral daco 45 mg/day or oral gef 250 mg/day. Pts were stratified by race and *EGFR* mutation type. **Results:** As of 17 February 2017, a total of 220 deaths (48.7%) occurred over a median follow-up of 31.3 months (mo): 103 (45.4%) in the daco arm (n = 227) and 117 (52.0%) in the gef arm (n = 225). Daco showed a significant improvement in OS compared to gef (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.582–0.993; 2-sided $P = 0.044$ based on stratified analysis). Median OS (95% CI) was 34.1 mo (29.5–37.7) with daco vs 26.8 mo (23.7–32.1) with gef. Survival rates at 30 mo were 56.2% with daco and 46.3% with gef. The table shows preliminary OS subgroup analyses by race and *EGFR* mutation type, with >55% of pts being censored in some subsets. OS subgroup analyses were consistent with the primary OS analysis across most baseline characteristics. **Conclusions:** In pts with advanced *EGFR* mutation-positive NSCLC, daco is the first to show a significant improvement in OS in a phase 3 trial compared with a standard-of-care tyrosine kinase inhibitor. Daco should be considered as one of the standard treatment options for these pts. Clinical trial information: NCT01774721.

	Daco (n = 227)		Gef (n = 225)			
	n	Median OS, mo (95% CI)	n	Median OS, mo (95% CI)	Daco vs Gef, HR (95% CI)	2-Sided *P* Value
Race						
Non-East Asian	57	29.5 (20.7–NR)	49	20.6 (16.1–25.5)	0.721 (0.433–1.201)	0.2073
Asian	170	34.2 (30.1–NR)	176	29.1 (25.2–NR)	0.812 (0.595–1.108)	0.1879
***EGFR* mutation status at randomization**						
Exon 19 del	134	34.1 (30.1–NR)	133	NR (25.0–NR)	0.880 (0.613–1.262)	0.4862
Exon 21 L858R	93	32.5 (25.5–NR)	92	23.2 (19.6–28.6)	0.707 (0.478–1.045)	0.0805

NR, not reached

9005 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). *First Author: Atsushi Nakamura, Sendai Kousei Hospital, Sendai, Japan*

Background: Although EGFR-TKI alone has been a standard first-line treatment for pts with advanced NSCLC with EGFR mutations, our phase II study (NEJ005) showed promising efficacy of GCP. NEJ009, an open-label, randomized phase III study, was conducted to evaluate the superiority of GCP vs G in progression-free survival (PFS), PFS2, and overall survival (OS). **Methods:** Pts with newly diagnosed stage III/IV/ recurrent NSCLC harboring an EGFR activating mutations (exon 19 deletion or exon 21 L858R) were randomized 1:1 to G 250 mg PO QD or GCP (G 250mg PO QD combined with carboplatin AUC 5 + pemetrexed 500mg/m2, every 3 weeks). The primary endpoints consisting of PFS, PFS2, and OS were sequentially analyzed according to a preplanned gate-keeping method. Secondary endpoints included objective response rate, safety, and quality of life. **Results:** In September 2017, a preplanned required number of events of PFS2 was observed. The ITT population included 344 pts with baseline characteristics fairly well balanced between the arms. Although GCP demonstrated significantly better PFS compared to G, there was no difference in PFS2 between the arms as below. Additional OS analysis (G:101 events vs GCP:83 events) revealed that median survival time of GCP was much longer than that of G (52.2 months vs 38.8 months, HR:0.695, p = 0.013). **Conclusions:** NEJ009 was the first phase III study which evaluated the efficacy of a combination of EGFR-TKI and platinum doublet chemotherapy in untreated advanced NSCLC pts with EGFR mutations. Although GCP regimen failed to demonstrate its superiority in PFS2, it may increase long survivors. ITT Population GCP (N = 169) G (N = 172) Median (months) Median (months) HR PFS 20.9 11.2 0.493 [95%CI: 18.0, 24.2] [95%CI: 9.0, 13.4] [95%CI: 0.390, 0.623] P < 0.001 PFS2 20.9 21.1 0.891 [95% CI: 18.0, 24.2] [95%CI: 17.9, 24.9] [95%CI: 0.708, 1.122] P = 0.806.

9006 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Phase III study comparing bevacizumab plus erlotinib to erlotinib in patients with untreated NSCLC harboring activating EGFR mutations: NEJ026. *First Author: Naoki Furuya, Division of Respiratory Medicine, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan*

Background: Development of treatment for EGFR-mutated non-small-cell lung cancer (NSCLC) had been focused on monotherapy of gefitinib, erlotinib, or afatinib. Combinations of EGFR-TKIs and VEGF inhibitors are one of candidates for next strategy for EGFR-mutated tumor. We conducted a phase III study comparing BE to E. **Methods:** Chemotherapy-naïve pts with advanced non-squamous NSCLC harbouring EGFR-mutation were randomly assigned to receive either combination with erlotinib (150 mg daily) plus bevacizumab (15 mg/kg iv q3w) or erlotinib (150 mg daily). Status of EGFR mutations in plasma samples were monitored routinely during the study treatment and a second-line treatment. The primary endpoint was PFS. Secondary endpoints were OS, RR, safety, and QoL. We hypothesized that hazard ratio of PFS was 0.63. It was estimated that 147 events would be needed for the study to have a power of 80% and a two-sided significance level of 5%. Accordingly, this study was planned to enroll 214 pts in total. **Results:** Between Jun 3, 2015, and Aug 31, 2016, 228 pts with EGFR mutations were enrolled. There were one cessation prior to the study treatment and one withdrawal of consent; the remaining 226 pts were assigned to BE (n = 112) and E (n = 114). The interim analysis preplanned was performed at 117 PFS events using full analysis set of 224 pts except for both an ineligible case and a case lost to follow-up in E. Pts were followed up for a median of 12.4 months. The interim analysis showed that the study met its primary endpoint. At data cutoff (Sept 21, 2017), median PFS was 16.9 months (95% CI 14.2-21.0) in BE and 13.3 months (11.1-15.3) in E (p = 0.0157) (HR 0.605, 95% CI 0.417-0.877). Though hemorrhage, proteinuria, and hypertension as toxicities significantly increased in BE compared to in E, there was no significant difference among other toxicities between BE and E. Five cases had low-grade pneumonitis in E but no pneumonitis in BE. There was no treatment-related death. **Conclusions:** In this study, BE as a combination of EGFR-TKIs and VEGF inhibitors achieved durable response and good tolerability. This regimen is considered as a new standard treatment in EGFR-mutated NSCLC. Clinical trial information: UMIN000017069.

9007 **Oral Abstract Session, Mon, 3:00 PM-6:00 PM**

Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive non-squamous non–small-cell lung cancer (NSCLC): Survival follow-up results of JO25567. *First Author: Noboru Yamamoto, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: In JO25567 (Clinical trials registry number. JapicCTI-111390), EB significantly prolonged progression-free survival (PFS) in patients with NSCLC with activating EGFR mutation compared with E alone. Overall survival (OS) data were immature at the cutoff date for the primary analysis (Seto T et al. Lancet Oncol. 2014;15:1236-44.). We conducted survival follow-up of the patients in JO25567. **Methods:** JO25567 was open-label randomized trial. Patients with stage 3b/4 or recurrent non-squamous EGFR mutation–positive NSCLC and no previous chemotherapy were randomly allocated to receive EB (E, 150 mg/day; B, 15 mg/kg every 3 weeks) or E (150 mg/day) until disease progression or unacceptable toxicity. Primary endpoint was PFS. To conduct this follow-up, written informed consents were obtained from alive patients. JO25567 data of the patients who were not enrolled into this follow-up due to death or lost to follow-up were also included into this analysis. **Results:** From 152 patients in JO25567 (EB, n = 75, E, n = 77), 52 patients had died and 25 patients were lost to follow-up at the start of this follow-up. Seventy-five patients (EB, n = 35; E, n = 40) were enrolled between June and October 2014. As of the data cut-off date of 31 October 2017, median OS from random assignment was 47.0 months for EB and 47.4 months for E (HR, 0.81; 95% CI, 0.53-1.23; log-rank $p = 0.3267$). Forty OS events (53.3%) had occurred in EB and 49 events (63.6%) in E. Five-year survival rate was 41% in EB and 35% in E. There were no major difference of OS between patient characteristics. Sixty-four patients (85.3%) in EB and 65 patients (84.4%) in E received post-study treatments. **Conclusions:** The median OS around 4 years were observed in both arms. There was a slight trend of survival improvement in EB than E alone, however, the significant difference of PFS was not directly translated into the difference of OS between these treatments. Clinical trial information: JapicCTI-142569.

9008 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Avelumab (anti–PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: Phase 1b results from JAVELIN Lung 101. *First Author: Alice Tsang Shaw, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: ALK tyrosine kinase inhibitors (TKIs) are standard of care for patients (pts) with advanced ALK+ NSCLC, and preclinical data suggest potential synergistic activity with checkpoint inhibitors in NSCLC irrespective of ALK status. Avelumab is a human anti–PD-L1 IgG1 monoclonal antibody approved in various countries for treatment of metastatic Merkel cell carcinoma, and in the US for advanced urothelial carcinoma that has progressed following platinum therapy. We report initial results from JAVELIN Lung 101 (NCT02584634), a phase 1b/2 dose-finding trial of avelumab + crizotinib (A+C) or the next-generation ALK TKI lorlatinib (A+L) in pts with advanced/metastatic ALK-negative/wildtype (ALK−) or ALK+ NSCLC, respectively. **Methods:** In phase 1b, pts with previously treated ALK− NSCLC received A (10 mg/kg Q2W) + C (250 mg BID) while pts with ALK+ NSCLC received A (10 mg/kg Q2W) + L (100 mg QD) (starting dose levels in each group). The primary endpoint was dose-limiting toxicities (DLTs); secondary endpoints included adverse events (AEs) and objective responses. **Results:** At data cutoff on Oct 27, 2017, 12 ALK− pts had received A+C and 28 ALK+ pts had received A+L. All ALK− pts had received prior anticancer therapy; ALK+ pts had received a median 2 prior ALK TKIs (range 1-3; data not reported for 1 ALK+ pt). DLTs occurred with A+C in 5 ALK− pts (41.7%): ALT and AST increase (2 pts each), febrile neutropenia, hepatitis, QT prolongation, and rash (1 pt each). No DLTs occurred with A+L in ALK+ pts. Grade ≥3 AEs of any causality occurred with A+C in 7 ALK− pts (58.3%; most common [≥10%] was ALT increase [16.7%, n = 2]), and with A+L in 15 ALK+ pts (53.6%; most common were hypertriglyceridemia [14.3%, n = 4] and GGT increase [10.7%, n = 3]). The confirmed objective response rate with A+C in ALK− pts was 16.7% (95% CI, 2.1-48.4; partial response [PR] in 2 pts), and with A+L in ALK+ pts was 46.4% (95% CI, 27.5-66.1; PR in 12 pts; complete response in 1 pt). **Conclusions:** A+L showed an acceptable safety profile, distinct from A+C, and promising antitumor activity in pts with ALK+ NSCLC, and will be evaluated in treatment-naive pts in phase 2. Clinical trial information: NCT02584634.

9009 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Safety and clinical activity results from a phase Ib study of alectinib plus atezolizumab in *ALK*+ advanced NSCLC (aNSCLC). *First Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, Korea, Republic of (South)*

Background: Alectinib has proven systemic and CNS efficacy in patients (pts) with *ALK*+ aNSCLC (ALEX study). Tumor cell death caused by alectinib may release antigens broadening the potential anti-tumor T cell response. The monoclonal antibody atezolizumab (atezo) releases T cell suppression by inhibiting PD-L1 binding and improves OS in second-line NSCLC treatment. We hypothesized atezo in combination with alectinib would lead to enhanced efficacy. **Methods:** This phase Ib enrolled treatment-naïve pts with *ALK*+ aNSCLC regardless of PD-L1 status, including pts with untreated asymptomatic brain metastases. Pts received alectinib 600 mg PO BID for 7 days (safety evaluation), followed by alectinib 600 mg PO BID with atezo 1200 mg IV q3w (expansion stage) until progression or unacceptable toxicity. The primary objective was to evaluate the safety and tolerability of the combination. Secondary objectives included evaluation of tumor response (ORR) per RECIST v1.1. **Results:** At cut-off (18 August 2017) 21 pts (safety stage n = 7; expansion stage n = 14) who received ≥1 dose of alectinib or atezo were considered safety evaluable. Median age was 53 years. Incidence of grade 3 and serious adverse events (AEs) were 62% (52.4% treatment-related) and 33%, respectively. No grade 4–5 AEs were reported. Four pts (19%) discontinued atezo and 2 pts (10%) discontinued alectinib due to AEs. 14 pts (67%) had alectinib dose interruptions/modifications. No dose-limiting toxicities were observed. At a median follow up of 13 months, (1–22), ORR was 81% (95% CI 58.1–94.6); median progression-free survival was 21.7 months (95% CI 10.3–21.7), median duration of response was 20.3 months (95% CI 11.5–20.3), however, only 6 pts had progressed at the time of data cut-off. On-treatment CD8+ T-cell increase was observed post-alectinib run-in. **Conclusions:** Combination of full dose alectinib and atezo appears to have an acceptable safety profile with no new safety findings for either agent. Early efficacy results are encouraging but further follow-up is needed to define the role of this combination in pts with treatment-naïve *ALK*+ NSCLC.

9010 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget). *First Author: Julien Mazieres, Hôpital Larrey, Centre Hospitalier Universitaire Toulouse, Toulouse, France*

Background: Data on ICI activity in patients with oncogenic driver are limited. The aim of this study was to collect further data across various molecular subgroups. **Methods:** We conducted a retrospective multicenter study of patients receiving ICI for stage IV NSCLC with genomic alterations. Anonymized data were evaluated for clinicopathologic characteristics and outcomes: best response (RECIST v1.1), progression-free survival (PFS) and overall survival (OS) from ICI initiation. **Results:** We included 527 patients treated in 25 centers The. Molecular alterations involved *KRAS* (n = 252), *EGFR* (n = 110), *BRAF* (n = 38), *MET* (n = 36), *HER2* (n = 23), *ALK* (n = 18), *RET* (n = 14), *ROS1* (n = 5), and multiple drivers (n = 31). Median age was 60 years, sex-ratio was 1:1, never/former/current smokers were 27/51/22%, and the majority of tumors were adenocarcinoma. ICIs were mainly anti-PD1 (92%) given in the first (5%), second (42%), third (26%), or later line (27%) settings. The best response rate was 19% [15-22%]. The median PFS and OS were 2.8 [2.5-3.1] and 13.3 [9.8-14.8] months, respectively. Outcomes by molecular subtypes are reported below (table 1). *EGFR*-mutant had shorter PFS compared to *KRAS*-mutant ($p < 0.001$). T790M mutation was associated with a shorter PFS than other *EGFR* mutations ($p = 0.0001$) whereas the benefit was the same across all *KRAS* mutation subtypes. Among MET alterations, exon 14 mutations were the most sensitive to ICI. PFS was positively influenced by smoking ($p = 0.003$) and PDL1 expression ($p = 0.02$) in the overall population but not for EGFR-mutant. **Conclusions:** ICI has inconstant efficacy in NSCLC harboring activating mutation. KRAS, BRAF and MET-exon 14 patients derive a greater benefit than EGFR, ALK and RET patients.

		Best response (%)			PFS			OS
Driver	n	CR/PR	SD	PD	Median (months*)	6 m PFS (%)	1 y PFS (%)	Median (months*)
BRAF	38	28.1	28.1	43.8	3.0	35	19	13.6
KRAS	252	27.2	23.1	49.8	3.2	39	26	13.5
ROS1	5	20	0	80	NA	NA	NA	NA
MET	36	15.6	34.4	50.0	3.4	33	23	18.4
EGFR	110	11.0	18.0	71.0	2.0	16	6	8.8
HER2	23	9.5	28.6	61.9	3.5	34	17	10.0
RET	14	7.1	21.4	71.4	2.2	16	8	6.5
ALK	18	0	21.4	78.6	2.1	16	8	17.0

**: from ICI initiation. CR/PR : Complete/Partial response, SD/PD Stable/Progressive disease.*

9011 Clinical Science Symposium, Fri, 4:30 PM-6:00 PM

Response and durability of anti-PD-(L)1 therapy in never- or light-smokers with non-small cell lung cancer (NSCLC) and high PD-L1 expression. *First Author: Justin F. Gainor, Massachusetts General Hospital, Boston, MA*

Background: PD-1 blockade is now standard first-line therapy for patients (pts) with advanced NSCLC and a PD-L1 tumor proportion score (TPS) ≥50%. Tumor mutation burden (TMB) is also a biomarker of response to PD-1 blockade and correlates with smoking status in patients with NSCLC. Never/minimal smokers usually have low TMB and diminished response to PD-1 blockade. The impact of high PD-L1 expression on response to PD-1 blockade among never- or light-smokers has not been well studied. **Methods:** We retrospectively identified pts with NSCLC at 3 centers who were never- or light-smokers (≤10 pack years) and had received PD-(L)1 blockade. High PD-L1 expression was determined using commercially-available (22C3 or 28-8) or institutional laboratory developed tests (E1L3N) and defined as TPS ≥50%. A subset of pts underwent hybrid-capture NGS of 341-468 genes (MSK-IMPACT) to determine TMB. **Results:** We identified 52 light- (56%) or never-smokers (44%) with TPS ≥50% who received PD-(L)1 blockade in the first- (63%), second- (21%) or ≥third-line (15%) setting. Oncogenic driver mutations included KRAS (21%), EGFR (12%), BRAF (7%), RET/HER2/MET (4% each). Among 21 pts with MSK-IMPACT testing, median TMB was expectedly low (4.1 mutations/Mb). Objective responses were observed in 16 (ORR 31%) pts, including 6 (ORR 26%) never-smokers. The median duration of response (DOR) was 5.6 months (range 1-23+). Median progression-free survival and overall survival were 3.0 months (95% CI 2.2-5.1 months) and 16.4 months (95% CI 10.7-18.7 months), respectively. **Conclusions:** In never- or light-smokers with advanced NSCLC and high PD-L1 expression, PD-(L)1 blockade is associated with a moderate objective response rate; however, the durability of this activity appears diminished compared to historical controls. The immunobiologic features determining initial response versus durability of benefit to PD-(L)1 blockade may be distinct.

9012 Poster Discussion Session; Displayed in Poster Session (Board #335), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Combination of gefitinib and olaparib versus gefitinib alone in EGFR mutant non-small-cell lung cancer (NSCLC): A randomized phase 2 study (GOAL, Spanish Lung Cancer Group). *First Author: Rosario Garcia Campelo, Medical Oncology Service, University Hospital A Coruña (XXIAC-SERGAS), A Coruña, Spain*

Background: Low BRCA1 mRNA levels correlate with longer progression free survival (PFS) in erlotinib treated EGFR mutant NSCLC patients (p), while risk of shortened PFS was associated with intermediate/high BRCA1 levels (HR, 8.46; P<0.0001). We explored the combination of the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib with gefitinib in EGFR mutant NSCLC p. In a previous phase 1 trial, the safety of the combination was confirmed. Recommended phase 2 dose (RP2D) is gefitinib, 250 mg daily, and olaparib, 200 mg thrice daily. **Methods:** Stage IV treatment naïve NSCLC p with centrally confirmed EGFR mutations and measurable disease were recruited in the study (NCT01513174). We randomly allocated p (1:1) to receive gefitinib 250 mg daily or the combination at the RP2D. The primary endpoint was PFS. PFS related to BRCA1 mRNA was a secondary endpoint, and 53BP1 and enhancer of zeste homolog 2 (EZH2) were analyzed as modulators of BRCA1, overall survival (OS), response rate (RR), safety and tolerability. Target accrual was 186 p. This sample provided 80% power to detect HR of 0.63 after 116 PFS events. The first PFS analysis, side effect profile and RR had a February 28th, 2018 cut-off, minimum follow-up of 18 months (mo). **Results:** Of the 182 p who underwent randomization, 91 received gefitinib and 91 received gefitinib+olaparib, with no differences in gender, age, never smoker, performance status, bone or brain metastases or EGFR mutation. Median PFS for exon 19 deletions and exon 21 L858R EGFR mutations was 10.4 mo for gefitinib group and 12.8 mo for gefitinib + olaparib group (HR for disease progression or death, 0.83; P=0.329). RR was 68% in gefitinib group and 78% in gefitinib + olaparib group. **Conclusions:** The gefitinib+olaparib combination did not provide significant benefit over gefitinib alone. Median PFS was 2.4 mo longer for the combination and risk of disease progression or death was 17% lower with gefitinib+olaparib than gefitinib alone. The pre-specified assessment of BRCA1, 53BP1 and EZH2 could determine if a subgroup of p might obtain major benefit from the combination. Clinical trial information: NCT01513174.

9013 Poster Discussion Session; Displayed in Poster Session (Board #336), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Combination of metformin plus TKI vs. TKI alone in EGFR(+) LUNG adenocarcinoma: A randomized phase II study. *First Author: Oscar Gerardo Arrieta Rodriguez, Instituto Nacional de Cancerologia (INCan), Mexico City, Mexico*

Background: Metformin has been shown to have antitumor activity by increasing AMPK through different mechanisms involving tumor suppressor gene, LKB1. LKB1 inactivation is common in Non-small cell lung cancer (NSCLC) and is associated with a more aggressive clinical phenotype. Retrospective studies have shown that metformin could effectively increase the sensitivity to TKIs in NSCLC, thus improving Progression Free Survival (PFS) and potentially impacting Overall Survival (OS) in these patients. We compared the effect of metformin in combination with EGFR-TKI versus TKIs alone on the clinical prognosis of adenocarcinoma patients with *EGFR* mutations. **Methods:** In this phase 2 clinical trial (NCT03071705) we randomly assigned 116 patients with stage IV *EGFR*-mutated lung adenocarcinoma to receive therapy with metformin + EGFR-TKI (M+TKI) (n = 49) or EGFR-TKI (TKI) alone (n = 67). TKI was chosen upon clinician´s discretion. Patients were excluded if they had a history of diabetes or had received therapy with metformin or TKIs (> 2 cycles) previous to enrollment. The primary endpoint was PFS, secondary endpoints included objective response rate (ORR), disease control rate (DCR) and OS. **Results:** Baseline characteristics were well balanced between treatment arms. Mean patient follow up was 12.9 (±10.9) months. Median PFS was significantly longer for patients receiving M+TKI compared to those who received TKI (14.0 months vs. 10.0 months; p = 0.017) . ORR was higher in the experimental arm of the trial, compared to the control group (67.4% vs. 47.5%; p = 0.044), although, the DCR was similar in the two groups (97% vs. 88.5%; p = 0.085). Median OS was 24.8 months. Patients receiving M+TKI had a longer OS compared to those receiving TKI (27.2 months vs. 19.0 months, p = 0.015). Multivariate analysis showed that, among others, the therapeutic arm (M+TKI vs. TKI) is an independently associated factor for both PFS and OS. **Conclusions:** Our study strongly suggests that the addition of Metformin to standard EGFR-TKI therapy has a significant effect in PFS, ORR and OS of patients with *EGFR*-mutated NSCLC. Metformin use is a safe and efficacious addition to the therapeutic scheme of *EGFR*+ NSCLC. Clinical trial information: NCT03071705.

9014 Poster Discussion Session; Displayed in Poster Session (Board #337), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor (TKI) naïve patients with advanced NSCLC. *First Author: Aaron Elliott Lisberg, UCLA, Los Angeles, CA*

Background: Despite the significant antitumor activity of pembrolizumab in non-small cell lung cancer (NSCLC), clinical benefit has been less frequently observed in patients whose tumors harbor epidermal growth factor receptor (*EGFR*) mutations compared to *EGFR* wild-type patients. Our single center experience on the KEYNOTE-001 trial suggested that pembrolizumab-treated EGFR-mutant patients, who were tyrosine kinase inhibitor (TKI) naïve, had superior clinical outcomes to those previously treated with a TKI. As TKI naïve EGFR-mutants have generally been excluded from pembrolizumab studies, data to guide treatment decisions in this patient population is lacking, particularly in patients with PD-L1 expression ≥50%. **Methods:** We conducted a phase II trial (NCT02879994) of pembrolizumab in TKI naive patients with *EGFR* mutation positive, advanced NSCLC and PD-L1 positive (≥1%, 22C3 antibody) tumors. Pembrolizumab was administered 200mg q3wks. The primary endpoint was objective response rate. Secondary endpoints included safety of pembrolizumab, additional pembrolizumab efficacy endpoints, and efficacy and safety of an *EGFR* TKI after pembrolizumab. **Results:** Enrollment was ceased due to lack of efficacy after 11 of 25 planned patients were treated. 82% of trial patients were treatment naïve, 64% had sensitizing *EGFR* mutations, and 73% had PD-L1 expression ≥50%. Only 1 patient had an objective response (ORR: 9%), but repeat analysis of this patient's tumor definitively showed the original report of an *EGFR* mutation to be erroneous. Observed treatment related adverse events were similar to prior experience with pembrolizumab, but two deaths within 6 months of enrollment, including one attributed to pneumonitis, were of concern. **Conclusions:** Pembrolizumab's lack of efficacy in TKI naïve, PD-L1+, EGFR-mutant patients with advanced NSCLC, including those with PD-L1 expression ≥50%, suggests that it is not an appropriate therapeutic choice in this setting. Clinical trial information: NCT02879994.

9015 Poster Discussion Session; Displayed in Poster Session (Board #338), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

First report of safety, PK, and preliminary antitumor activity of the oral EGFR/HER2 exon 20 inhibitor TAK-788 (AP32788) in non–small cell lung cancer (NSCLC). *First Author: Robert Charles Doebele, University of Colorado Cancer Center, Aurora, CO*

Background: TAK-788 is an investigational TKI with potent, selective preclinical activity against activating EGFR and HER2 mutations, including exon 20 insertions. We report the first results of a phase 1/2 first-in-human, open-label, multicenter study of TAK-788 (NCT02716116). **Methods:** Pts with advanced NSCLC refractory to standard therapy received daily oral doses (5–120 mg) of TAK-788 in the ongoing dose-escalation phase (3+3 design). Preliminary antitumor activity (by RECIST v1.1), safety, and PK are reported for pts receiving ≥1 dose. **Results:** As of 8 September 2017, 34 pts (median age, 60 y; female, 65%; ≥2 prior anticancer therapies, 88%; Table) were treated and 10 remain on TAK-788 at data cutoff. $AUC_{0\text{-}24,ss}$ increased in a dose-proportional manner over the dose range with effective $t_{1/2}$ of ~16 (range 6–28) h. Most common treatment-emergent AEs (TEAEs; ≥20% of pts): diarrhea (47%), nausea (26%), fatigue (21%). Grade ≥3 TEAEs in ≥2 pts (excluding disease progression): dyspnea (n = 3, 9%); anemia, asthenia, dehydration, lung infection, pleural effusion, pneumonia, pneumonitis (n = 2 each, 6%). Two DLTs, both pneumonitis, were reported (80 mg, grade 3; 120 mg, grade 5). Of 14 evaluable pts, 3 had PR (80 mg, n = 2, both confirmed; 120 mg, single PR awaiting confirmation), 6 had SD (40 mg, n = 3; 80 mg, n = 2; 120 mg, n = 1), and 5 had PD as best response (40 mg, n = 3; 80 mg, n = 1; 120 mg, n = 1); all pts with PR or SD had EGFR exon 20 insertions. **Conclusions:** TAK-788 exhibits antitumor activity in pts with EGFR exon 20 insertions with an AE profile consistent with other EGFR TKIs. Phase 2 will begin after determination of the RP2D, with 4 molecularly defined cohorts in NSCLC.Clinical trial information: NCT02716116.

Baseline characteristics.

	5 mg (n = 4)	10 mg (n = 5)	20 mg (n = 5)	40 mg (n = 6)	80 mg (n = 7)	120 mg (n = 7)	Total (n = 34)
Mutation type,[a] %							
Common EGFR mutations (exon 19 deletion / L8585R)	25	20	0	0	0	0	6
EGFR-T790M+	0	0	0	0	14	0	3
EGFR exon 20 insertion	50	40	60	83	71	57	62
HER2	0	20	40	17	14	29	21

[a]One pt (20 mg) had both EGFR and HER2 mutations; 1 pt (80 mg) had EGFR exon 20 insertion + T790M.

9016 Poster Discussion Session; Displayed in Poster Session (Board #339), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Tepotinib in patients with advanced non-small cell lung cancer (NSCLC) harboring *MET* exon 14-skipping mutations: Phase II trial. *First Author: Enriqueta Felip, Hospital Universitari de la Vall d'Hebron, Barcelona, Spain*

Background: *MET* mutations causing exon 14 skipping (*METΔex14*) produce c-Met receptors lacking a negative regulatory site, with the result that *METΔex14* mutations are oncogenic drivers. 3-4% of NSCLCs harbor *METΔex14* mutations; these tumors appear to be sensitive to c-Met inhibition. Selective c-Met inhibitors have the potential to be effective and well tolerated in patients (pts) with NSCLC. This single-arm phase II trial (NCT02864992) is investigating the efficacy and safety of the potent, selective c-Met inhibitor tepotinib in pts with *METΔex14*+ NSCLC. **Methods:** Adults with stage IIIB/IV *METΔex14*+ NSCLC without EGFR-activating mutations or *ALK* rearrangements who have received 0–2 lines of prior therapy are eligible. *METΔex14* mutations are identified in tumor and/or circulating tumor DNA (ctDNA) in plasma by a central laboratory. Pts receive tepotinib 500 mg QD until disease progression, intolerable toxicity, or withdrawal for other reasons. Primary endpoint: objective response. Secondary endpoints include safety. Recruitment of approx. 90 pts (60 tumor + 60 ctDNA *METΔex14*+, overlap anticipated) in Europe, USA, and Japan is planned. **Results:** 34 pts have been treated to date; data are available for 22 (male, n=16; Caucasian/Asian, n=17/5; median age 73.5 years; prior lines of therapy: 0, n=8, 1, n=8; 2, n=5; 3, n=1; *METΔex14*+ tumor and ctDNA, n=11, *METΔex14*+ tumor only, n=10, *METΔex14*+ ctDNA only, n=1); 19 remain on treatment. Based on investigator assessment, 9/15 (60.0%) evaluable pts had a confirmed PR and 3 (20.0%) had SD. All responders remain in response. 13 pts were evaluable for response by independent review: confirmed PR, n=6 (46.2%); SD, n=1 (7.7%). 13/22 pts with data available had tepotinib-related treatment-emergent adverse events (TRTEAEs; G1/2 peripheral edema = 9, G1/2 diarrhea = 7), with 3 having G3 TRTEAEs (asymptomatic amylase increase = 2; GGT increase = 1) and one a serious TRTEAE (interstitial pneumonia). 2 deaths not related to therapy have occurred (disease progression and bronchopulmonary hemorrhage). **Conclusions:** Tepotinib 500 mg QD has promising activity in *METΔex14*+ NSCLC. Its safety profile is as expected based on prior studies. Recruitment is ongoing. Clinical trial information: NCT02864992.

9017 Poster Discussion Session; Displayed in Poster Session (Board #340), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Results from a second-line (2L) NSCLC cohort treated with M7824 (MSB0011359C), a bifunctional fusion protein targeting TGF-β and PD-L1. *First Author: Luis G. Paz-Ares, University Hospital 12 de October, Madrid, Spain*

Background: Inhibiting the transforming growth factor β (TGF-β) pathway, which promotes tumor immunosuppression, may enhance the response to PD-(L)1 monoclonal antibodies (mAbs). 2L+ overall response rates (ORRs) with PD-(L)1 inhibitors in patients (pts) with advanced NSCLC range from 12% to 19% (PD-L1 unselected), highlighting the need for better treatments. M7824 is an innovative first-in-class bifunctional fusion protein composed of a human anti–PD-L1 IgG1 mAb fused with 2 extracellular domains of TGF-β receptor II (a TGF-β "trap"). **Methods:** In this expansion cohort of the ongoing, phase 1 trial NCT02517398, pts with advanced NSCLC unselected for PD-L1 who progressed following 1L standard treatment (no prior immunotherapy) were randomized to receive M7824 500 mg (n = 40) or 1200 mg (n = 40) q2w until disease progression, unacceptable toxicity, or trial withdrawal. The primary objective is to assess BOR per RECIST v1.1; other objectives include dose exploration and safety/tolerability assessment. Tumor cell PD-L1 expression was evaluable in 75 pts (Ab clone 73-10 [$>$ 80% = $>$ 50% with 22C3]). **Results:** As of October 25, 2017, 80 pts received M7824 for a median of 11.9 (range, 2-48) wk, with a median follow-up of 35.2 wk; 17 pts remain on treatment. Investigator-assessed unconfirmed ORR was 25.0% (500 mg ORR, 22.5%; 1200 mg ORR, 27.5%). Clinical activity was observed across PD-L1 expression levels (Table); ORR was 40.7% in PD-L1+ and 71.4% in PD-L1–high pts at 1200 mg. The most common treatment-related adverse events (TRAEs) were pruritus (18.8%), maculopapular rash (17.5%), and decreased appetite (12.5%). Grade ≥3 TRAEs occurred in 20 pts (25.0%). 6 pts (500 mg, n = 2; 1200 mg, n = 4) discontinued treatment due to TRAEs. No treatment-related deaths occurred. Clinical trial information: NCT02517398. **Conclusions:** M7824 monotherapy had promising efficacy across PD-L1 subgroups, with an ORR at the RP2D of 1200 mg of 40.7% and 71.4% in PD-L1+ and –high pts, respectively. Treatment was well tolerated.

ORR	500 mg	1200 mg	Total
All	9/40, 22.5	11/40, 27.5	20/80, 25.0
PD-L1+ (≥1%) pts, n, %	7/31, 22.6	11/27, 40.7	18/58, 31.0
PD-L1 high (≥80%) pts, n, %	2/6,33.3	5/7,71.4	7/13,53.8

9018 Poster Discussion Session; Displayed in Poster Session (Board #341), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Responses and durability in NSCLC treated with pegilodecakin and anti-PD-1. *First Author: Edward B. Garon, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA*

Background: Responses in NSCLC to agents targeting the PD-1/PD-L1 axis are correlated with PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB), interferon associated mRNA Expression Profile (GEP) and the absence of liver metastases. Anti-PD-1 impedes the inhibition of T cells while pegilodecakin (AM0010) stimulates the survival, and expansion of intra-tumoral, antigen activated CD8+ T cells (Mumm et al., 2010). This provides a rationale for combining anti-PD-1 agents with pegilodecakin. **Methods:** Pretreated NSCLC subjects (n = 34), received pegilodecakin (10-20μg/kg QD, SC) with pembrolizumab (2mg/kg, q3wk IV; n = 5) or nivolumab (3mg/kg, q2wk IV; n = 29). Median follow-up is 31.2 months (range 28.3 to 33+) and 17.5 months (range 8.3 to 25.9+), respectively. Responses were assessed by irRC. Twenty subjects had sufficient tissue for PD-L1 testing with the 22C3 IHC assay (CLIA) and 10 subjects had sufficient tissue for TMB evaluation by whole exome sequencing (WES) and pre-treatment GEP by Nanostring. **Results:** In 26 subjects evaluable for response, the ORR was 41% (11 PRs). Another 12 subjects (46%) had SD as best response. As investigators were asked to preferentially enroll PD-L1 negative patients, PD-L1 expression was $<$ 1% in 12 of 20 PD-L1 evaluable subjects with 4 achieving a PR. Ten subjects had sufficient tissue for TMB and GEP, including 6 PRs. Five of the 8 who tested low to intermediate for TMB (≤ 243 mut) had a PR as did 2 of 6 GEP negative subjects. In addition, 5 of 8 subjects with liver metastasis had a PR. The mPFS and mOS of the five NSCLC subjects (4/4 tested PD-L1 $<$ 1%) treated with pegilodecakin + pembrolizumab was 10.9 and 32.2 months, respectively. The mPFS and mOS for the pegilodecakin + nivolumab cohort (8/16 PD-L1 $<$ 1%) has not been reached. **Conclusions:** Pegilodecakin when added to anti-PD-1 therapy in advanced NSCLC patients was associated with response rates and durability of benefit greater than has been seen with anti-PD-1 alone. Responses were seen in settings in which anti-PD-1 therapy has demonstrated limited benefit, such as absent PD-L1 expression, low TMB and/or the presence of liver metastasis. These preliminary findings support further studies of pegilodecakin with anti-PD-1 therapies. Clinical trial information: NCT02009449.

9019 Poster Discussion Session; Displayed in Poster Session (Board #342), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

First comprehensive report of impact of genomic alterations, chemotherapy, targeted therapy and immunotherapy on outcomes in the genomics driven squamous master protocol LungMAP. *First Author: Vassiliki Papadimitrakopoulou, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Lung-MAP (S1400) is an umbrella protocol for genomic screening of previously treated squamous cell lung cancer patients and evaluation of targeted therapies in biomarker-matched groups and immunotherapy in patients without putative drivers. The protocol opened on June 16, 2014. Nine sub-studies have activated; the original 5 are closed, 4 are currently accruing. **Methods:** Tumor samples are analyzed by FoundationOne NGS assay. Completed studies evaluated taselisib (T) for PI3K mutations, palbociclib(P) for cell cycle gene alterations (CCGA), AZD4547(A) for FGFR alterations, rilotumumab and erlotinib(RE) for c-MET positive tumors, and durvalumab(Dur) . Originally including randomization to docetaxel(Doc), the studies were amended to single-arm phase 2 . Outcomes by treatment and biomarkers were assessed using a Cox model adjusting for performance status, lines of therapy, age, and gender. Prognosis of biomarkers was evaluated from time of study assignment. **Results:** As of January 5, 2018, 1407 patients registered to screening, 1244 with biomarker results and 529 patients have registered to a sub-study. Fifty-six eligible patients registered to Doc, 66 to Dur, and 90 to a targeted therapy arm (25 to A, 31 to P, 26 to T, 5 to E, 3 to RE). Relative to the Doc (median = 7.6 months(m)), overall survival was better for Dur (HR [95%CI]: 0.63 [0.42-0.96], median = 11.6 m). There was no significant difference with targeted therapy versus Doc (HR [95%CI]:1.05 [0.68-1.65], median = 7.0 m). FGFR alterations may be associated with worse prognosis (p = 0.06). Clinical trial information: NCT02154490. **Conclusions:** The outcomes with targeted therapies in these genomically complex tumors suggest limited efficacy and support the efficacy of immunotherapy. FGFR alterations are associated with poor survival. Continued evaluation of novel targets and therapeutics including immunotherapy within LungMAP are planned.

Biomarker	Prevalence	Biomarker + (Median in months)	Biomarker - (Median in months)	HR [95% CI], p-value
PI3K	8%	6.7	6.8	1.0 [0.78-1.29], 0.88
CCGA	19%	6.6	6.9	1.03 [0.85-1.24], 0.81
FGFR	16%	5.4	7.0	1.20 [0.99-1.46], 0.06

9020 Poster Discussion Session; Displayed in Poster Session (Board #343), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Nivolumab (Nivo) + Ipilimumab (Ipi) vs Platinum-Doublet Chemotherapy (Chemo) as First-line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Safety Analysis and Patient-Reported Outcomes (PROs) From CheckMate 227. *First Author: Martin Reck, LungenClinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany*

Background: CheckMate 227 (NCT02477826) is a large phase 3 study of 1L nivo + ipi, nivo, or nivo + chemo vs chemo in advanced NSCLC. The study met its co-primary endpoint demonstrating significantly prolonged progression-free survival with nivo + ipi vs chemo in patients (pts) with tumor mutational burden ≥10 mutations/Mb. The safety profile of 1L nivo + low-dose ipi was consistent with previous reports. Additional detailed analyses may inform the management of immune-related adverse events. **Methods:** Pts (N = 1739) with chemo-naive, stage IV/recurrent NSCLC without known sensitizing *EGFR*/*ALK* mutations were randomized 1:1:1 to nivo (3 mg/kg Q2W) + ipi (1 mg/kg Q6W), nivo monotherapy (240 mg Q2W), or chemo for pts with ≥1% tumor PD-L1 expression and to nivo + ipi, nivo (360 mg Q3W) + chemo, or chemo for pts with < 1% tumor PD-L1 expression. Tx continued until disease progression or unacceptable toxicity for up to 2 yr. Safety and PROs were exploratory endpoints. Safety analyses included time to onset and resolution of select treatment-related adverse events (select TRAEs; those with a potential immunologic cause) and corticosteroid use. PROs were assessed using the Lung Cancer Symptom Scale and EQ-5D instruments. **Results:** Minimum follow-up was 11.2 mo. Median duration of therapy was 4.2 mo with nivo + ipi and 2.6 mo with chemo. Rates of any grade and grade 3–4 TRAEs were 75% and 31% with nivo + ipi, and 81% and 36% with chemo, respectively. TRAEs led to discontinuation in 17% of pts receiving nivo + ipi and in 9% of pts receiving chemo. Most frequent grade 3–4 select TRAEs in pts receiving nivo + ipi were hepatic (8%), endocrine (4%), skin (4%), pulmonary (3%), and gastrointestinal (2%). Median time to onset of select TRAEs ranged from 2–15 wk, and the majority resolved with corticosteroid use (median time to resolution was ≤10 wk). PRO results will be reported in the final presentation. **Conclusions:** In CheckMate 227, nivo + low-dose ipi was well tolerated in NSCLC. Toxicities were manageable with previously established tx algorithms, including corticosteroids. Clinical trial information: NCT02477826.

9021 Poster Discussion Session; Displayed in Poster Session (Board #344), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Health-related quality of life (HRQoL) in the KEYNOTE-189 study of pembrolizumab (pembro) or placebo (pbo) + pemetrexed (pem) + platinum (plt) for metastatic NSCLC. *First Author: Marina Chiara Garassino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: In the double-blind, phase 3 KEYNOTE-189 study (NCT02578680), pembro + pem + plt significantly improved OS and PFS over pbo + pem + plt as first-line therapy for nonsquamous NSCLC. Grade 3-5 drug-related AE rates were higher with pembro. We report the prespecified patient-reported outcome (PRO) analyses from KEYNOTE-189. **Methods:** 616 patients (pts) were randomized to pembro 200 mg Q3W or pbo for 2 y; all pts received pem + 4 cycles of carboplatin or cisplatin. The EORTC QLQ-C30 and QLQ-LC13 were administered at cycles 1-5, then every 3 cycles during yr 1 and every 4 cycles during yrs 2 and 3. Key PRO outcomes were change from baseline to wks 12 and 21 in the QLQ-C30 global health status/QoL score and time to deterioration in the composite of cough, chest pain, or dyspnea. PROs were analyzed in all treated pts who completed ≥1 PRO instrument (n = 602). *P* values are nominal and 2-sided. **Results:** QLQ-C30 and QLQ-LC13 compliance was ~90% at baseline and wk 12 in both arms and was ~75% with pembro and ~63% with pbo at wk 21. Mean baseline scores were 61.98 and 60.56 in the pembro and pbo arms. At wks 12 and 21, global health status/QoL scores were stable with pembro and decreased with pbo, with significantly greater decrement with pbo at wk 21 (Table). The proportion of improved global health status/QoL was similar at wk 12 (28.9% with pembro vs 26.5% with pbo; $P = .5450$) but was greater with pembro at wk 21 (30.1% vs 22.5%; $P = .0496$). Median time to deterioration in the composite of cough, chest pain, or dyspnea was NR with pembro (95% CI 10.2 mo-NR) vs 7.0 mo (95% CI, 4.8-NR) with pbo (HR 0.81; 95% CI 0.60-1.09; nominal 2-sided $P = .081$). **Conclusions:** In this double-blind trial, pembro + pem + plt maintained or improved HRQoL over pem + plt alone despite a higher grade 3-5 treatment-related AE rate. Along with superior efficacy, these data support the use of pembro + pem + plt as first-line therapy for metastatic nonsquamous NSCLC. Clinical trial information: NCT02578680.

9022 Poster Discussion Session; Displayed in Poster Session (Board #345), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Clinical and molecular features predicting long-term response (LTR) to anti-PD-(L)1 based therapy in patients with NSCLC. *First Author: Hira Rizvi, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The transcendent feature of response to anti-PD-(L)1 therapy is durable, long-term responses, which can last up to years. Much effort in biomarkers has focused exclusively on initial response, but not all responses remain durable. The features predicting which patients will derive long-term response (LTR) may be even more important to identifying with precision those patients who most profoundly benefit from PD-1 blockade. **Methods:** Patients with advanced NSCLC who were treated with anti-PD-(L)1 based therapy from April 2011 through November 2016 were identified. LTR was defined as patients with progression-free survival lasting longer than 18 months. Efficacy was assessed by RECIST v1.1. Tumor mutation burden (TMB) was determined using MSK-IMPACT and PD-L1 expression by IHC. Fisher's exact test was used to compare proportions between two groups and Mann-Whitney *U* to compare continuous variables. **Results:** Of 766 patients with NSCLC treated with anti-PD-(L)1 based therapy, 62 (8%) had LTR. Among those with LTR, 77% had complete/partial response as best response and 68% remain progression-free (median follow up 2.5 years). The median TMB was 12.24 mutations/Mb (n = 32), which represents the 82th percentile of all NSCLC cases profiled by MSK-IMPACT (n = 3000, median 5.66 mutations/Mb). No patient with LTR harbored an EGFR mutation. Of 36 patients with PD-L1 testing, 75% had PD-L1 expression ≥ 1% and 44% had PD-L1 expression ≥ 50%. When compared to patients without LTR, those with LTR were more likely to be smokers (81% vs 92%, p = 0.026), PD-L1 expression > 0% (44% vs 75%, p < 0.001) and ≥ 50% (35% vs 44%, p = 0.01), and TMB > median (54% vs 78%, p = 0.009). When compared to those with transient response (< 18 months), those with LTR had significantly higher TMB (p = 0.002), but not PD-L1 expression (p = 0.44). **Conclusions:** Smoking status, PD-L1 expression, and TMB correlate with long-term response in NSCLC patients treated with anti-PD-(L)1 based therapy. TMB, but not PD-L1 expression, is distinctly increased in those with LTR compared to those with transient response. The features predicting initial response compared to durable response may be distinct.

9023 Poster Discussion Session; Displayed in Poster Session (Board #346), Sun, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sun, 11:30 AM-12:45 PM

Randomized phase II study of pembrolizumab after stereotactic body radiotherapy (SBRT) versus pembrolizumab alone in patients with advanced non-small cell lung cancer: The PEMBRO-RT study. *First Author: Willemijn Theelen, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: High dose radiation can lead to increased tumor antigen release, improved antigen presentation and T-cell infiltration. It may therefore enhance the effects of checkpoint inhibition. We evaluated if stereotactic body radiation therapy (SBRT) on a single metastasis preceding pembrolizumab treatment in patients with NSCLC is well tolerated and leads to an increased tumor response. **Methods:** Patients (n = 74) with advanced NSCLC (≥2^{nd} line) regardless of PD-L1 status were randomized (1:1) between pembrolizumab (200mg q3w) alone (control arm) or pembrolizumab preceded by SBRT (3x8Gy within 7 days prior to the first cycle) on a single metastasis (experimental arm). Sequential biopsies were obtained from the same, non-irradiated tumor site at baseline and after two cycles of pembrolizumab. The primary endpoint was improvement in overall response rate (ORR) at 12 weeks from 20% in the control arm to 50% in the experimental arm according to RECIST 1.1. **Results:** From July 2015 until the time of writing, 72 patients had been randomized and 64 patients who received at least one cycle of pembrolizumab could be evaluated for the primary endpoint. ORR at 12 weeks was 19% in the control arm (n = 32) vs 41% in the experimental arm (n = 32); the number of patients with a CR, PR, SD and PD were 0/6/7/19 and 1/12/6/13, respectively. Median PFS was 1.8 months in the control arm vs 6.4 months in the experimental arm; HR 0.55 (CI 0.31 – 0.98, p = 0.04). Grade ≥3 toxicity was experienced in 22% of patients in the control arm vs 17% in the experimental arm. The most common AEs were fatigue, nausea, fever and hypothyroidism. No increase in treatment related toxicity was observed in the experimental arm. **Conclusions:** With 86% of patients evaluable, we conclude that pembrolizumab preceded by SBRT resulted in a doubling of the ORR without increase in toxicity. The primary endpoint of 50% DCR was not (yet) met. This is a well-tolerated and promising treatment strategy to augment the anti-tumor immune response with checkpoint blockade. Definitive results as well as correlations with PD-L1 expression will be available and discussed at ASCO. Clinical trial information: NCT02492568.

9024 Poster Session (Board #347), Sun, 8:00 AM-11:30 AM

Quality of life analysis of Pemetrexed versus Erlotinib maintenance in EGFR mutation negative advanced non small cell lung cancer. *First Author: Vivek Agarwala, Tata Memorial Centre, Mumbai, India*

Background: Both Pemetrexed and Erlotinib have shown survival benefit when used as maintenance therapy in advanced non small cell lung cancer (NSCLC) after platinum doublet chemotherapy. Hence this study was planned to compare the outcomes between the 2 drugs. The current abstract is focused on quality of life (QOL) results. **Methods:** This was a open label, randomized, phase 3 study done in adult palliatively treated EGFR-negative, NSCLC patients who had non progressive disease post administration of first line chemotherapy Pemetrexed-Carboplatin. Patients were 1:1 randomized between tablet Erlotinib 150 mg orally administered once daily versus injection Pemetrexed 500 mg/m2 administered intravenously every 3 weeks. The therapy was continued either till disease progression or development of intolerable side effects. The primary endpoint was to compare the QOL between the 2 arms at 3 months. Other secondary endpoints were to study and compare the progression free survival (PFS), overall survival (OS) and adverse event rate. We had 200 patients in this study and the sample size had 80% power, with type 1 error of 5% to detect a difference of 0.3 in effect size. **Results:** Total 200 patients were recruited in the study. The median follow up was 25.37 months (95%CI 21.4-29.3 months). There was no difference in global QOL between the 2 arms at 3 months (p=0.384). There was no difference in any domain of QOL except a higher score for diarrhea was seen in the Erlotinib arm (p=0.001). The PFS (HR 0.99; 95% CI 0.73-1.34, p=0.939) and OS (HR 0.88; 95%CI 0.62-1.27, p=0.493) were similar between both the arms. **Conclusion:** Maintenance Pemetrexed post Pemetrexed-Platinum chemotherapy fails to improve QOL or time to event outcomes (OS & PFS) over maintenance Erlotinib in EGFR mutation negative advanced NSCLC. Clinical trial information: CTRI/2014/08/004847.

9025 Poster Session (Board #348), Sun, 8:00 AM-11:30 AM

A randomized phase 3 study of abemaciclib versus erlotinib in previously treated patients with stage IV NSCLC with *KRAS* mutation: JUNIPER. *First Author: Jonathan Wade Goldman, UCLA Medical Center, Los Angeles, CA*

Background: Approximately 30% of NSCLC tumors harbor *KRAS* mutations, for which there is no specific treatment. Abemaciclib is a potent and selective inhibitor of CDK4 & 6 approved for treatment of HR+, HER2- advanced breast cancer. In a Phase 1 study, abemaciclib showed greater clinical activity in patients with advanced NSCLC with *KRAS* mutant tumors versus *KRAS* wild type tumors. This study compared abemaciclib with erlotinib, both with best supportive care, in previously treated patients with advanced NSCLC and *KRAS* mutations. **Methods:** This was a global, Phase 3, comparator-controlled, multicenter, open-label trial for patients with confirmed stage IV NSCLC, detectable *KRAS* mutations in codons 12 or 13, with progressive disease after platinum-based chemotherapy and 1 additional line of therapy, measurable disease by RECIST v1.1, ECOG performance status 0-1, and adequate organ function. Patients were randomized 3:2 to receive either abemaciclib 200 mg PO Q12H or erlotinib 150 mg PO Q24H until disease progression or unacceptable toxicity. Primary objective was overall survival (OS). Secondary objectives included progression-free survival (PFS), objective response rate (ORR, complete response + partial response), and safety and tolerability. **Results:** A total of 453 patients were randomized, 270 to abemaciclib and 183 to erlotinib. Median OS was 7.4 months with abemaciclib and 7.8 months with erlotinib (HR [95% CI]: 0.97 [0.77, 1.22]; stratified log-rank, p = 0.77). Median PFS was 3.6 months with abemaciclib and 1.9 months with erlotinib (HR [95% CI]: 0.58 [0.47, 0.72]; stratified log-rank, $p < 0.001$). The ORR was 8.9% (95% CI: 5.5, 12.3%) with abemaciclib and 2.7% (0.4, 5.1%) with erlotinib (p = 0.01). The disease control rate was 54.4% (95% CI: 48.5, 60.4%) with abemaciclib and 31.7% (25.0, 38.4%) with erlotinib. There were no new safety signals with abemaciclib in this study. **Conclusions:** In previously treated patients with stage IV NSCLC harboring *KRAS* mutations, abemaciclib did not improve OS but demonstrated improvement in PFS and ORR compared with erlotinib. Further molecular subgroup analysis based on abemaciclib's mechanism of action is underway. Clinical trial information: NCT02152631.

9026 Poster Session (Board #349), Sun, 8:00 AM-11:30 AM

24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. *First Author: Ryan D. Gentzler, University of Virginia, Charlottesville, VA*

Background: Cohort G of the phase 1/2 KEYNOTE-021 study (NCT02039674) evaluated pembrolizumab (pembro) + pemetrexed and carboplatin (PC) vs PC in first-line advanced nonsquamous NSCLC. With median follow-up of 10.6 mo, ORR (estimated treatment difference, 26%; $P = 0.0016$) and PFS (HR, 0.53; $P = 0.010$) significantly improved with pembro + PC vs PC. The HR for OS was 0.90 (95% CI, 0.42–1.91). We present results after approximately 2 y of follow-up. **Methods:** Pts with previously untreated stage IIIB/IV nonsquamous NSCLC without *EGFR* mutations/*ALK* translocations were randomized 1:1 to 4 cycles of carboplatin AUC 5 mg/mL/min + pemetrexed 500 mg/m^2 Q3W with or without pembro 200 mg Q3W for 2 y (maintenance pemetrexed permitted in both arms). Eligible pts with radiologic disease progression could cross over from PC to pembro. Response was assessed by BICR per RECIST v1.1. Primary endpoint was ORR; PFS and OS were secondary endpoints. *P* values are nominal. **Results:** 123 pts were randomized. As of Dec 1, 2017, median follow up was 23.9 mo (range, 0.8–35.1 mo). 11 pts in the pembro + PC arm and 2 in the PC arm completed randomized treatment. Among pts in the PC arm who discontinued/completed, 41/56 (73%) subsequently received anti–PD-(L)1 agents, including 26 who crossed over to pembro on study. ORR was 57% with pembro + PC vs 30% with PC ($P = 0.0016$). PFS was significantly improved with pembro + PC vs PC (HR, 0.53; 95% CI, 0.33–0.86; $P = 0.0049$). Median (95% CI) PFS was 24.0 (8.5–NR) mo for pembro + PC vs 9.3 (6.2–14.9) mo for PC. HR for OS was 0.56 (95% CI, 0.32–0.95; $P = 0.0151$). Median (95% CI) OS was not reached (24.5 mo–NR) for pembro + PC and 21.1 (14.9–NR) mo for PC; 24-mo OS rates were 67% and 48%, respectively. Grade 3–5 treatment-related AE incidence was 41% with pembro + PC vs 27% with PC. 3 pts had treatment-related fatal AEs (pembro + PC, n = 1; PC, n = 2). **Conclusions:** After median follow-up of approximately 24 mo, the risk of death for pembro + PC vs PC was reduced by nearly half (HR, 0.56; nominal $P = 0.0151$) despite a high crossover rate among patients in the PC arm. Improvements in PFS and ORR persisted, and median PFS in the pembro + PC arm was 24.0 mo compared to 9.3 mo in the PC alone arm. Clinical trial information: NCT02039674.

9027 Poster Session (Board #350), Sun, 8:00 AM-11:30 AM

Early clearance of plasma EGFR mutations as a predictor of response to osimertinib in the AURA3 trial. *First Author: Frances A. Shepherd, University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: In the Phase III AURA3 trial (NCT02151981), osimertinib, a third-generation EGFR-TKI, had significantly greater efficacy than platinum-pemetrexed in patients (pts) with advanced NSCLC and T790M-mediated acquired resistance to first-line EGFR-TKI. We investigate whether the presence of plasma EGFR mutations at 3 and 6 wks post-osimertinib treatment (80 mg, once daily) is associated with clinical outcomes, and identify pre-existing genomic aberrations that may impact outcomes. **Methods:** EGFR mutation analysis (Ex19del/L858R/T790M) was conducted at baseline, wks 3 and 6, by droplet digital (dd)PCR (Biodesix). Next generation sequencing (NGS, Guardant Health; 73 genes) was conducted on baseline plasma samples to explore mechanisms of innate resistance. Clinical outcomes (median progression-free survival [mPFS], objective response rate [ORR]) were investigator assessed, per RECIST 1.1. **Results:** Of 207 pts with a valid plasma ddPCR result at baseline (all T790M+), 150 had detectable EGFR-TKI sensitizing mutations (EGFRm; Ex19del/L858R) and 57 did not. mPFS was 14.0 mo (95% CI 12.4, not calculable) in pts without detectable baseline EGFRm vs 8.3 mo (95% CI 6.9, 10.9) in pts with detectable baseline EGFRm; EGFRm allelic fraction in baseline plasma was not related to ORR or mPFS. Of the 129 pts with baseline EGFRm and evaluable plasma samples at wk 3, 48 had detectable EGFRm (EGFRm+) and 81 had undetectable EGFRm (EGFRm-). mPFS was 5.7 mo (95% CI 4.1, 9.7) in pts EGFRm+ vs 10.9 mo (95% CI 8.3, 12.7) in pts EGFRm-; hazard ratio (HR) 2.0 (95% CI 1.3, 3.2), p = 0.001; HR > 1 favors pts EGFRm-. ORR was 50% vs 82%, respectively. A similar trend was observed at wk 6 (n = 132): PFS, HR 2.8 (95% CI 1.8, 4.3), $p < 0.0001$. NGS of baseline plasma showed no association between pre-existing genomic aberrations (*TP53*, *BRAF*, *KRAS*, *MET/HER2* amp) and clinical outcome; additional analyses are ongoing. **Conclusions:** In pts with tissue T790M+ NSCLC and detectable baseline plasma EGFRm, continued presence of EGFRm at wks 3 and 6 was associated with less favorable outcomes with osimertinib. Early dynamic changes of plasma EGFR mutations may predict clinical outcome in pts receiving osimertinib for T790M+ NSCLC. Clinical trial information: NCT02151981.

9028 Poster Session (Board #351), Sun, 8:00 AM-11:30 AM

Association of STK11/LKB1 mutations with primary resistance to PD-1/PD-L1 axis blockade in PD-L1 positive non-squamous NSCLC. *First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The genomic determinants of response to PD-1/PD-L1 axis blockade in non-squamous NSCLC are incompletely understood. We previously identified *STK11/LKB1* alterations as a major genomic driver of low tumor cell PD-L1 expression and primary resistance to PD-1 inhibitors in *KRAS*-mutant lung adenocarcinoma. A critical unanswered question is whether *STK11/LKB1* alterations predict for lack of response to PD-1/PD-L1 blockade independently of PD-L1 expression. Here, we report the impact of *STK11/LKB1* alterations on clinical outcomes with PD-1/PD-L1 inhibitors in PD-L1-positive non-squamous NSCLC. **Methods:** 66 patients with non-squamous NSCLC treated with PD-1/PD-L1 inhibitors at MDACC (61% pembrolizumab, 24% nivolumab, 8% atezolizumab, 5% durvalumab/tremelimumab) with available *STK11/LKB1* NGS-based genomic profiling and positive tumor cell PD-L1 expression (≥1%, based on the FDA-approved 22C3 pharmDx assay) were identified retrospectively. Response assessment was based on RECIST1.1. **Results:** In this PD-L1-positive population of non-squamous NSCLC, *STK11/LKB1* alterations were associated with significantly lower ORR to PD-1/PD-L1 blockade compared to tumors with intact *STK11/LKB1* status (ORR 0% versus 34.5%, P = 0.026). *STK11/LKB1*-mutant tumors exhibited significantly shorter progression-free survival (mPFS 1.7 months versus 19.3 months, HR 4.76, 95% CI 2.0-11.1, P = 0.00012, log-rank test) and overall survival (mOS 11.1 months versus 26.5 months, HR 14.3, 95% CI 3.4-50.0, P < 0.0001, log-rank test) with PD-1/PD-L1 blockade. Although fewer *STK11/LKB1*-mutant tumors expressed high (≥50%) levels of PD-L1 (45.5% versus 61.8%), the difference did not reach statistical significance (P = 0.5). **Conclusions:** *STK11/LKB1* genomic alterations are associated with *de novo* resistance to PD-1/PD-L1 inhibitors even among PD-L1-positive non-squamous NSCLC patients, suggesting that their effect is at least partially independent of PD-L1 expression. Evaluation of *STK11/LKB1* genomic status may enhance the predictive utility of a composite PD-1/PD-L1-inhibitor predictive biomarker panel incorporating PD-L1 expression and TMB.

9029 Poster Session (Board #352), Sun, 8:00 AM-11:30 AM

Meta-analysis exploring the effect of oncogenic driver mutations on outcome of metastatic non-small cell lung cancer (mNSCLC) patients (pts) treated with immune checkpoint inhibitors (ICI) or docetaxel (doc). *First Author: Abena Agyeman, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Recent reports suggest that pts with mNSCLC with tumor EGFR mutations (EGFRm) receiving ICI as second line-plus (2L+) therapy may have better clinical outcomes with doc compared to ICI. We aimed to further investigate the role of ICI in pts with oncogenic driver mutations. **Methods:** We performed a patient-level meta-analysis on 4 randomized controlled, 2L+ trials of ICI versus doc controlling for EGFRm status, PD-L1 status, as well as common prognostic factors (e.g. race). A separate analysis was performed to assess the effect of KRASm, excluding EGFRm as a covariate. If EGFRm or KRASm status was unknown, pts were excluded from these analyses. A Cox proportional hazards model stratified by trial was used to estimate hazard ratios (HR) for EGFRm and KRASm. Median OS was estimated using Kaplan-Meier methods on aggregate data. **Results:** Treatment effect was evaluable in 2752 patients; 76% had EGFR mutation data and 17 % had KRAS mutation data. Of the 2078 pts with known EGFR status, 246 (12%) had EGFRm and 1832 (88%) had EGFR wildtype (wt). Of the 477 pts with known KRAS status, 136 (29%) had KRASm and 341 (71%) had KRASwt. The results of subgroup comparisons are summarized in the table. **Conclusions:** Pts with EGFRwt tend to have better outcomes than pts with EGFRm when treated with ICI. Pts with EGFRm may have longer OS when treated with doc than ICI, although this finding is inconclusive. The KRAS data is limited by small numbers, but it appears that KRASwt derive the expected benefit from ICI. Future studies should include full data capture of key oncogenic driver status on all NSCLC pts, and clarify the role of ICI on different biomarker subsets.

Subgroup comparison	Median OS; HR (95% CI)
EGFRm vs EGFRwt (Doc)	12.8 vs. 9.3; 0.86 (0.65, 1.13)
EGFRm vs EGFRwt (ICI)	9.4 vs. 12.8; 1.40 (1.10, 1.78)
ICI vs Doc (EGFRwt)	12.8 vs. 9.3; 0.72 (0.60, 0.87)
ICI vs Doc (EGFRm)	9.4 vs. 12.8; 1.18 (0.83, 1.68)
KRASm vs KRASwt (Doc)	8.8 vs. 11.0; 1.29 (0.92, 1.80)
KRASm vs KRASwt (ICI)	14.3 vs. 12.1; 0.79 (0.54, 1.16)
ICI vs Doc (KRASwt)	12.1 vs. 11.0; 0.64 (0.41, 0.99)
ICI vs Doc (KRASm)	14.3 vs. 8.8; 1.03 (0.75, 1.41)

9030 Poster Session (Board #353), Sun, 8:00 AM-11:30 AM

4-year overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from KEYNOTE-001. *First Author: Enriqueta Felip, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Pembrolizumab (pembro) has shown antitumor activity in patients (pts) with advanced NSCLC and is standard-of-care therapy for pts with PD-L1–expressing tumors (first-line, TPS ≥50%; previously treated, TPS ≥1%). KEYNOTE-001, an open-label phase 1b study, evaluated pembro monotherapy in treatment-naive or previously treated pts with advanced NSCLC (NCT01295827). We report a 4-y update of KEYNOTE-001. **Methods:** Pts had confirmed locally advanced/metastatic NSCLC and provided a contemporaneous tumor tissue sample for evaluation of PD-L1 levels by IHC using the 22C3 antibody. Pts received pembro 2 mg/kg Q3W or 10 mg/kg Q2W or Q3W. Primary efficacy endpoint was ORR. OS was a secondary endpoint. **Results:** As of data cutoff (Sep 1, 2017), among 550 pts enrolled (treatment-naive, n = 101; previously treated, n = 449), median (range) follow-up was 46.5 (37.7–63.8) mo. ORR (by investigator per irRC) was 41.6 % (95% CI, 31.9–51.8) for treatment-naive pts and 22.9% (95% CI, 19.1–27.1) for previously treated pts. Median OS was 22.3 mo (95% CI, 17.1–32.3) for treatment-naive pts and 10.5 mo (95% CI, 8.6–13.2) for previously treated pts; estimated 4-y OS rates were 27.2% and 16.4 %, respectively. Kaplan-Meier curves for OS appeared to plateau after 42 mo for treatment-naive pts and 36 mo for previously treated pts. Increased PD-L1 expression was associated with improved OS (Table). Immune-mediated AEs occurred in 24.8% of treatment-naive and 17.4% of previously treated pts. No additional grade 5 treatment-related AEs occurred (compared with 3-y follow-up; data cutoff Sep 1, 2016). **Conclusions:** Pembro provides long-term OS benefit for both treatment-naive and previously treated advanced NSCLC that expresses PD-L1. These data represent the longest efficacy and safety follow-up for pts with advanced NSCLC treated with pembro. Clinical trial information: NCT01295827.

OS in subgroups defined by PD-L1 TPS.

	Treatment-Naive (N = 101)			Previously Treated (N = 449)		
	n	Median (95% CI), mo	Est. 4-y rate	n	Median (95% CI), mo	Est. 4-y rate
TPS ≥50%	27	35.4 (20.3–NE)	48.1%	138	15.4 (10.6–18.8)	24.8%
TPS 1%–49%	52	19.5 (10.7–26.3)	NE	168	8.5 (6.0–12.6)	15.6%
TPS ≤1%		Not reported*		90	8.6 (5.5–10.6)	6.5%

NE = not estimable. *Due to small pt numbers (n = 12).

9031 Poster Session (Board #354), Sun, 8:00 AM-11:30 AM

Economic impact of next generation sequencing vs sequential single-gene testing modalities to detect genomic alterations in metastatic non-small cell lung cancer using a decision analytic model. *First Author: Nathan A. Pennell, Cleveland Clinic, Cleveland, OH*

Background: Metastatic non-small cell lung cancer (mNSCLC) patients (pts) should be tested for genomic alterations (GA) to inform treatment decisions. This study assesses the economic impact of next generation sequencing (NGS) vs sequential single-gene testing modalities for Center for Medicare and Medicaid Services (CMS) Medicare and US commercial payers. **Methods:** In a decision analytic model, newly diagnosed mNSCLC pts were modeled to receive PD-L1 and GA tests (*EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *HER2*, *RET*, *NTRK1*) using 1) sequential tests, 2) exclusionary mutation (*KRAS*) test followed by sequential tests 3) panel test or 4) upfront NGS, including all GAs and *KRAS*. Pts in modalities 1-3 were tested for GAs with currently approved treatment (*EGFR, ALK, ROS1, BRAF*) followed by single-gene tests or NGS for other GAs (e.g., *HER2*); a proportion were assumed to need rebiopsy. Inputs included turnaround time, unit costs and mNSCLC prevalence based on literature, public data and expert opinion. Time to receive results and total cost (test + rebiopsy) were calculated for each modality and compared with NGS. **Results:** For hypothetical 1 million-member plans, an estimated 2,066 CMS Medicare and 156 commercially insured mNSCLC pts would be tested for GA. Estimated time to receive results was 2.0 weeks for NGS and panel, 2.7 and 2.8 weeks faster than exclusionary and sequential, respectively. Using CMS reimbursement, NGS represented savings of $1,393,678 vs exclusionary, $1,530,869 vs sequential and $2,140,795 vs panel. For commercial payers, NGS remained the least expensive by $3,809 (vs exclusionary) to $250,842 (vs panel). **Conclusions:** Our model estimated that upfront NGS leads to the same (as panel) or shorter (vs exclusionary and sequential testing) wait time for results and the lowest payer cost to establish GA status for newly diagnosed mNSCLC pts to inform treatment decisions.

	Sequential	Exclusionary	Panel	NGS
CMS Medicare N = 2 066				
Total cost	3 721 368	3 584 177	4 331 295	2 190 499
Savings with NGS	1 530 869	1 393 678	2 140 795	
Commercial N = 156				
Total cost	747 771	624 178	871 211	620 369
Savings with NGS	127 402	3 809	250 842	

9032 Poster Session (Board #355), Sun, 8:00 AM-11:30 AM

Lorlatinib in patients (Pts) with previously treated ALK$^+$ advanced non-small cell lung cancer (NSCLC): Updated efficacy and safety. *First Author: Benjamin Besse, Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France*

Background: Despite advancement of 2nd generation (gen) ALK tyrosine kinase inhibitors (TKIs), ALK$^+$ NSCLC pts continue to develop resistance and CNS metastases (mets) become more difficult to manage. Lorlatinib, a potent brain-penetrant 3rd gen ALK/ROS1 TKI, has shown robust clinical activity in ALK$^+$ or ROS1$^+$ NSCLC pts, most of whom had CNS mets and failed ≥1 ALK TKI. **Methods:** This ongoing ph 2 study (NCT01970865) enrolled 275 pts with ALK$^+$ or ROS1$^+$ advanced NSCLC ± CNS mets in cohorts (ALK: EXP 1–5; ROS1: EXP 6) based on prior treatment; starting dose was lorlatinib 100 mg QD. Antitumor activity (by independent central review per RECIST 1.1), safety and biomarkers were evaluated. **Results:** In 198 ALK$^+$ pts assessed for antitumor activity (ITT population) in pooled subgroups (EXP 2–3A [only prior crizotinib ± chemotherapy (CT)], EXP 3B [only 1 prior 2nd gen ALK TKI ± CT], and EXP 4–5 [2 or 3 prior ALK TKIs ± CT]), lorlatinib led to rapid (median time to response 1.4 mo) deep and durable systemic and intracranial (IC) responses (Table). Of a total 139 pts in EXP 3B + EXP 4–5, 62, 47 and 8 received alectinib, ceritinib and brigatinib, respectively, as last ALK TKI prior to lorlatinib. Additional efficacy, including PFS, in all cohorts will be presented. The most common treatment-related AEs (TRAEs) and grade 3/4 TRAEs across all cohorts (N = 275) were hypercholesterolemia (84%/16%) and hypertriglyceridemia (66%/16%); 32% and 24% of pts had TRAEs that led to dose delays and reductions, respectively. No treatment-related deaths occurred; TRAEs led to permanent discontinuation in 8 pts. Antitumor activity was seen across a range of *ALK* resistance mutations, eg G1202R and G1202del. Clinical trial information: NCT01970865. **Conclusions:** Lorlatinib showed clinically meaningful benefit in ALK$^+$ NSCLC pts with ≥1 prior ALK TKI and was generally tolerable with AEs managed by dose modification or supportive therapy.

	ORR		Median	IC ORR		Median	IC ORR Target Lesion Only[a]	
	N	n (%)	DOR, mo (95% CI)	N	n (%)	IC DOR, mo (95% CI)	N	n (%)
EXP 2–3A	59	43 (73)	NR (10, NR)	37	25 (68)	19 (19, NR)	23	20 (87)
EXP 3B	28	11 (39)	7 (4, NR)	13	6 (46)	NR (4, NR)	9	6 (67)
EXP 4–5	111	43 (39)	7 (6, 13)	81	38 (47)	15 (8, 20)	48	24 (50)

[a]≥1 measurable brain lesion at baseline
DOR, duration of response; NR, not reached

9033 Poster Session (Board #356), Sun, 8:00 AM-11:30 AM

YH25448, a 3rd generation EGFR-TKI, in patients with EGFR-TKI-resistant NSCLC: Phase I/II study results. *First Author: Byoung Chul Cho, Severence Hospital, Seou, Republic of Korea*

Background: The epidermal growth factor receptor (EGFR) T790M mutation is one of the most common acquired resistance mechanism to EGFR tyrosine kinase inhibitors (TKIs). YH25448 is an oral, potent, irreversible EGFR TKI that is highly selective for activating (EGFRm) and T790M resistance mutations. **Methods:** Patients with EGFRm advanced NSCLC with acquired resistance to EGFR-TKIs with or without asymptomatic brain metastases were enrolled in an open-label, multicenter, phase I/II study with dose escalation and expansion cohorts. YH25448 was administered once daily at doses of 20 to 240 mg in a 21 day cycle. Patients were assessed for safety, tolerability, pharmacokinetics and efficacy. T790M status was confirmed in the expansion cohorts. **Results:** A total of 105 patients (median age 62 years, female 61%) were enrolled. The dose escalation cohort included 33 patients administered with 20 to 240 mg once daily across 6 dose levels, and 72 patients in the dose expansion cohort were administered with 40 to 240 mg. No dose-limiting toxicities were observed. The most common treatment-emergent adverse events (AEs) were pruritus (12%), decreased appetite (11%), rash (11%), and constipation (10%). AEs of grade 3 or higher were observed in 5% of the patients. Systemic exposure increased dose-dependently. Of the evaluable patients (n = 91) at data cut-off, the objective response rate (ORR) was 64% (95% confidence interval [CI], 53.0 to 73.6). The ORR for 76 of the T790M-positive patients was 67% (95% CI, 55.4 to 77.5), and for 15 of the T790M-negative patients was 47% (95% CI, 21.3 to 73.4). In patients with brain metastases (n = 9), the overall intracranial ORR was 56% (95% CI, 21.2 to 86.3). **Conclusions:** YH25448 was well tolerated and exhibits promising systemic and intracranial antitumor activity at multiple dose levels in EGFR T790M+ NSCLC patients. Clinical trial identifier: NCT03046992.

ORR in T790M+ patients.

Dose, QD	20 mg	40 mg	80 mg	120 mg	160 mg	240 mg
Evaluable patients*, n	2	25	18	21	8	2
ORR, n (%)	2 (100)	17 (68)	11 (61)	15 (71)	4 (50)	2 (100)

**Patients are evaluable for response if they have post-baseline radiological assessment (RECIST 1.1) or patients who discontinued prior to the post-baseline assessment.*

9034 Poster Session (Board #357), Sun, 8:00 AM-11:30 AM

***RET*-rearranged lung cancers: Immunophenotype and response to immunotherapy.** *First Author: Joshua K. Sabari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: In patients with *RET*-rearranged lung cancers, multikinase inhibitors (e.g. cabozantinib and vandetanib) and specific (e.g. pemetrexed-containing) chemotherapy regimens have documented activity. In contrast, PD-L1 expression, tumor mutational burden (TMB), and the treatment outcomes of immunotherapy are not well characterized in this genomic subset. **Methods:** Patients with a pathologically confirmed diagnosis of lung cancer harboring a *RET* rearrangement were identified between January 2012 and December 2017. PD-L1 expression was determined by IHC (E1L3N Clone). TMB was calculated in tumors that underwent NGS (Mutations/Mb, MSK-IMPACT). Objective response rate (ORR) to immunotherapy was evaluated by RECIST. **Results:** 74 patients with *RET*-rearranged lung cancers were identified. The median age was 63 (range 34-80 years), 55% were women, and 68% were never smokers. The majority (97%) had adenocarcinoma and 85% had metastatic disease. In patients with sufficient tissue for analysis, tumor PD-L1 expression was as follows: PD-L1 ≥50% in 21% (5/24, 95% CI 5-37%), PD-L1 1-49% in 25% (6/24, 95% CI 8-42%), and PD-L1 0% in 42% (13/24, 95% CI 22-62%). The median TMB of *RET*-rearranged lung cancers was 3.3 Mt/Mb (range 0.82-9.84, n = 43) and lower than the median TMB of 5.7 Mt/Mb in unselected NSCLCs (n = 1,769, $p < 0.001$). 12 patients received PD-1/PD-L1 blockade and 1 patient received 2 lines: pembrolizumab (6), nivolumab (4), atezolizumab (2), and durvalumab (1). ORR by RECIST was 0% (0/5 evaluable). The median duration of therapy was 1.4 months (m) (range 0.5-8.7m). Responses were not enriched in those with positive PD-L1 expression (≥1%) nor in those with TMB > median of all NSCLCs. The overall survival of patients who received immunotherapy did not differ from patients who did not receive immunotherapy (n = 51): 18.2 vs 17.9m, p = 0.6. **Conclusions:** While PD-L1 expression occurs in a substantial proportion of *RET*-rearranged lung cancers, TMB is lower compared to unselected lung cancers, and response to immunotherapy is poor. RET-directed targeted therapy strategies and platinum doublet chemotherapy should be considered prior to single-agent immunotherapy.

9035 Poster Session (Board #358), Sun, 8:00 AM-11:30 AM

Multi-kinase RET inhibitor vandetanib combined with mTOR inhibitor everolimus in patients with RET rearranged non-small cell lung cancer. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *RET* fusions (RET+) occur in 1-2% of NSCLCs. Tumors eventually become refractory to multi-kinase RET inhibitor monotherapy. We evaluated the pre-clinical and clinical activity of the combination of Vandetanib (V), an inhibitor of RET, VEGF, and EGFR, and the mTOR inhibitor everolimus (E). **Methods:** Clinical activity of V + E was evaluated in pts with advanced NSCLC in a Phase 1 trial. V and E were administered orally QD in a 28 day cycle. Responses were assessed by RECIST 1.1. RET fusions were detected by FISH and/or or Next generation sequencing (NGS) in tumor tissue and/or plasma. Preclinical studies were performed using the *CCDC6-RET* + LC-2/ad NSCLC cells. **Results:** Among 19 stage IV NSCLC pts enrolled, median age was 59 yrs & 8 pts (42%) were males. 13 pts (93%) were RET+ by NGS and/or FISH. Concordance rate between the two tests was 40%. The overall ORR in 13 RET+ pts was 54% (7 PR). The ORR in RET+ by NGS was 70% (7 PR/10 patients) while the ORR in FISH+ patients was 20% (1 PR/5 patients). No responses were seen in NGS-/FISH+ patients (0/3 = 0%). The combination was active in RET+ NSCLC brain metastases (3/3) and in a cabozantinib progressor. The median PFS of all 13 RET+ patients was 4.4 months (95% CI 3.4, NR); the median PFS of RET NGS+ patients (n = 10) was 8 months (95% CI 0.1, 1.1). Grade 3/4 toxicities included diarrhea (21%), thrombocytopenia (16%), QTc prolongation (5%) and rash (5%). 17/ 19 (89%) pts required dose modifications after cycle 1 due to toxicity. Preclinical studies demonstrated that resistance to RET inhibition was associated with activation of the EGFR, VEGFR, and downstream mTOR pathways and that the combination of everolimus with the RET/VEGFR/EGFR inhibitor vandetanib abrogated this resistance in preclinical models. **Conclusions:** V+E has significant activity in RET+ NSCLC identified by NGS, with an ORR of 70% and a median PFS of 8 months. Preclinical data shows the V+E combination to be superior to either drug alone and may target potential resistance pathways. The combination merits further investigation in RET+ NSCLC. Clinical trial information: NCT01582191.

9036 Poster Session (Board #359), Sun, 8:00 AM-11:30 AM

Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBRO) in patients with non-small cell lung cancer (NSCLC) previously treated with anti-PD-(L)1 therapy. *First Author: Leena Gandhi, NYU Perlmutter Cancer Center, New York, NY*

Background: Treatment options are limited in pts who progress on anti-PD-(L)1 therapy. HDAC inhibitors have the potential to modulate myeloid-derived suppressor cell (MDSC) function and may synergize with PD-(L)1 inhibition. We report the preliminary results of a Phase 2 trial of entinostat (ENT), a class I selective histone deacetylase (HDAC) inhibitor, plus pembrolizumab (PEMBRO) in patients with NSCLC previously treated with anti-PD-(L)1 therapy. **Methods:** ENCORE-601 is an open-label study evaluating the combination of ENT + PEMBRO in pts with recurrent or metastatic NSCLC and prior progression on anti-PD-1/PD-L1 therapy. Pts were eligible irrespective of histology or baseline PD-L1 expression. Pts were treated with ENT 5 mg PO weekly and PEMBRO 200 mg IV Q3W. The primary endpoint was ORR as assessed by irRECIST. The study was designed as a Simon 2-stage study such that if 3 of 31 pts responded in Stage 1, the study would enroll up to 56 pts. The study was further revised to accrue up to 70 patients to increase statistical power and decrease Type I error. Tumor biopsies and blood samples for immune correlates were taken pre- and on-treatment in a subset of patients. **Results:** Of the first 57 patients enrolled, 17 had refractory disease to prior to PD-(L)1 therapy, and only 2 had a documented prior response. Median duration of prior PD-(L)1 therapy was $<$ 6 months and the median time from last dose of prior PD-(L)1 therapy was 65 days. To ENT + PEMBRO, 5 of 57 patients achieved a confirmed PR (ORR = 9%, 95% CI: 2.9-19.3). Of the responders, 4 had PD-L1 expression $<$ 1% in tissue collected at baseline. The median duration of response is 4.2 months, with 3 responders ongoing. 20 pts (35.1%) experienced Grade 3/4 related AEs; 6 pts (10.5%) experienced Grade 3/4 related irAEs (3 events of pneumonitis). The most frequent ($>$ 15%) related AEs (irrespective of grade) include fatigue, anemia, decreased appetite, and diarrhea. Evaluation of gene expression and circulating immune cells to identify biomarkers of response is in progress. **Conclusions:** ENT + PEMBRO demonstrated anti-tumor activity and acceptable safety in patients with NSCLC who have progressed on prior PD-(L)1 blockade. Clinical trial information: NCT02437136.

9037 Poster Session (Board #360), Sun, 8:00 AM-11:30 AM

Comparison of outcomes with PD-L1 tumor proportion score (TPS) of 50-74% vs 75-100% in patients with non-small cell lung cancer (NSCLC) treated with first-line PD-1 inhibitors. *First Author: Elizabeth Jimenez Aguilar, Dana-Farber Cancer Institute, Boston, MA*

Background: Among patients with NSCLC and a PD-L1 TPS $\geq$50%, the response rate to the PD-1 inhibitor pembrolizumab is ~45%. Whether certain subsets of patients with a PD-L1 TPS $\geq$50% are more likely to benefit from treatment with a PD-1 inhibitor is currently unknown. We compared outcomes among NSCLC patients treated with first-line PD-1 inhibitors and different PD-L1 TPS groupings: 50-74% vs 75-100%. **Methods:** We retrospectively analyzed patients who received a PD-1 inhibitor as first-line treatment for NSCLC with a PD-L1 TPS of $\geq$50% from the Dana-Farber Cancer Institute and Memorial Sloan Kettering Cancer Center. Clinicopathologic characteristics and clinical outcomes were compared among patients with a PD-L1 TPS of 50-74% vs 75-100%. Event-time distributions were estimated using Kaplan-Meier and compared with the log-rank test. **Results:** 112 patients were identified for inclusion in this study: 39.3% (N = 44) had a PD-L1 TPS of 50-74%, and 60.7% (N = 68) had a TPS of 75-100%. There were no significant differences in smoking history, histology, sex, *KRAS* or *EGFR* mutation status, and age between both groups of patients. In the entire cohort, the overall response rate (ORR) was 33.9%, median progression-free survival (mPFS) was 4.2 months (95% CI: 2.8-6.2), median overall survival (mOS) was 20.3 months (95% CI: 17.7-NR). Patients with TPS 75-100% had a significantly higher ORR (13.6% vs 47.1%, P $<$ 0.01), significantly longer mPFS (2.5 mo [95% CI: 1.8-4.5] vs 5.1 mo [95% CI: 3.8-7.4], P = 0.02), and higher estimated 12-month OS (76.4% vs 54.4%) compared to patients with TPS 50-74%. **Conclusions:** In the first-line setting for NSCLC, higher PD-L1 TPS levels of 75-100% is associated with improved clinical outcomes compared to patients with a TPS of 50-74%.

9038 Poster Session (Board #361), Sun, 8:00 AM-11:30 AM

Gemcitabine-cisplatin (GC) + necitumumab (N) versus GC as first-line treatment for stage IV squamous cell lung cancer (SqCLC): An open-label randomized multicenter phase Ib-II trial in Japan. *First Author: Hiroshige Yoshioka, Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan*

Background: A randomized global phase III trial (SQUIRE) demonstrated statistically significant improvement in OS and PFS for GC+N versus GC in patients (pts) with advanced SqCLC. **Methods:** Phase Ib part was a single arm (GC+N) study to determine the recommended dose for the phase II part. Phase II part was a randomized study and pts were assigned on a 1:1 basis to GC+N or GC (G, 1250 mg/m^2 on Days 1 and 8 based on the result from the phase 1b part; C, 75 mg/m^2 on Day 1 of maximum four 3-week cycles; N, 800 mg on Days 1 and 8 continued until PD). The primary endpoint of phase II part was overall survival (OS). Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), time to treatment failure (TTF), health outcomes and safety. **Results:** Of 183 pts randomized, each 90 and 91 pts received GC+N or GC in the phase II part. Baseline patient characteristics were balanced between arms. The OS was prolonged in GC+N compared with GC (Hazard ratio (HR) = 0.656 [95% Confident Interval, CI = 0.465, 0.926]; p = 0.0161). The median OS was 14.9 months (mos) and 10.8 mos for GC+N and GC, respectively. The HR for PFS was 0.562 [0.406, 0.777]; p = 0.0004, and the median PFS was 4.2 mos and 4.0 mos for GC+N and GC, respectively. The ORR was 51.1% and 20.9%, respectively; the HR for TTF was 0.588 [0.433, 0.800]; p = 0.0006. The analysis of health outcomes assessed by the Lung Cancer Symptom Scale and the EuroQol-5D suggested that QOL was not negatively impacted by the addition of N. No deaths occurred on treatment. Grade $\geq$3 adverse events with GC+N that showed a $>$ 5% increase over GC were neutrophil count decreased (42.2% vs. 35.2%), febrile neutropenia (12.2% vs. 3.3%), decreased appetite (11.1% vs. 4.4%) and dermatitis acneiform (5.6% vs. 0). The safety data obtained in the study were consistent with the safety profile expected for GC+N. **Conclusions:** The study demonstrates a clinically meaningful treatment benefit for GC+N in the first-line treatment of Japanese pts with stage IV SqCLC. GC+N was well tolerated. The totality of the efficacy data with the safety profile of N+GC demonstrates a favorable benefit-risk profile for this combination treatment. Clinical trial information: NCT01763788.

9040 Poster Session (Board #363), Sun, 8:00 AM-11:30 AM

Characterization of 1,233 NSCLCs with non-del19/L858R *EGFR* mutations (*EGFR*m) using comprehensive genomic profiling (CGP). *First Author: Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, Irvine, CA*

Background: Exon 19 deletions (del19) and L858R are classic activating *EGFR*m with sensitivity to approved tyrosine kinase inhibitors (TKIs). Recently, FDA-approval of afatinib was broadened to include some more rare *EGFR*m (S768I, L861Q, G719X) in addition to del19/L858R. **Methods:** CGP was performed on 34,328 NSCLCs, of which 5,240 samples (15%; 4,592 tissue and 648 blood-based ctDNA) from 4,872 patients (pts) were positive for short variant *EGFR*m. Pts profiled both pre- and post-EGFR TKI were included. Variants of unknown significance were excluded from our analysis. Tumor mutational burden (TMB) was determined up to 1.2 Mbp of sequenced DNA. **Results:** Del19/L858R were identified in 76% of *EGFR*m NSCLC cases. However, less common *EGFR*m included exon 18 or 20 indels (11%), G719X (5.2%), L861Q (2.8%), extracellular domain (ECD, 2.6%), S768I (2.4%), E709X (1.7%), transmembrane domain (TMD, 0.1%), and other kinase domain (KD, 7.5%) mutations. Frequent mutations were: ECD: A289V/TD (20%), L62R (17%) and R108K (15%); TMD: V651M (75%); KD-other: V834L (9%), L833V (7%), V774M (7%), V769L (6%), and L861R (5%). No notable differences in pt age, gender or disease histology were observed between subsets, except that L861Q pts were more often female (76%, vs 66% all *EGFR*m, P = 0.02). $\geq$1 primary *EGFR*m was common in cases with E709X (100%), S768I (94%), TMD (75%), G719X (70%), KD-other (63%), ECD (57%), and L861Q (31%) relative to del19/L858R (7%), or other indels (2%). T790M co-occurred in 21% of del19/L858R cases, but only 4% of non-del19/L858R *EGFR*m cases. *KRAS*m co-occurred in 1% of del19/L858R cases, 0-3% of cases with G719X, L861Q, S768I, E709X, or exon 18 or 20 indels, and 8% of KD-other. *EGFR* amplification was present in 10-17% of cases with E709X, ECD, KD-other, G719X, or S768I, and 20-25% of remaining *EGFR*m subsets. Median TMB was lowest (2.6 mut/Mb) in cases with del19/L858R or other indels, and highest (5.2 mut/Mb) in cases with G719X or ECDm. Clinical outcomes will be presented for a subset of cases. **Conclusions:** Diverse non-del19/L858R *EGFR*m represent almost 25% of *EGFR*m NSCLC. Many of these *EGFR*m co-occur in a single sample, and may be targetable using currently approved or investigational EGFR TKIs.

9041 Poster Session (Board #364), Sun, 8:00 AM-11:30 AM

Safety and activity of durvalumab + tremelimumab in immunotherapy (IMT)-pretreated advanced NSCLC patients. *First Author: Edward B. Garon, UCLA Medical Center, Los Angeles, CA*

Background: The combination of anti-PD-L1 antibody durvalumab (D) with anti-CTLA-4 antibody tremelimumab (T) showed antitumor activity and manageable tolerability in IMT-naïve patients with advanced NSCLC in the dose-escalation part of a phase 1b study. Here we report safety and clinical activity in one of 3 expansion cohorts. **Methods:** Eligible patients had received up to 3 prior lines of therapy, including prior anti-PD-1 or anti-PD-L1 monotherapy to which they did not respond ("refractory") or responded and then progressed ("relapsed"). Patients had no subsequent systemic therapy until start of study treatment, and had not had any toxicity leading to discontinuation of prior IMT. Patients received D IV 20 mg/kg Q4W for up to 12 months and T IV 1 mg/kg Q4W with the first 4 cycles of D. **Results:** As of 27 Nov 2017, 78 patients received therapy and were followed for a median of 18.4 (0.7–28.0) months. 80% had non-squamous histology, 19% were *KRAS* mutant and 3% were *EGFR* mutant. 94% had received ≥2 lines of prior therapy, including 5 patients with 2 prior IMT. Median time to progression on prior IMT was 7.0 months in relapsed and 2.6 months in refractory patients. Treatment-related AEs were reported in 72% of patients; the most common were fatigue (26%), diarrhea (23%), and nausea (14%). Grade 3/4 treatment-related AEs occurred in 28% of patients, with diarrhea (6%) being most common. 5 patients (6%) discontinued due to a treatment-related AE, (diarrhea in 4%) and no treatment-related deaths occurred. Clinical outcomes are summarized in the Table. DCR24 was 21.8% (95% CI, 13.2–32.6); for these 17 patients, median duration of exposure was 9.5 months, compared with 6.1 months on prior IMT. **Conclusions:** D+T had a manageable safety profile in IMT-pretreated patients with prolonged stable disease or better seen in some patients. Clinical trial information: NCT02000947.

	IMT-relapsed n = 40	IMT-refractory n = 38	Total N = 78
Confirmed ORR (CR + PR)			
n (%)	2 (5.0)	2 (5.3)	4 (5.1)
(95% CI)	(0.6–16.9)	(0.6–17.7)	(1.4–12.6)
DCR at 24 wks			
n (%)	9 (22.5)	8 (21.1)	17 (21.8)
(95% CI)	(10.8–38.5)	(9.6–37.3)	(13.2–32.6)
PFS			
Median, mo	2.5	1.7	1.8
(95% CI)	(1.6–3.5)	(1.6–1.8)	(1.6–2.5)
OS			
Median, mo	8.5	8.3	8.4
(95% CI)	(4.0–14.3)	(6.0–10.4)	(6.2–10.4)
12-mo rate (%)	37.5	30.1	34.1

9042 Poster Session (Board #365), Sun, 8:00 AM-11:30 AM

Tumor mutation burden and efficacy of targeted therapy in patients with *EGFR* mutant lung cancers. *First Author: Michael David Offin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor mutation burden (TMB) is a biomarker of response to immune checkpoint blockade. The impact of TMB on outcomes with targeted therapies has not been explored. We hypothesized that TMB would inversely correlate with efficacy of targeted therapy in patients with *EGFR* mutant lung cancers proposing that additional mutations represent potential pathways for resistance with targeted therapies. **Methods:** We studied patients (pts) with metastatic *EGFR* mutant lung cancers with sensitizing exon 19 deletion (ex19del) or L858R variants treated with first/second generation tyrosine kinase inhibitors (TKIs) with pre-treatment targeted next generation sequencing (NGS; IMPACT) identified between January 2010 and September 2017. TMB was assessed in pre-TKI tissue defined as total non-synonymous mutations/Mb as assessed by the IMPACT platform. The effect of TMB on time on treatment (ToT) and overall survival (OS) were evaluated in univariate and multivariate analyses. **Results:** We identified 153 pts with metastatic *EGFR* mutant lung cancers profiled with MSK-IMPACT. Median TMB was 3.8 mutations/Mb (7.4 mutations/Mb for unselected lung cancers), but exhibited a wide range (0.82-17.9). In those with ≤ median TMB, ToT and OS were higher compared to those with > median TMB (ToT 17 vs. 10 months, HR 0.56, p = 0.006; OS 41 vs. 29 months, HR 0.52, p = 0.03). Within subgroups (never smokers, former smokers, TP53 co-mutant, age ≥ or < 65, man and woman), efficacy was consistently higher in those with ≤ median TMB. In multivariate analysis incorporating TMB, *TP53* status, and *EGFR* ex19del vs. L858R, ToT remained improved in those with TMB ≤ median (HR 0.93, p = 0.02) but OS was not significant (HR 0.94, p = 0.3). **Conclusions:** Low TMB is associated with longer time on treatment in patients with metastatic *EGFR* mutant lung cancers treated with targeted therapy. This relationship is the reverse of that is seen with immune checkpoint blockade. TMB can serve as a relevant biomarker in lung cancers, with varied implications based on the nature of therapy being used.

9043 Poster Session (Board #366), Sun, 8:00 AM-11:30 AM

Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. *First Author: D. Ross Camidge, University of Colorado, Aurora, CO*

Background: The primary ALEX (NCT02075840) analysis showed superior investigator (INV)-assessed PFS with ALC vs CZ (HR 0.47, 95% CI 0.34–0.65, p<0.001; median 11.1 months [m] CZ, not estimable [NE] ALC) in untreated ALK+ NSCLC. We report updated data (cutoff Dec 1 2017). **Methods:** ALEX enrolled patients (pts) with stage IIIB/IV ALK+ NSCLC (by central IHC) and no prior systemic therapy for advanced NSCLC; asymptomatic CNS metastases (mets) were allowed. Pts were randomized 1:1 to receive ALC 600mg BID (n = 152) or CZ 250mg BID (n = 151). Primary endpoint: PFS (INV, RECIST v1.1), with q8w CNS imaging in all pts. Secondary endpoints: ORR, time to CNS progression, DOR, OS, and safety. **Results:** With 10m longer follow-up (median 22.8m CZ vs 27.8m ALC), ALC significantly reduced risk of disease progression/death by 57% vs CZ (ITT; stratified HR 0.43, 95% CI 0.32–0.58): median PFS (INV) was 34.8m ALC vs 10.9m CZ. Median PFS by baseline (BL) CNS mets status was 27.7m ALC vs 7.4m CZ (HR 0.35, 95% CI 0.22–0.56) in pts with, and 34.8m vs 14.7m (HR 0.47, 95% CI 0.32–0.71) in pts w/out BL CNS mets. In the BL CNS mets group, the number of pts who received WBRT (n = 16 ALC, n = 17 CZ) or SRS (n = 4 ALC, n = 6 CZ) was balanced, as was the number of BL lesions (median 2 per arm). Updated secondary endpoint data (INV): ORR 82.9% ALC (95% CI 75.95–88.51; n = 152) vs 75.5% CZ (95% CI 67.84–82.12; n = 151); median DOR 33.3m ALC (95% CI 31.1–NE; n = 126) vs 11.1m CZ (95% CI 7.5–13.0; n = 114), stratified HR 0.33, 95% CI 0.23–0.48. OS data are still immature (events ALC 28.3%, CZ 31.8%; stratified HR 0.76, 95% CI 0.50–1.15). Despite significantly longer treatment (Tx) duration with ALC (27.0m vs 10.8m), proportion of pts with grade 3–5 AEs (44.7% vs 51.0%), AEs leading to dose reduction (16.4% vs 20.5%) or interruption (22.4% vs 25.2%) were lower with ALC vs CZ. Proportion of pts with AEs leading to discontinuation: 13.2% each arm. Fatal AEs: 5% CZ (2 Tx-related AEs) and 4% ALC pts (0 Tx related). **Conclusions:** ALC 600mg BID showed superior efficacy vs CZ (PFS HR 0.43, median 34.8m ALC vs 10.9m CZ) in untreated ALK+ NSCLC, regardless of BL CNS mets, and favorable and durable tolerability despite longer Tx duration, consolidating ALC as the new standard of care. Clinical trial information: NCT02075840.

9044 Poster Session (Board #367), Sun, 8:00 AM-11:30 AM

Exome analysis to reveal genomic markers associated with better efficacy of nivolumab in lung cancer patients. *First Author: Corentin Richard, Research Platform in Biological Oncology, Center GF Leclerc, Dijon, France*

Background: Monoclonal antibodies targeting immune checkpoint inhibitors revolutionized the treatment of lung cancer. However, only one-quarter of non-small cell lung cancer patients (NSCLC) benefit from these new therapies. The assessment of PD-L1 tumor expression by IHC is used to select responder patients and is considered as the gold standard biomarker in many studies; however, this marker does not predict the absence of anti-PD-1 efficacy. Recent studies suggest that high tumor mutational burden (TMB) is associated with better efficacy of Nivolumab compared with chemotherapy. In addition, transcriptomic and exome analyses have revealed potential biomarkers needing further confirmation. It is thus of major importance to define biomarkers that efficiently predict Nivolumab efficacy. **Methods:** We performed somatic and constitutional exome analyses for 77 patients with NSCLC treated with Nivolumab. We studied: 1-tumor-related characteristics: aneuploidy, tumor copy number alteration clonality, mutational signatures, TMB, mutations in WNT, AKT, MAPK and DNA repair pathways, and 2-immunological characteristics: number of intratumoral TCR clones, HLA type, number of neoantigens, and Type I IFN mutation pathway; and 6 clinical parameters. **Results:** A high TMB per Mb, a high number of neoantigens, mutational signatures 1A and 1B, mutations in DNA repair pathways and a low number of TCR clones are associated with greater PFS. Using the least absolute shrinkage and selection operator method, we established an exome-based model with 9 parameters that could discriminate patients with good or poor PFS ($p < 0.0001$) and OS ($p = 0.002$) independently from clinical data. Moreover, this model had improved ability to predict outcomes compared with a PD-L1 clinical model with or without TMB (Area Under Curve: Clinical = 0.80, TMB = 0.81, exome-derived = 0.93). The model was externally validated on another cohort of 34 patients treated with Pembrolizumab (Rizvi *et al.*, 2015). **Conclusions:** Altogether, these data provide a validated biomarker that predicts the efficacy of Nivolumab or Pembrolizumab in lung cancer patients. Our biomarker appears to be superior to PD-L1 labelling and TMB models.

9045 Poster Session (Board #368), Sun, 8:00 AM-11:30 AM

BRAF-mutant non-small cell lung cancer (NSCLC): Patient (pt) characteristics and outcomes by class of mutation. *First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA*

Background: *BRAF* mutations (muts) occur in 2-4% of NSCLC. Recent work suggests that *BRAF* muts may be grouped into 3 classes: 1) V600 muts that signal as monomers, 2) activating non-V600 muts that function as dimers, and 3) kinase-impaired non-V600 muts that require RAS input. Whether mut class is associated with specific clinicopathologic features or clinical outcome is unknown. **Methods:** We performed a retrospective analysis of NSCLC pts with *BRAF* muts treated at Massachusetts General Hospital and Dana-Farber Cancer Institute between 2006 and 2017 to determine clinicopathologic characteristics and estimate overall survival (OS). **Results:** We identified 237 pts with Stage I-IV BRAF-mutant NSCLC (107 (45%) class 1, 76 (32%) class 2, and 54 (23%) class 3). Most pts were white (85%) smokers (88%) with adenocarcinoma (90%). Smoking status was similar for pts with class 2 and 3 muts (3% vs 6% never-smokers, $p = 0.649$), but pts with class 1 muts were more likely to be never-smokers (22%; $p < 0.001$ vs class 2, $p = 0.011$ vs class 3). The frequency of concurrent *RAS* (KRAS or NRAS) co-alterations in class 1 was 1%, which was significantly lower than the frequency in class 2 (12%, $p = 0.002$) and class 3 (24%, $p < 0.001$). Nine (47%) of 19 kinase-dead tumors had *RAS* co-alterations. Among 140 pts with metastatic NSCLC, median OS was 40.1 months (mos, n = 69, 95% CI:17.5-56.1) for class 1, 13.9 mos (n = 39, 95% CI:7.4-18.7) for class 2, and 15.6 mos (n = 32, 95% CI 8.9-37.4) for class 3 pts. OS was not different for class 2 and 3 pts ($p = 0.591$), but presence of a class 1 mut was associated with improved OS (median 40.1 vs 15.6 mos when class 2 and 3 pts were pooled, HR = 0.5,95% CI 0.3-0.8, $p = 0.002$). When 40 pts who received therapies targeting the mitogen-activated protein kinase pathway were excluded, there was still a trend toward improved OS for class 1 muts (median 39.1 vs 13.9 mos for class 2 and 3 pts; HR = 0.6, 95% CI 0.3-1.0, $p = 0.059$). **Conclusions:** Pts with class 2 and 3 BRAF-mutant NSCLC share clinicopathologic features and outcomes that may be distinct from pts with class 1 muts. Our findings highlight the need for therapies that effectively target class 2 and 3 BRAF muts.

9046 Poster Session (Board #369), Sun, 8:00 AM-11:30 AM

Phase I/Ib study of pembrolizumab and vorinostat in patients with metastatic NSCLC (mNSCLC). *First Author: Andreas Nicholas Saltos, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: The oral histone deacetylase inhibitor (HDACi) vorinostat (V) enhances tumor immunogenicity through several mechanisms and may augment response to PD-(L)1 blockade (IO). We report mature results from a phase I/Ib trial testing the combination of V with pembrolizumab (P) in mNSCLC. **Methods:** In phase I, pts with either IO-naïve or IO-pretreated mNSCLC were treated with P (200mg IV q3 wk) + V (200 or 400 mg PO daily). In phase Ib expansion, pts were required to have progressed on prior IO treatment. Primary endpoints were safety/tolerability; secondary endpoints included RR, PFS, DOR, and OS. Tissue and blood specimens from pre- and post-treatment were collected for correlative analyses to determine tumor gene expression changes, levels of myeloid-derived suppressor cells and changes in peripheral T-cell phenotype. **Results:** Between 3/2016 - 9/2017, Phase I: 14 pts were treated (4 at 200mg, and 10 at 400mg V dose); and Phase Ib: 20 pts were treated. Median age: 67 (range 38-82); Females: 11 (32%); ECOG 1: 32 (94%); and never/former/current smokers: 3/23/8 (9%/68%/23%). No DLTs were observed. The RP2D is P 200mg and V 400mg. Most common AE of any grade were fatigue (11%), anorexia (9%) and nausea/vomiting (8%). Most common G3 AE were myalgia, anemia and diarrhea. There were no G4/5 AEs. 3 (9%) pts had treatment discontinued due to toxicity. 30 pts are evaluable for response. PD-L1 expression was $\geq$ 1% in 18/30 (60%), and $\geq$ 50% in 11/30 (37%). 6 pts were IO-naïve and 24 IO-pretreated. 4 (13%) had PR (2 confirmed), 16 (53%) had SD, and 10 (33%) had PD for a disease control rate of 67%. In the IO-pretreated Ib cohort, 2 pts (1 confirmed; 1 pending repeat CT) had a PR and 10 had SD (8 confirmed). For IO-pretreated pts, mPFS was 3.2 months. For IO-naïve, mPFS was 7.6 months. Preliminary tumor RNA-seq studies showed increase in IFN gamma and HDACi target gene expression, including CXCL9. **Conclusions:** V + P was well tolerated. The combination demonstrates preliminary anti-tumor activity despite progression on prior IO treatment and gene expression changes consistent with mechanism of HDACi action. A randomized phase II portion of this study, examining P combined with V vs. placebo in immunotherapy naïve pts, is ongoing. Clinical trial information: NCT02638090.

9047 Poster Session (Board #370), Sun, 8:00 AM-11:30 AM

Patient-reported outcomes (PROs) in the randomized, phase III IMpower150 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous metastatic NSCLC (mNSCLC). *First Author: Martin Reck, LungenClinic Grosshansdorf, German Center for Lung Research, Grosshansdorf, Germany*

Background: Atezo (anti–PD-L1) + bev (anti-VEGF) + chemo prolonged PFS vs bev + chemo in patients (pts) with 1L nonsquamous mNSCLC in the randomized, Phase III IMpower150 study. PRO data, including symptom burden, functioning and health-related quality of life (HRQoL), were evaluated to assess overall clinical benefit in each treatment (Tx) arm. **Methods:** Pts received atezo 1200 mg + carboplatin (C) AUC 6 + paclitaxel (P) 200 mg/m^2 (Arm A) or atezo + bev 15 mg/kg + C + P (Arm B) vs bev + C + P (Arm C) IV q3w for 4 or 6 cycles per investigator decision, then maintenance atezo, atezo + bev, or bev, respectively. PRO data were collected using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Prespecified analyses included the mean change from baseline in symptoms, functioning and HRQoL and time to deterioration (TTD) in lung cancer symptoms. Clinically meaningful change was defined as a $\geq$10-point change in score from baseline. **Results:** PRO completion rates were high ($\geq$70% through cycle 23 for all arms). Mean changes from baseline indicated that a clinically meaningful worsening ($\geq$10-point change) was not observed in any arm through cycle 13 ($\approx$25% of pts remain in Arm C); HRQoL and physical functioning scores minimally decreased (Arm A: -2.83 and -3.39; Arm B: -1.8 and -3.98; Arm C: -1.92 and -2.6) with concurrent numerical worsening in Tx-related symptom scores (e.g., fatigue, constipation, nausea/vomiting). Following chemo completion, scores returned to baseline or numerically improved. HRQoL, physical functioning and Tx-related symptoms were comparable between Arms B and C. No difference was observed between arms in the TTD in lung cancer symptoms assessed. All arms reported numerical improvement in multiple lung cancer symptoms while on Tx. **Conclusions:** These data suggest that prolonged PFS in Arm B was achieved without compromising HRQoL or physical functioning despite higher Tx-related AEs than Arm C. PRO data reflected a minimal Tx burden across arms, further reduced following chemo discontinuation. Overall, PRO data support the positive benefit:risk of the clinical data with atezo + bev + chemo in 1L nonsquamous mNSCLC. Clinical trial information: NCT02366143.

9048 Poster Session (Board #371), Sun, 8:00 AM-11:30 AM

Detection and clearance of *RET* variants in plasma cell free DNA (cfDNA) from patients (pts) treated with LOXO-292. *First Author: Geoffrey R. Oxnard, Dana-Farber Cancer Institute, Boston, MA*

Background: LOXO-292 is a novel, highly-selective, small molecule RET inhibitor in clinical development for pts with advanced cancers harboring oncogenic *RET* alterations (e.g. non-small cell lung cancer [NSCLC], medullary thyroid cancer [MTC], papillary thyroid cancer [PTC], and any other cancer). Here we study modulation of *RET* variant allele frequencies (AF) in plasma cfDNA with LOXO-292 therapy. **Methods:** LOXO-292 is being studied in an ongoing Phase 1 study in pts with advanced solid tumors, with enrollment enriched for pts with *RET* alterations (NCT03157128). Blood is collected pretreatment, after 15 days of treatment, and at each restaging for cfDNA analysis by next-generation sequencing (NGS, Guardant). **Results:** As of 1/5/18, 57 pts were enrolled (35 *RET* fusion+ (27 NSCLC, 7 PTC, 1 other), 20 *RET*-mutant MTC, 2 other) to 7 doses (20mg QD→160mg BID). 213 plasma samples were collected. Here we report on 44 pts with plasma NGS results available. Of 41 pts enrolled based on a *RET* variant detected in a tumor sample, concordant *RET* alterations were detected in 26 (63%) of the corresponding pre-treatment plasma samples, including 15/22 (68%) pts with *RET*-fusion NSCLC and 8/12 (67%) pts with *RET*-mutant MTC. Median AF was higher for MTC (6.9%) than NSCLC (0.7%). In negative pre-treatment samples, peak AF for other detected alterations was low (0.3% median), suggesting low tumor DNA shed into plasma. Of 18 pts with a detectable pre-treatment plasma *RET* alteration and day 15 plasma NGS, *RET* alteration AF decreased by a median of 92%, with complete clearance in 7 pts (39%). Day 15 plasma clearance was observed at multiple doses (20-60mg BID), and was more common in *RET* fusion-positive (55%) than *RET*-mutant (14%) pts. Data for additional pts will be updated at the time of presentation. **Conclusions:** The rapid clearance of *RET* variants from plasma cfDNA on LOXO-292 supports its observed clinical activity across a range of doses, tumor types and *RET* alterations. NGS of plasma cfDNA can detect a range of targetable *RET* variants, though tumor genotyping remains critical if the initial plasma NGS is negative. Serial plasma genotyping warrants continued study as an early pharmacodynamic marker for novel targeted therapies. Clinical trial information: NCT03157128.

9049 Poster Session (Board #372), Sun, 8:00 AM-11:30 AM

Prognostic relevance of tumor sequencing in metastatic lung adenocarcinomas. *First Author: Ronglai Shen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Routine next generation sequencing (NGS) testing for patients with lung cancer allows the rapid identification of a broad array of targetable molecular drivers. We hypothesized that the results of routine NGS testing, exploring both driver and non-driver oncogenes, could be used to develop a prognostic risk score for patients with metastatic lung adenocarcinoma. **Methods:** We employed an ensemble penalized proportional hazards model to derive a genetic risk score using sequencing results of 341 cancer associated genes in 1,054 patients with metastatic lung adenocarcinoma. A 3-fold cross-validation was used to obtain unbiased estimates of prediction accuracy. **Results:** A total of 341 genes mutated at least once across the cohort were included in the analysis. The most frequently mutated genes were TP53 (55%), KRAS (30%), EGFR (29%), STK11 (18%), KEAP1 (18%). Mutations in TP53, KRAS, STK11, KEAP1, and SMARCA4 were associated with poor prognosis. Based on the risk score, patients were categorized into risk groups. Patients in the low risk group had a median overall survival of 32.8 months (95% CI: 26.3-38.5) as compared to 7.3 months (95% CI 5.5-10.9) in the high risk group. The three-year survival probability is 47% in the low risk group versus 12% for the high risk group. Concurrent mutations in both STK11 and KEAP1 had the largest adverse prognostic implications. While overall mutation burden and clonal heterogeneity were moderately associated with survival, they did not provide additional prognostic value over the genetic risk score system. The risk score remains a significant independent predictor after adjusting for clinical variables (age, sex, smoking history). **Conclusions:** Using the results of routine NGS testing, we developed a molecular prognostic risk score for patients with metastatic lung adenocarcinoma. These results demonstrate that NGS testing for patients with lung cancer can be used not only to identify targetable molecular drivers, but also be leveraged to develop a powerful molecular scoring system that can be used for stratification in clinical trials as well as comparisons of patient populations derived from real world data.

9050 Poster Session (Board #373), Sun, 8:00 AM-11:30 AM

An open-label, multicenter, phase II single arm trial of osimertinib in non-small cell lung cancer patients with uncommon EGFR mutation (KCSG-LU15-09). *First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, Korea, Republic of (South)*

Background: Approximately 10% of EGFR mutants harbor uncommon mutations, which represent a heterogeneous group of rare molecular alterations within exons 18-21 and the sensitivity to EGFR TKIs is variable. Osimertinib is a potent irreversible inhibitor of both sensitizing EGFR mutation and T790M. In preclinical data, the potency of osimertinib against uncommon EGFR mutants other than exon 20 insertion was fairly good. Here we present the efficacy and safety of osimertinib in patients with uncommon EGFR mutation positive NSCLC. **Methods:** Patients with histologically confirmed metastatic or recurrent NSCLC with activating EGFR mutation other than exon 19 deletion, L858R, T790M and insertion in exon 20 were eligible. Patients received 80mg of osimertinib per oral daily until progression or unacceptable toxicity. Response was assessed every 8 weeks by investigator. The trial was registered with ClinicalTrials.gov, number NCT03424759. **Results:** Between Mar 2016 and Oct 2017, 36 patients were enrolled. Median age was 59.5, 61% male, 44% never smoker, 97% adenocarcinoma. 61% of patients were treated as first-line therapy. The most common mutations are G719A/C/D/S/X (19, 52.8%) followed by L861Q (9, 25%), S768I (8, 22%), and others (4, 11%). The overall response rate was 50.0% (95% CI 32.8-67.2) and DCR was 88.9% (95% CI 78.1-99.7). Seven patients (77.8%) with L861Q mutation achieved partial response; 10 (52.6%) with G719A/C/D/S/X mutation; three (37.5%) with S768I mutation. At data cutoff (Nov, 2017), the median PFS was 9.5 months (range 1.0-20.1) and median duration of response was 7.0 months (95% CI 4.7-9.3). The most common adverse events were rash (n = 11, 30.6%), anorexia (n = 8, 22.2%), and diarrhea (n = 7, 19.4%). Grade 3 or 4 AEs were reported in 8 of 36 patients (22%), but all of AEs were manageable. **Conclusions:** Osimertinib showed highly active and durable in NSCLC patients harboring uncommon EGFR mutation with manageable safety profile, consistent with previous reports. Further analysis will be updated. Clinical trial information: NCT03424759.

9051 Poster Session (Board #374), Sun, 8:00 AM-11:30 AM

Dendritic-cell vaccine (DCVAC) with first line chemotherapy in patients with stage IV NSCLC primary analysis of phase 2, open-label, randomized, multicenter trial. *First Author: Libor Havel, Thomayer's Hospital, 1st Faculty of Medicine of Charles University in Prague, Prague, Czech Republic*

Background: Immunotherapy for induction of tumor cell specific immune responses destroying tumor cells, has emerged as a promising treatment modality in lung cancer (LuCa). Autologous DCVAC can present tumor antigens to elicit a durable immune response. We hypothesized that adding DCVAC to the standard of care chemotherapy (ct) could prolong progression-free survival (PFS) and overall survival (OS). **Methods:** This study evaluated the efficacy and safety of DCVAC/LuCa (active cellular immunotherapy based on dendritic cells) concomitantly added to ct (carboplatin/paclitaxel) - Arm A (A) vs DCVAC/LuCa + immune modulators (IFN-α and hydroxychloroquine) - Arm B (B) vs ct - Arm C (C) in NSCLC patients (pts). Randomization 1:1:1; pts in A and B received up to 15 doses of DCVAC, ct was given 4-6 cycles in A and C. Stage IV NSCLC was confirmed histologically or cytologically, ECOG 0-1 pts were eligible. Stratification was done by histology subtype and smoking history. Primary efficacy analysis compared A vs C only as enrollment to B was closed early based on Sponsor's assessment of further clinical development potential, there were no safety concerns or signals. **Results:** 112 pts at 12 sites were randomized (A/45 B/29 C/38). Patients characteristics were comparable across the study groups with the exception of gender (m/f, %: 50/50 (A) and 26/74 (C) and smoking history (75 % of smokers in A, 97 % in C). Median follow up time was 14.1 months, range 0.032-29,765. Median OS was 15.5 months in A compared to 11.8 months in C, hazard ratio (HR) 0.56, p-value 0.05, 95% CI, data maturity 65%. Median PFS was 6.73 in A and 5.65 months in C HR 0.64, p-value 0.05, 95% CI, data maturity 81%. Overall response rate was 45% in A vs 22.9% in C. Most TEAEs were related to ct (anemia [37%-A, 32%-C], neutropenia [48% in A, 21%-C], thrombocytopenia [28% in A, 27% in C]). There were no grade $\geq$ 3 TEAEs solely related to DCVAC. Most common leukapheresis-related AEs were haematoma and hypotension. **Conclusions:** Addition of DCVAC-based immunotherapy to the standard of care chemotherapy significantly improved OS in stage IV NSCLC. Clinical trial information: EudraCT 2014-003084-37.

9052 Poster Session (Board #375), Sun, 8:00 AM-11:30 AM

Association of EGFR and HER-2 exon 20 mutations with distinct patterns of response to immune checkpoint blockade in non-small cell lung cancer. *First Author: Marcelo Vailati Negrao, Department of Thoracic / Head and Neck Medical Oncology - The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint blockade has led to unprecedented durable clinical benefit in metastatic non-small cell lung cancer (NSCLC), but response rates are low for patients with targetable driver mutations. EGFR and HER-2 exon 20 mutations account for ~4% of NSCLC, but outcomes for these patients when treated with immune checkpoint blockade have not been previously reported. **Methods:** We queried GEMINI, a MD Anderson Lung Cancer Moon Shot funded database for prospective collection of clinical information for patients with NSCLC, for patients with driver mutations in EGFR exon 19, 20, 21 and HER-2 exon 20 and treated with immune checkpoint inhibitors. We assessed overall survival (OS), progression-free survival (PFS) and overall response rate (ORR). **Results:** From 2014 to 2018, 90 patients with classic EGFR mutations (exon 19 del + exon 21 L858R, n = 38), EGFR exon 20 mutations (n = 36; no T790M included) and HER-2 exon 20 mutations (n = 16) had been treated with checkpoint inhibitors. Compared to classic EGFR mutants, EGFR exon 20 mutants demonstrated a higher disease control rate at 6 and 12 months as well as higher ORR. Also, EGFR exon 20 mutants demonstrated significantly higher PFS (HR 0.45, p = 0.002) and OS (HR 0.2, $p < 0.001$) (Table). These differences remained significant in multivariate analysis after adjusting for age, smoking status, radiation prior to treatment initiation and treatment with concurrent agents such as chemotherapy and/or radiation. HER-2 exon 20 mutants had similar ORR and PFS compared to classic EGFR mutants (HR 1.1, p = 0.8) (Table). **Conclusions:** EGFR exon 20 mutations are associated with superior outcome from immune checkpoint inhibitors compared to classic EGFR and HER-2 exon 20 mutations. Further studies on PD-L1 status and tumor mutation burden in these molecularly-defined groups are ongoing to address potential underlying mechanisms associated with these findings.

	EGFR exon 20 N = 36	Classic EGFR N = 38	HER-2 exon 20 N = 16
Disease control – N (%)			
6 months	13 (36)	6 (16)	0 (0)
12 months	4 (11)	0 (0)	0 (0)
Response rate – N (%)			
CR	1 (3)	0 (0)	0 (0)
PR	8 (22)	0 (0)	1 (6)
SD	9 (25)	6 (16)	2 (13)
PD	15 (42)	32 (84)	13 (81)
NA	3 (8)	0 (0)	0 (0)
Survival – median			
PFS	2.9	1.9	1.8
OS	NR	11.5	17.1

9053 Poster Session (Board #376), Sun, 8:00 AM-11:30 AM

Efficacy and safety results of ramucirumab in combination with osimertinib in advanced T790M-positive *EGFR*-mutant NSCLC. *First Author: David Planchard, Gustave Roussy, Villejuif, France*

Background: Progression of *EGFR*-mutant non-small cell lung cancer (NSCLC) occurs in most patients (pts) despite initial benefit with a first-line EGFR tyrosine kinase inhibitor (TKI). A first- or second generation EGFR TKI + a VEGF- or EGFR-directed monoclonal antibody (mAb) has shown promising results in pts with EGFR-mutant NSCLC. **Methods:** This ongoing, single-arm, Phase 1study (NCT02789345) enrolled pts with T790M-positive *EGFR*-mutant (Ex19del or L858R) NSCLC with prior progression on first-line EGFR TKI therapy. The primary phase 1b objective was assessment of safety/tolerability of ramucirumab (Ram), a VEGFR2 mAb, + osimertinib (Osi), a novel third-generation EGFR TKI. Key secondary efficacy endpoints were investigator assessed objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS). **Results:** Pts (N = 25) were 45-80 years (median 64) with ECOG-PS 0 (n = 3) or 1 (n = 22) and tobacco history of current (n = 5), former (n = 8), or never (n = 12). Pts received Ram 10mg/kg IV (Day 1 Q2W) + Osi 80mg QD. At interim analysis, median therapy duration was 13 cycles (IQR: 6-16) for Ram and 13 cycles (IQR: 7-15) for Osi. Median follow-up was 7.2 months (90% CI: 6.51, 7.92). All pts had ≥1 treatment-related adverse event (TRAE), most commonly hypertension (44%), diarrhea (32%), stomatitis (24%). Grade (G) 3 TRAEs were hypertension (8%), platelet count decreased (8%), anemia (4%), congestive heart failure (CHF) (4%), neutrophil count decreased (4%). No G4 TRAEs were reported. Ram was discontinued for G3 CHF in a 76-year-old pt, who subsequently experienced a G5 TRAE of subdural hemorrhage ~7 weeks after the last dose of Ram. Fifteen pts remain on study drug. ORR was 76% (19/25), with CR 4% (1/25), PR 72% (18/25), SD 16% (4/25), PD 4% (1/25), and non-evaluable 4% (1/25). DCR was 92%. Median DOR was not reached (90% CI: NR, NR). DOR rate at 6 months was 81.6% (90% CI: 59.0, 92.4). Median PFS was not reached (90% CI: 5.49, NR). PFS rate at 6 months was 64.0% (90% CI: 43.7, 78.6) with 64% of pts censored. **Conclusions:** Ram + Osi demonstrated encouraging anti-tumor activity. The safety profile was consistent with monotherapy for each drug, with no additive toxicities. Clinical trial information: NCT02789345.

9054 Poster Session (Board #377), Sun, 8:00 AM-11:30 AM

Survival disparities among African American (AA) patients (pts) with *EGFR*-mutated non-small cell lung cancer (NSCLC). *First Author: Haiying Cheng, Department of Medical Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY*

Background: Little is known about whether AA pts with *EGFR*-mutated NSCLC exhibit similar clinical characteristics and outcomes compared to non-AA pts. **Methods:** We retrospectively reviewed the cancer registry at Montefiore Medical Center, a community-based academic center, for lung cancers diagnosed between 01/2009 and 12/2015 (n = 2773). We restricted our analyses to nonsquamous NSCLC pts with available pathology (n = 1350). EGFR testing was performed via PCR-based technology spanning exons 18-21 (n = 672) during that period. **Results:** Our patient population was 38% AA, 45% White, and 17% other. The *EGFR* mutation rate was 15% (98/672) in all pts, compared to 13% (35/266) in AA and 16% (63/406) in non-AA. The mutational spectrum varied by race with Del 19, L858R and uncommon mutations being 46%, 23% and 31% in AA, compared to 43%, 35% and 22% in non-AA. Among pts with *EGFR*-mutated NSCLC, AA pts had shorter survival in comparison to non-AA pts (p = 0.015, using cox proportional hazard model after adjusting for smoking, gender and age) (2-yr survival rates: 33% vs. 61%), which was evident for earlier stages (I-III) (p = 0.0078) (2-yr survival rates: 50% vs. 87%) and suggested for metastatic disease (p = 0.10). However, there was no evidence for racial disparity in survival among patients with *EGFR* wild type (wt) (p = 0.80) (2-yr survival rates: 38% vs. 39%). Further, AA pts were heavier than non-AA pts with *EGFR* mutations (75.1 kg vs. 65.6 kg, p = 0.012). No significant differences were identified for age at diagnosis, gender, presenting stages, smoking history, socioeconomic status, and the standard uses of EGFR TKIs between AA and Non-AA. The similar survival among EGFR wt pts argues further against the treatment disparity between AA and non-AA pts. **Conclusions:** This is the first report of inferior survival among AA NSCLC pts with *EGFR* mutations, relative to non-AA pts. These results may be related to higher frequency of uncommon mutations or possibly PK differences secondary to higher average weight. Confirmation studies in larger pt cohorts and further investigation on how weight difference and tumor biology may contribute to the racial disparity in survival are warranted.

9055 Poster Session (Board #378), Sun, 8:00 AM-11:30 AM

Prevalence and prognosis of DNA repair deficiency in squamous cell carcinoma (SCC) patients enrolled on the S1400 LungMAP study. *First Author: Taofeek Kunle Owonikoko, Emory University, Atlanta, GA*

Background: DNA homologous recombination repair deficiency (HRRD) is a vulnerability that has been exploited for PARP inhibitor therapy. This concept is currently being evaluated in S1400G substudy of LungMAP where HRRD(+) SCC patients are treated with a PARP inhibitor, talazoparib. We assessed the prevalence and characteristics of HRRD(+) SCC patients screened on LungMAP. **Methods:** All patients receive Foundation One NGS screening platform for enrollment on LungMAP sub-studies. HRRD is defined as genetic alteration predicted to have functional consequence in genes involved in HRR (ATM, ATR, BARD1, BRCA1, BRCA2, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCF, FANCM, NBN (NBS1), PALB2, RAD51, RAD51B (RAD51L1), RAD54L, RPA1) but also define a key subgroup based on a set of the best clinically validated genes: ATM, ATR, BRCA1, BRCA2, and PALB2 . Survival was measured from the date of sub-study assignment. **Results:** Biomarker results were available for 1244 eligible patients screened between June 2014 and October 2017. HRRD was detected in 190 (15.3%) patients, higher than the 9% rate assumed for the design of S1400G substudy. HRRD(+) and HRRD(-) patients did not differ in terms of median age (67 vs. 66 years); male gender (68% vs. 67%); race (85% vs. 84% and 11% vs. 9% for White and Black) or tobacco exposure (94% vs. 95%). BRCA2 alteration was the most frequent of the HRRD gene alterations. Survival was not different by HRRD(+) versus HRRD(-) status (HR[95%CI]: 1.11 [0.91-1.37], p = 0.29). Alterations in BRIP1 (0.58 [0.28-1.23]; p = 0.16), CHK2 (0.43[0.16-1.15]; p = 0.09), FANCM (1.48[0.87-2.52]; p = 0.15) and FANC-A/C/D2 (1.70[1.07-2.72]; p = 0.03) showed a trend in prognostic association. **Conclusions:** HRRD is frequent in SCC and could define a large subset of SCC for targeted therapy if validated in the ongoing S1400G substudy of LungMAP.

	Overall prevalence	Prevalence among HRRD alterations
BRCA2	3.9%	23.0%
FANCM	2.0%	11.7%
BRCA1	1.7%	9.9%
BRIP1	1.3%	7.5%
ATM	1.1%	6.6%
PALB2	1.1%	6.6%
ATR	1.0%	6.1%
CHEK2	1.0%	5.6%
FANCA	0.8%	4.7%
FANCC	0.7%	4.2%
FANCD2	0.4%	2.3%
BARD1	0.3%	1.9%
CHEK1	0.3%	1.9%
FANCF	0.2%	1.4%
RAD51L1	0.2%	1.4%
RAD51	0.2%	1.4%
NBN	0.2%	0.9%
RAD51B	0.2%	0.9%
RAD54L	0.2%	0.9%
RPA1	0.2%	0.9%

9056 Poster Session (Board #379), Sun, 8:00 AM-11:30 AM

Differential outcomes in patients with uncommon EGFR exon 19 mutations. *First Author: Tyler Stewart, Yale New Haven Hospital, New Haven, CT*

Background: Exon 19 deletions (ex19 dels) account for ~50% of EGFR-mutant NSCLCs. The E746_A750 ex19 del accounts for 75% of these cases. Two frequent uncommon ex19 dels are L747_P753 > S and L747_A750 > P. Studies have largely grouped outcomes of ex19 dels together despite mutational differences. We previously demonstrated *in vitro* that erlotinib and osimertinib suppress phosphorylation of EGFR (pEGFR) in the E746_A750 and L747_P753 > S mutants, but do not effectively suppress pEGFR in the L747_A750 > P mutant, whereas afatinib suppresses pEGFR in all 3 mutant types. Here we investigate the clinical outcomes in patients (pts) with various EGFR ex19 dels treated with erlotinib. **Methods:** We assessed progression free survival (PFS), duration on treatment (DOT) and overall survival (OS) in pts with EGFR exon 19 dels (E746_A750, L747_P753 > S or L747_A750 > P) who received erlotinib as first-line therapy for advanced disease. Primary resistance was defined as progression on first scan after initiation of therapy. **Results:** 32 pts met criteria: 24 with the common E746_A750 mutation, and 4 each with the L747_P753 > S and L747_A750 > P mutations. Patients with the L747_A750 > P mutation demonstrated significantly worse PFS, DOT and OS than those with the E746_A750 and L747_P753 > S mutations (see Table). There was no difference between the E746_A750 and L747_P753 > S groups. Two of four pts with L747_A750 > P mutations demonstrated primary resistance to erlotinib, whereas no pts with E746_A750 or L747_P753 > S mutations exhibited primary resistance. **Conclusions:** This study shows differential clinical outcome to EGFR-directed therapy within EGFR ex19 del tumors, specifically that pts with ex19 del L747_A750 > P have inferior outcomes versus those with E746_A750 or L747_P753 > S when treated with erlotinib. Understanding outcomes with other EGFR inhibitors based on the specific EGFR del 19 mutation present may allow for more precise treatment that results in superior patient outcomes.

Outcomes by EGFR Exon 19 Mutations (Months)

	E746_A750 (n = 24)	L747_P753 > S (n = 4)	L747_A750 > P (n = 4)	p-value
PFS	11.7	13.1	4.1	0.0003
DOT	14.8	14.3	5.9	0.0001
OS	47.0	36.4	14.1	0.0031

9057 Poster Session (Board #380), Sun, 8:00 AM-11:30 AM

Correlation between nivolumab exposure and treatment outcome in NSCLC. *First Author: Stijn L.W. Koolen, Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Treatment with anti-PD-1 therapy is subject to large inter-individual variation in clinical outcome. This may be influenced partly by differences in nivolumab exposure between patients. The objective of the current analysis was to investigate whether an exposure-response relationship exists for nivolumab-treated NSCLC patients. **Methods:** 84 patients started nivolumab treatment between May 5th 2016 and August 1st 2017 and were included for prospective collection of serum samples prior to each nivolumab cycle. Clinical data were collected until November 1st 2017. Patients were classified according to best objective response (BOR) according to RECIST v1.1 and the occurrence of grade ≥3 toxicities according to CTCAE v4.03. Geometric mean nivolumab trough concentrations after 2, 4, and 10 weeks of treatment were compared using ANOVA with respect to BOR and *t*-test with respect to toxicity in patients without dose delays until that particular time point. **Results:** 76 patients were evaluable for analysis; 4 patients had no follow-up tumor evaluation, and 4 patients had no follow-up blood sample. At each time point, partial responders (PR; n = 15) had higher geometric mean trough concentrations when compared to patients with progression (PD; n = 33): at 2 weeks : 27.4 μg/mL (95% CI: 22.3 – 33.6 μg/mL) vs. 18.7 μg/mL (95% CI: 16.7 – 20.9 μg/mL; p = 0.001; 47% higher), at 4 weeks: 46.2 μg/mL (95% CI: 37.4 – 57.0 μg/mL) vs. 30.2 μg/mL (95% CI: 25.0 – 36.4 μg/mL; p = 0.008; 53% higher), at 10 weeks: 79.4 μg/mL (95% CI: 60.7 – 103.8 μg/mL) vs. 45.8 μg/mL (95% CI: 35.6 – 58.9 μg/mL; p = 0.002; 73% higher). Moreover, PR patients had higher trough concentrations when compared to patients with stable disease (SD; n = 28) at week 2 (p = 0.034) and at week 4 (p = 0.047). Exposure was not significantly related to the occurrence of grade ≥3 toxicity (n = 15) at any time point. **Conclusions:** This analysis shows that NSCLC patients with an objective response to nivolumab have significantly higher nivolumab exposure than patients with early progressive disease, indicating an exposure-response relationship. Further clinical research is needed to explain and quantify this relation. If confirmed, more rational and individualized dosing-strategies can improve patient outcome.

9058 Poster Session (Board #381), Sun, 8:00 AM-11:30 AM

Durvalumab in ≥ 3rd-line advanced NSCLC: Updated results from the phase 2 ATLANTIC study. *First Author: Marina Chiara Garassino, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: The Phase 2 ATLANTIC study investigated the anti-PD-L1 antibody durvalumab in heavily pretreated pts with advanced NSCLC. Here we report updated results for two of the three pt cohorts (defined by tumor PD-L1 expression and *EGFR/ALK* mutation status) for which data have reached further maturity. **Methods:** ATLANTIC (NCT02087423) is an open-label, single-arm trial of advanced NSCLC pts who had progressed after ≥2 regimens. After initially enrolling all-comers, the study was restricted to pts with PD-L1-expressing tumors (≥25% of tumor cells [TC]). Pts received durvalumab 10 mg/kg IV every 2 weeks ≤12 months. The primary endpoint was ORR by independent central review (ICR) using RECIST v1.1 in pts with TC ≥25%. Pts in Cohort 1 were *EGFR+/ALK+* and pts in Cohorts 2 (not reported) and 3 (TC ≥90% only) were *EGFR−/ALK−*. Interim results were reported for a prior data cutoff (DCO; June 3, 2016). **Results:** As of the latest DCO (November 7, 2017), 444 pts had received durvalumab, 111/68 in Cohorts 1/3. Median age was 61.0 years in both cohorts, 0.9%/29.4% had squamous histology, and the mean number of prior therapies in each cohort was 3.8/2.6. Median OS was 13.3/13.2 months, with a 1-year OS rate of up to 53%, in pts with higher PD-L1 expression (Table). Grade ≥3 treatment-related AEs (CTCAE v4.03) occurred in 5.4%/19.1%. Immune-mediated AEs were manageable, occurring with similar incidences as that reported previously for the earlier DCO. Clinical trial information: NCT02087423. **Conclusions:** These findings demonstrate durable efficacy and a promising effect on OS with durvalumab in a subset of heavily pretreated, advanced NSCLC pts.

	Cohort 1 (*EGFR+/ALK+*)		Cohort 3* (*EGFR−/ALK−*; TC≥90%)
	TC < 25% (n = 28)	TC ≥25%† (n = 74)	(n = 68)
Confirmed ORR,‡ n (%) [95% CI]	1 (3.6) [0.1–18.3]	9 (12.2) [5.7–21.8]	21 (30.9) [20.2–43.3]
Median DoR (IQR),‡ months	7.9 (7.9–7.9)	7.4 (5.6–9.2)	NR (NR–NR)
	n = 30¶	n = 77¶	n = 67¶
Median PFS (95% CI),‡ months	1.9 (1.8–1.9)	1.9 (1.8–3.6)	2.4 (1.8–5.5)
Median OS (95% CI), months	9.9 (4.2–13.3)	13.3 (6.3–24.5)	13.2 (5.9–NC)
1-year OS (95% CI), %	40.4 (22.5–57.6)	53.3 (40.6–64.4)	51.8 (39.2–63.1)

*Includes pts with unknown *EGFR/ALK* status; †Includes pts with TC ≥90%; ‡Evaluable per ICR (based on the prior DCO); ¶Full analysis set. NC, not calculated; NR, not reached.

9059 Poster Session (Board #382), Sun, 8:00 AM-11:30 AM

A randomized phase 2 study of abemaciclib versus docetaxel in patients with stage IV squamous non-small cell lung cancer (sqNSCLC) previously treated with platinum-based chemotherapy. *First Author: Giorgio V. Scagliotti, Department of Oncology - University of Torino, Turin, Italy*

Background: Abemaciclib is a potent and selective inhibitor of CDK4 & 6 approved for treatment of HR+, HER2- metastatic breast cancer. In a Phase 1 study, abemaciclib showed activity in pts with advanced and/or metastatic NSCLC. This Phase 2 study evaluated the safety and efficacy of abemaciclib vs docetaxel in pts with Stage IV sqNSCLC previously treated with platinum-based chemotherapy. **Methods:** This multicenter, randomized, open-label trial, evaluated abemaciclib (200 mg PO every 12 hours daily) vs docetaxel (75 mg/m^2 IV on Day 1); both on 21 day cycle until disease progression. Adults with confirmed Stage IV NSCLC with measurable disease, ECOG PS ≤1, and who progressed during/after platinum-based chemotherapy were eligible. Pts were randomized 2:1 to receive abemaciclib or docetaxel. Primary endpoint was investigator-assessed PFS. Key secondary endpoints were ORR, DCR, OS, and safety. **Results:** 159 pts were randomized to abemaciclib (N = 106) and docetaxel (N = 53). Median age was 64 years. 84.3% pts were men. In ITT pts 125 PFS events were observed with median PFS of 2.5 m (95% CI: 1.7, 2.9) for abemaciclib and 4.2 m for docetaxel (95% CI: 2.8, 5.7; stratified HR: 1.77 [95% CI: 1.17, 2.67]; P = .0068). ORR was 2.8% (95% CI: 0.0, 6.0) for abemaciclib and 20.8% (95% CI: 9.8, 31.7) for docetaxel. The DCR (CR + PR + SD) was 50.9% (95% CI: 41.4, 60.5) for the abemaciclib treatment arm and 64.2% (95% CI: 51.2, 77.1) for the docetaxel treatment arm. Median OS was 7.0 m (95% CI: 5.0, 8.8) for abemaciclib and 12.4 m for docetaxel (95% CI: 7.1, 16.0; stratified HR: 1.33 [95% CI: 0.88, 2.02]; P = .1746). Exploratory biomarker data will be available at the meeting. The most common TEAEs with abemaciclib were anemia and diarrhea. **Conclusions:** In this Phase 2 study, single agent abemaciclib 200 mg did not improve the progression-free survival time over docetaxel; the instantaneous rate of disease progression/death at any given time point was higher with abemaciclib vs docetaxcel. No specific safety concerns were observed. Clinical trial information: NCT02450539.

9060 Poster Session (Board #383), Sun, 8:00 AM-11:30 AM

PD-L1 expression, tumor mutation burden and response to immune checkpoint blockade in patients with *HER2*-mutant lung cancers. *First Author: Wei-Chu Victoria Lai, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *HER2* mutations are present in 3% of lung cancers. Response to immune checkpoint blockade (ICB) in this subset of lung cancers is unknown. We evaluate the landscape of PD-L1 and tumor mutation burden (TMB) in *HER2*-mutant lung cancers (*HER2*m) and their response to ICB. **Methods:** Patients (pts) with advanced *HER2*m were identified retrospectively. PD-L1 expression was determined by immunohistochemistry (IHC); TMB was estimated by next-generation sequencing (NGS) using MSK-IMPACT. Objective response rate (ORR) to ICB was determined using RECIST v1.1. Kaplan-Meier was used for PFS and OS analyses. **Results:** We identified 122 pts with *HER2*m, of whom 87 had PD-L1 IHC and 84 had NGS. 26 pts with known activating mutations in *HER2*m were treated with ICB. PD-L1 expression was < 1% in 67 (77%), 1-49% in 9 (10%), and ≥50% in 11 (13%) pts. PD-L1 expression was lower when compared to an unselected cohort (n = 578) of lung cancers profiled at our center (p = 0.006). Median TMB (5.7 Mt/Mb, range 0.8-91.8) was the same as the median TMB of an unselected cohort (n = 3000) of lung cancers (p = 0.21). In those treated with ICB, ORR was 12% (3/26, 95% CI 3-30%), including 3 PR, 8 SD, 15 PD. In the 3 responders: none had an *HER2* YVMA mutation; 2 (66%) had PD-L1 ≥50%; 2 (66%) had TMB ≥median; median response duration was 3.4 months (range 1.4-21.2); and 1 (33%) remained on treatment with PR. From the start of ICB, median PFS was 1.9 months (95% CI 1.5-4.0), and median OS was 10.4 months (95% CI 5.9-NR). **Conclusions:** In pts with *HER2*-mutant lung cancers, PD-L1 expression is lower but TMB is similar to unselected lung cancers. Response to PD-(L)1 blockade is uncommon in pts with *HER2*-mutant lung cancers, but treatment with ICB can still be considered, particularly in the context of high PD-L1 expression or higher TMB.

9061 Poster Session (Board #384), Sun, 8:00 AM-11:30 AM

Brigatinib (BRG) in crizotinib (CRZ)-refractory ALK+ non–small cell lung cancer (NSCLC): Efficacy updates and exploratory analysis of CNS ORR and overall ORR by baseline (BL) brain lesion status. *First Author: Rudolf M. Huber, University Hospital of Munich, Thoracic Oncology Centre Munich, Munich, Germany*

Background: ALTA (NCT02094573) evaluated 2 doses of the ALK inhibitor BRG post-CRZ. Overall ORR contains both CNS and extra-CNS target lesion data. **Methods:** In ALTA, stratification included BL CNS disease (+/−). Pts were randomized to BRG 90 mg qd (arm A) or 180 mg qd with a 7-day lead-in at 90 mg (arm B). To differentiate CNS and extra-CNS efficacy we compared CNS ORR with overall ORR by BL CNS status. **Results:** 222 pts were randomized (n = 112/110, arm A/B); 71%/67% had BL CNS lesions. Of 247/204 total target lesions in A/B, 38 (15%) and 32 (16%), respectively, were in the CNS; 28 (25%) pts in A and 23 (21%) in B had ≥1 target CNS lesion. Median follow-up was 19.6/24.3 mo. Per independent review, CNS ORR in pts with measurable BL CNS lesions (n = 26/18, A/B) was 50%/67%; in pts with any BL CNS lesions (n = 81/74, A/B), median intracranial PFS (iPFS) was 12.8/18.4 mo. Table shows long-term overall efficacy updates by BL CNS status. Dose reductions or discontinuations due to AEs (A/B): 7%/29% and 4%/11%. **Conclusions:** With > 24 mo follow-up, the recommended BRG 180 mg dose (with lead-in) continues to demonstrate long PFS and iPFS and high CNS ORR. Comparable CNS ORR (67%) and overall ORRs in pts with (61%) or without (55%) BL CNS target lesions support BRG's broad whole-body activity. Clinical trial information: NCT02094573.

	Investigator Assessed		Independent Review	
	Arm A (n = 112)	Arm B (n = 110)	Arm A (n = 112)	Arm B (n = 110)
Confirmed ORR, %				
All pts	46 (35–57[a])	56 (45–67[a])	51 (41–61[b])	56 (47–66[b])
BL CNS target lesions	43 (25–63[b])	61 (39–80[b])	—	—
Yes (n = 28/23, A/B)	47 (36–58[b])	55 (44–66[b])	—	—
No (n = 84/87, A/B)				
Median DoR, responders,[c] mo	12.0 (9.2–17.7[b])	13.8 (10.2–19.3[b])	16.4 (7.4–24.9[b])	15.7 (12.8–21.8[b])
Median PFS,[c] mo	9.2	15.6	9.2	16.7
Events, %	(7.4–11.1[b]) 69	(11.1–21.0[b]) 58	(7.4–12.8[b]) 58	(11.6–21.4[b]) 49
OS[c]				
Median, mo	29.5 (18.2–NR[b])	34.1 (27.7–NR[b])	—	—
1-y,[c] %	70 (61–78[b])	80 (71–87[b])	—	—
2-y,[c] %	55 (44–64[b])	66 (56–74[b])	—	—

DoR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. [a]97.5% CI (primary endpoint); [b]95% CI; [c]Kaplan-Meier estimate.

9062 Poster Session (Board #385), Sun, 8:00 AM-11:30 AM

Crizotinib in patients (pts) with MET-amplified non-small cell lung cancer (NSCLC): Updated safety and efficacy findings from a phase 1 trial. *First Author: D. Ross Camidge, Medical Oncology Department, University of Colorado, Aurora, CO*

Background: MET amplification (amp) has been reported in a subset of NSCLC with the frequency varying depending on the definition used. Crizotinib, an ALK/ROS1/MET inhibitor approved in ALK- or ROS1-positive NSCLC, also has proven clinical activity in cases of MET exon 14 alterations and MET amp. Here we present an updated analysis of crizotinib in pts with low, medium (med), and high (hi) levels of MET amp in advanced NSCLC. **Methods:** In this ongoing, open-label, multicenter, phase 1 trial (NCT00585195), MET amp was locally tested; pts with MET/CEP7 ratios ≥1.8 were eligible. Pts received crizotinib 250 mg BID and were assigned to categories based on low (≥1.8–≤2.2), med (> 2.2–< 5), or hi (≥5) MET/CEP7 ratios. The latter 2 thresholds were revised to > 2.2–< 4 and ≥4; data were then reanalyzed to better delineate predictive biomarkers of response. Selected endpoints included best overall response (BOR) per RECIST v1.0, time to tumor response (TTR), progression-free survival (PFS), duration of response (DOR) and safety. **Results:** At data cut-off (31 Oct 2017), 40 pts were treated; 3 had no MET amp. Baseline characteristics were comparable among the revised amp categories. Median TTR was 8.0 wk (range, 7.1–9.1). BOR, DOR, and PFS are shown in the. 3 MET hi pts remain on treatment. The adverse event profile in this cohort was consistent with the established safety profile of crizotinib. **Conclusions:** Pts with NSCLC with hi MET amp (MET/CEP7 ≥4) showed clinically meaningful antitumor activity with rapid and durable responses. Crizotinib was generally well tolerated. Coincidence with MET exon 14 alterations and other targets of crizotinib is being explored. Clinical trial information: NCT00585195.

MET/CEP7 Category	Low (N =3)	Med (N =14)	Hi (N =20)
Response evaluable	n = 3	n = 14	n = 20
Objective response rate, %[a] (95% CI)	33.3 (0.8, 90.6)	14.3 (1.8, 42.8)	40.0 (19.1, 63.9)
Complete response, n	0	0	2
Partial response, n	1	2	6
Stable disease, n	0	4	6
Progressive disease (PD), n	1	4	3
Early death, n	1	3	1
Indeterminate, n	0	1	2
Median DOR, mo (range)[b]	12.1 (12.1–12.1)	3.7 (3.7–3.7)	5.5 (3.3–25.8)
Median PFS, mo (95% CI)[c]	1.8 (0.8, 14.0)	1.9 (1.3, 5.5)	6.7 (3.4, 7.4)

[a]Response-evaluable population
[b]Objective responders
[c]Based on Kaplan-Meier method

9063 Poster Session (Board #386), Sun, 8:00 AM-11:30 AM

A multicenter phase II study of low-dose erlotinib in frail patients with EGFR mutation-positive, non-small cell lung cancer: Thoracic oncology research group (TORG) trial 1425. *First Author: Kazuhiko Yamada, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan*

Background: We previously reported that low-dose erlotinib has a certain degree of efficacy with lower toxicity in patients with non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations (Eur J Cancer 2015). This multicenter phase II study was undertaken to investigate the efficacy and safety of low-dose erlotinib for those patients with frailty. **Methods:** Chemotherapy-naïve NSCLC patients with *EGFR* mutations who had frailty were enrolled and received erlotinib 50 mg/d. Dose escalation was allowed to those with stable disease after 4 weeks. Patient's frailty was defined as follows: (Group 1) 20 to 74 years of age with Eastern Cooperative Oncology Group performance status (PS) ≥2 or Charlson Comorbidity Index (CCI) ≥6 points; (Group 2) 75 to 80 years of age with PS ≥1 or CCI ≥6 points; (Group 3) ≥81 years of age with any PS and CCI. The primary endpoint was independent review committee (IRC)-confirmed objective response rate (ORR) to the low-dose erlotinib, with target ORR of 65% and threshold of 50% (SWOG two-stage design). **Results:** Eighty patients were enrolled between December 2014 and April 2017: males/females 26/54; median age 80 (range 49-90); Group 1/2/3 15/28/37; Ad/Sq/Others 76/1/3. *EGFR* mutation types were: exon 19/21 42/38. All 80 patients were included in efficacy and safety analysis. The IRC-confirmed ORR was 60.0% (90%CI: 50.2-69.2%), and the primary endpoint was met. The disease control rate was 86.3% (90%CI: 78.3-92.1%). Median progression-free survival was 9.2 months. Although overall survival data are immature, median survival time and 1-year survival rate were 26.3 months and 68.9%, respectively. Toxicities were generally mild, with a few grade 3 or more toxicities. There was no case of interstitial lung disease or treatment-related death. **Conclusions:** This is the first prospective study evaluating low-dose erlotinib for frail patients with *EGFR* mutation-positive NSCLC. Low-dose erlotinib is active and could be a treatment option for those patients. Clinical trial information: UMIN 000015949.

9064 Poster Session (Board #387), Sun, 8:00 AM-11:30 AM

Time to treatment discontinuation (TTD) as a pragmatic endpoint in metastatic non-small cell lung cancer (mNSCLC): A pooled analysis of 8 trials. *First Author: Yutao Gong, US Food and Drug Administration, Silver Spring, MD*

Background: Progression-free survival (PFS) is an important efficacy endpoint in oncology trials. However, clinical trials increasingly allow treatment beyond objective radiographic progression (TBP) for patients deriving clinical benefit from therapy. Furthermore, treatment discontinuation due to toxicity is increasingly uncommon in trials of targeted therapies. Thus, TTD may represent a practical endpoint for real-world evidence (RWE) studies. **Methods:** We pooled data from patients (pts) with mNSCLC treated on 13 arms of 8 randomized controlled trials of tyrosine kinase inhibitors (TKI), immune checkpoint inhibitors (ICI), or chemotherapy (Chemo) initiated between 2007-2014; 3 chemo arms with planned discontinuation without maintenance therapy were excluded. We measured the pt-level correlation (corr) between TTD and PFS within each drug category (EGFR TKI; ALK TKI; ICI; or Chemo), and determined rates of disparity between TTD and PFS greater than 3 months. **Results:** 2369 pts met criteria for analysis. 1868 pts (79%) had a TTD event, and 1638 pts (69%) had a PFS event. Overall, median TTD was 5.7 months, and median PFS was 6.6 months. Pt-level analysis of the difference between PFS and TTD revealed recurring outliers (TABLE), with early TTD seen on chemo (PFS-TTD > 3 months in 10.9% of pts) and late TTD seen on TKI (TTD-PFS > 3 months in 12.1% of pts). Overall, the correlation between TTD and PFS was 0.91, stronger in pts treated with TKI or ICI (0.92) and weaker in pts treated with chemo (0.78; TABLE). **Conclusions:** Pt-level analysis indicates TTD is strongly correlated with PFS in contemporary trials of pts with mNSCLC, particularly those treated with TKI or ICI. Among pts treated with TKI or ICI, TTD exceeds PFS by > 3 months in several cases. These results indicate a need for further investigation of TTD across cancers and treatments to assess its role as an endpoint in RWE studies.

Subgroup	N	Median PFS	Median TTD	Corr	Early TTD %	Late TTD %
All	2369	5.7	6.6	0.91	5.2	7.3
EGFR TKI	595	12.1	10.9	0.95	0.7	10.9
ALK TKI	475	12.6	13.3	0.89	3.0	13.5
ICI	581	3.5	3.8	0.88	4.7	7.1
Chemo	718	2.8	4.2	0.78	10.9	0.6

9065 Poster Session (Board #388), Sun, 8:00 AM-11:30 AM

Predictive value of CD73 expression in *EGFR*-mutation positive non-small-cell lung cancer patients received immune checkpoint inhibitors. *First Author: Hidenobu Ishii, Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume, Japan*

Background: CD73 dephosphorylates and converts extracellular adenosine monophosphate to adenosine, leading to immune escape of malignancies. Although epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC showed high expression of CD73, the predictive relevance of CD73 expression in patients with *EGFR* mutation received immune checkpoint inhibitors (ICIs) is unknown. **Methods:** We screened 67 patients with Stage I-III *EGFR* mutation-positive NSCLC received complete resection (cohort A), 17 patients with advanced or recurrent NSCLC received immune checkpoint inhibitors after resistance to EGFR-TKI treatment (cohort B), and 31 patients with *EGFR* mutation-negative NSCLC treated with ICIs. CD73 expression was evaluated by immunohistochemical analysis, and tumors with staining in over 50% of tumor cells were scored as high expression. **Results:** In cohort A, the high CD73 expression group showed relatively shorter disease-free survival and overall survival than the low CD73 group in patients with Stage I-III *EGFR* mutation-positive NSCLC received complete surgical resection. In cohort B, the overall response rate of ICIs was significantly higher in patients with high CD73 expression than those with low CD73 expression (66.7% versus 0%, $p = 0.006$), and the high CD73 expression group showed significantly longer progression-free survival (PFS) than low CD73 group (median 16.0 months versus 1.2 months, $p = 0.024$). Meanwhile, there was no significant difference in PFS of ICIs between in the high and low CD73 expression groups of *EGFR* mutation-negative NSCLC (median PFS; 2.8 months versus 2.8 months, $p = 0.394$). **Conclusions:** In patients with *EGFR* mutation-positive NSCLC, expression of CD73 may predicts a favorable outcome of ICIs treatment unlike in *EGFR* mutation-negative patients.

9066 Poster Session (Board #389), Sun, 8:00 AM-11:30 AM

Impact of central nervous system (CNS) involvement in advanced non-small cell lung cancer (NSCLC) patients (pts) treated with immune checkpoint inhibitors (ICI). *First Author: Lizza Hendriks, Gustave Roussy, Department of Medical Oncology, Villejuif, France*

Background: CNS metastases (CNS+) are frequent in NSCLC. Unfortunately, pts with (untreated) CNS+ are often excluded from ICI clinical trials so that their outcome on ICI is largely unknown. **Methods:** Retrospective data collection of all consecutive advanced ICI treated NSCLC pts in 2 French centers (nov 2012 – jan 2018). Progression free survival (PFS), overall survival (OS), intracranial objective response rate (iORR) and site of progression (PD) (CNS, extracranial or both) on ICI was collected. Active brain metastases (BM) were defined as non-irradiated new and/or growing lesions on brain imaging < 6 weeks before ICI start. **Results:** 483 pts were included, 65% male, 84% WHO PS 0-1, median age 64 years, 75% nonsquamous, 10% targetable driver mutations, 37% known PD-L1 (66% $\geq$1% expression). ICI treatment was median 2nd line (range 1-12), 95% had monotherapy PD(L)-1 inhibition. 137 pts (28%) had CNS+ at start ICI, 93% had only BM, the others had BM +/- leptomeningeal metastases. 42% had active CNS+. CNS+ pts had significantly more often a smoking history compared to CNS- pts (97 vs 91% $p = 0.02$), were younger (61 vs 64 years, $p = 0.002$), had more often adenocarcinoma (73 vs 62%, $p = 0.04$), and had a higher number of organs with metastases (3.3 vs 2.4, $p < 0.001$). Baseline characteristics did not differ for active vs non-active CNS+. With a median follow-up of 16 mo (95% CI 14-21 mo), median iORR, PFS and OS were not significantly different for those with CNS+ vs CNS- and active CNS+ vs non-active CNS+ (table). CNS failure was significantly more often in CNS+ pts vs CNS- pts (CNS only PD: 12% vs 5%, CNS and extracranial PD: 19% vs 6%: $p < 0.001$). The proportion of CNS failure did not differ significantly for active and non-active CNS+ ($p = 0.12$). **Conclusions:** (Active) CNS involvement does not negatively impact outcome on ICI although CNS failure is more common in CNS+ compared to CNS- pts.

Pts, nr	iORR in evaluable pts (%)	Median PFS (95% CI), months	p-value	Median OS (95% CI), months	p-value
Total 483		2 (1-2)		10 (8-13)	
CNS status					
CNS-346		2 (1-2)	0.17	11 (8-16)	0.28
CNS+137	29	2 (1-3)		9 (6-13)	
Active CNS+57	29	2 (1-6)	0.71	8 (4-NR)	0.81
Non-active CNS+ 76 (4 no recent imaging)	29	1 (1-4)		10 (7-17)	

9067 Poster Session (Board #390), Sun, 8:00 AM-11:30 AM

Immune-related adverse events and nivolumab outcomes in non-small cell lung cancer patients: A multi-institutional, retrospective cohort study. *First Author: Rebecca Jane Moor, Princess Alexandra Hospital & University of Queensland, Brisbane, Australia*

Background: Immune checkpoint inhibitors are routinely used in Non Small Cell Lung Cancer (NSCLC) patients following progression on first-line therapy. Immune-related Adverse Events (IrAEs) have been associated with the efficacy of PD-1 inhibitors in melanoma. The association between the development of IrAEs and efficacy of nivolumab remains unclear in NSCLC. **Methods:** We retrospectively collected data from patients who received nivolumab for advanced NSCLC on an Open Access Program across seven oncology institutions in Queensland, Australia, and analyzed whether there was an association between outcomes and the development of immune-related toxicity. **Results:** One hundred and ninety six patients were enrolled to this ethics committee approved audit – 77 females (39%) and 119 (61%) males; PS 0-1 (62%); PS 2-3 (38%); median age 67 (range 42-84). An objective response was recorded in 24% of patients; partial response (47/196) with one complete response, in addition 28% (55/196) had stable disease. The median overall survival was 9.2 months; 13.4 months in PS 0-1 patients and 4.2 months in PS 2-3 patients. At 1 year, the overall survival rate was 42%; 57% in patients with PS 0-1 and 18% in PS 2-3 patients. The presence of IrAEs of any grade occurred in 36% of patients and was associated with a longer median PFS of 5.9 months versus 2.3 months (P value < 0.01, 95% CI) in patients with no immune toxicity on Kaplan Meier analysis. The median OS of patients experiencing an IrAE was 24.3 months compared with 6.5 months without (P value < 0.01, 95% CI). A durable clinical benefit was observed in 72% of patients who developed at least one IrAE versus 37% in those without any immune mediated toxicity. Analysis of the prognostic relevance of routine histological, hematological and biochemical parameters is ongoing with a multivariate analysis planned. **Conclusions:** Nivolumab had clinically significant long-term benefits in the treatment of locally advanced and metastatic NSCLC with 12 month survival rates in keeping with clinical trials in PS 0-1 patients. The development of IrAEs was associated with improved outcomes including median PFS, OS and higher rates of clinical response in this cohort.

9068 Poster Session (Board #391), Sun, 8:00 AM-11:30 AM

Next generation sequencing (NGS) based mutation profiling and heterogeneity of resistance mechanisms to AZD9291. *First Author: Jun Zhao, Beijing Cancer Hospital, Beijing, China*

Background: AZD9291, a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), is active against patients with *EGFR* T790M-mutant non–small cell lung cancer (NSCLC) who failed prior treatment with EGFR TKIs. However, acquired resistance to AZD9291 is inevitable. In this study, we retrospectively analyzed mechanisms of acquired resistance to AZD9291 in advanced NSCLC. **Methods:** A total of 293 advanced lung adenocarcinoma patients with signs of AZD9291 resistance were enrolled in the study from January to October 2017. Tissue biopsy was the first choice for mutation profiling, and ctDNA testing was used as an alternative. All samples were analyzed using next-generation sequencing based ER-Seq method, which enables simultaneously assess single-nucleotide variants, insertions/deletions, rearrangements, and somatic copy-number alterations across at least 59 genes (59-1021). **Results:** At resistance, 3 molecular subtypes emerged: 66 cases (22.5%) lost original *EGFR* activating mutation and T790M mutation; 130 cases (44.4%) lost the T790M mutation despite detecting of the underlying *EGFR* activating mutation; 97 cases (33.1%) maintained both *EGFR* activating mutation and T790M mutation. Known resistance mechanisms detected in 11/66 (16.7%), 56/130 (43.1%), 62/97 (63.9%) cases respectively for all the 3 subtypes. The most frequently known mechanism was *EGFR* C797S which was identified in 60 cases, while *EGFR* L792H/V, G796S, L718Q/V, G719A, and E709K were in 27 cases. Activating mutations of PI3K-AKT-mTOR signaling, amplification of the *MET*, activating mutation / amplification of *ERBB2*, *ALK*/*ROS1*/*RET* fusion, activating mutation of *BRAF*, or *KRAS* were identified in 37, 16, 14, 9, 8, 5 patients respectively. Moreover, 24 cases had *Rb1* loss of function mutation. Co-occurrence of resistance mechanisms were observed in 31 patients. **Conclusions:** There was a high frequency of inter and intra-patient heterogeneity of resistance mechanisms after AZD9291 therapy. Comprehensive NGS analysis may facilitate the broad exploration of potential resistance mechanisms.

9069 Poster Session (Board #392), Sun, 8:00 AM-11:30 AM

Mechanisms of acquired resistance to MET tyrosine kinase inhibitors (TKIs) in MET exon 14 (METex14) mutant non-small cell lung cancer (NSCLC). *First Author: Mark M. Awad, Dana-Farber Cancer Institute, Boston, MA*

Background: Non-small cell lung cancers (NSCLC) harboring METex14 activating mutations can respond dramatically to treatment with MET TKIs, but the mechanisms of acquired resistance to these therapies are not well understood. **Methods:** We performed next generation sequencing on serial plasma samples and/or tumor biopsies and one autopsy case from patients with METex14 mutant NSCLC to identify mechanisms of resistance to the type 1 MET TKI crizotinib and the type 2 MET TKI glesatinib. **Results:** Samples from 12 patients with METex14 mutant NSCLC were included in this analysis. In 4 cases (33%), acquired MET alterations were identified including one case with amplification of the mutated METex14 allele and three cases with MET tyrosine kinase domain secondary site mutations; in two of these cases, more than one MET resistance mutation was present in the same patient. Secondary mutations in MET included H1094Y, G1163R, L1195F, L1195V, D1228N, Y1230H, and Y1230S. In 4 cases (33%), bypass track activation was identified, including massive genomic amplification of wild-type *KRAS*, *BRAF*, and/or *EGFR*. In 4 cases (33%), the resistance mechanism was not identifiable. A case of acquired resistance to glesatinib with acquired amplification of the mutated METex14 allele had a confirmed partial response after switching to crizotinib. Data from resistant preclinical models and patient-derived cell lines and mouse xenografts will be presented. **Conclusions:** Novel therapeutic strategies will be needed to delay or overcome multiple complex mechanisms of acquired MET TKI resistance in METex14 mutant NSCLC.

9070 Poster Session (Board #393), Sun, 8:00 AM-11:30 AM

Immuno-oncology biomarker study in a large cohort of LC-SCRUM-Japan: Assessment of PD-L1 expression and tumor mutation burden in non-small cell lung cancer patients treated with immune checkpoint inhibitors. *First Author: Kiyotaka Yoh, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: PD-L1 high expression and high tumor mutation burden (TMB) are reported to be correlated with high sensitivity to immune checkpoint inhibitor (ICI) in non-small cell lung cancer (NSCLC). This immuno-oncology biomarker study is ongoing as part of nationwide genomic screening by LC-SCRUM-Japan. Planned accrual is 1000 patients. **Methods:** Lung cancer patients enrolled in LC-SCRUM-Japan were primarily screened with targeted next-generation sequencing with Oncomine™ Comprehensive Assay (OCA) and monitored clinical course and survival every 6 months. To explore new biomarkers for ICI in the treatment of NSCLC, further analyses of 4 immunohistochemistry (IHC) assays for PD-L1 expression (22C3, 28-8, SP263 and SP142) and whole-exome sequencing (WES) to determine TMB level were conducted in 1000 and 400 patients, respectively. **Results:** Among 1635 patients with lung cancer enrolled in LC-SCRUM-Japan between Feb 2017 and Jan 2018, 621 NSCLC patients were enrolled in this immuno-oncology biomarker study. The results of PD-L1 IHC with 420 patients, OCA with 380 patients, WES with 50 patients, were analyzed at data cutoff point of Jan 4, 2018. Median TMB level by WES was 72 (2 to 515) and median TMB level by OCA was 7.6 mutation/Mb (0 to 30.8). There was no significant association between each PD-L1 expression and TMB by WES. TMB by OCA had a weak correlation with TMB by WES (R^2= 0.31). Seventy-seven patients treated with ICI were evaluable for clinical response. Among 6 responders to ICI, TMB level by WES was various (19, 26, 26, 109, 144, and 249). Of these, 2 had both high TMB by WES (≥ median 72) and PD-L1 high expression; 2 had TMB low/PD-L1 high; 1 had TMB high/PD-L1 low: 1 had TMB low/PD-L1 low but high TMB by OCA (15.4 mutation/Mb). **Conclusions:** High TMB level appears to produce high sensitivity to ICI in patients with NSCLC, independent of PD-L1 high expression. Based on WES analyses in a large cohort, the findings to explore a precise predictive immuno-oncology biomarker to maximize the therapeutic benefits will be reported at the meeting.

9071 Poster Session (Board #394), Sun, 8:00 AM-11:30 AM

Refining the sensitivity of plasma cell-free DNA (cfDNA) genotyping by controlling for plasma tumor content. *First Author: Catherine Meador, Department of Medicine, Brigham and Women's Hospital, Boston, MA*

Background: Plasma cfDNA genotyping has been widely adopted for NSCLC diagnosis due to its convenience and high positive predictive value. However, limited assay sensitivity means negative plasma genotyping requires reflex tumor testing. We hypothesized that quantification of plasma tumor content could be used to aid interpretation of results. **Methods:** EGFR T790M plasma genotyping results were studied from patients (pts) with pretreated EGFR mutation-positive (EGFRm) advanced NSCLC and confirmed tumor T790M from two multicenter trials (AURA, AURA3). Quantitative plasma genotyping was performed for AURA using BEAMing (Sysmex) and for AURA3 using next-generation sequencing (NGS, Guardant) and droplet digital PCR (ddPCR, Biodesix). Using EGFR Ex19del/L858R allele frequency (driver AF) as an adequacy assessment, T790M sensitivity was studied across a range of plasma tumor content. **Results:** Overall T790M sensitivity from AURA was 70%, but 96% (95/99) in pts with detected driver AF > 0.5% and 39% (15/38) in pts with detected driver AF ≤0.5% (Table). In AURA3, T790M sensitivity with NGS (66%) and ddPCR (61%) increased to 97% for both methods (173/178 and 112/115) in pts with detected driver AF > 1% (Table). Combining AURA and AURA3 data (BEAMing and NGS), T790M false negative rate was 48% (54/112) with detected driver AF ≤1%, and 3% (9/265) with detected driver AF > 1%. **Conclusions:** In pts with pretreated EGFRm NSCLC and T790M-negative plasma genotyping, high driver AF suggests a low likelihood of missed T790M, but missed T790M is common in pts with low driver AF. While a negative plasma result should trigger reflex tumor testing, these emerging data may inform the decision to proceed with tumor biopsy, especially in high-risk pts. Investigations are planned to study whether cfDNA adequacy assessments are broadly applicable in pts with NSCLC undergoing plasma testing. Clinical trial information: NCT01802632; NCT02151981.

	Driver AF, %					
Sensitivity	**Negative**	**≤0.5**	**0.5 to ≤1**	**1 to ≤5**	**5 to ≤10**	**> 10**
AURA BEAMing 111/158 (70%)	1/21 (5%)	15/38 (39%)	12/12 (100%)	23/25 (92%)	11/11 (100%)	49/51 (96%)
AURA3 NGS207/ 316 (66%)	3/76 (4%)	15/39 (38%)	16/23 (70%)	54/58 (93%)	30/30 (100%)	89/90 (99%)
AURA3 ddPCR 126/205 (61%)	3/48 (6%)	6/26 (23%)	5/16 (31%)	27/30 (90%)	15/15 (100%)	70/70 (100%)

9072 Poster Session (Board #395), Sun, 8:00 AM-11:30 AM

Pooled overall survival and safety data from the pivotal phase II studies (NP28673 and NP28761) of alectinib in ALK-positive non-small cell lung cancer (NSCLC). *First Author: Sai-Hong Ignatius Ou, Chao Family Comprehensive Cancer Center, University of California, Orange, CA*

Background: Alectinib, a highly selective inhibitor of ALK tyrosine kinase, has demonstrated systemic and central nervous system activity in ALK+ NSCLC. Two single-arm, open-label phase II studies (NP28673; global [NCT01801111] and NP28761; North American [NCT01871805]) have previously demonstrated robust overall survival (OS) in crizotinib-resistant ALK+ NSCLC (Yang et al, J Thorac Oncol 2017). We report final pooled phase II OS and safety data after a longer duration of follow-up. **Methods:** Patients with locally advanced or metastatic ALK+ NSCLC (possible prior chemotherapy) who had progressed on or were intolerant to crizotinib, received twice-daily alectinib 600mg orally until progression, death or withdrawal. This pooled analysis assessed OS and safety after a median follow-up of 92.3 weeks (almost 2 years) (NP28673 105.5 weeks, data cut-off 27 October 2017; NP28761 75.7 weeks, data cut-off 12 October 2017). **Results:** The pooled data set included 225 patients. At the time of final data cut-off 53.3% of patients had died, 39.1% were alive and in follow-up, and 7.6% had withdrawn consent or been lost to follow-up. Alectinib demonstrated a median OS of 29.1 months (95% CI: 21.3–39.0) in the pooled analysis (NP28673 29.2 months [95% CI: 21.5–44.4]; NP28761 27.9 months [95% CI: 17.2–NE]). Mean dose intensity 94.2%. Grade ≥3 adverse events (AEs; any cause) occurred in 44.0% of patients, with no AE term reported in >4% of patients. The most common AEs (any grade) included constipation (39.1%), fatigue (35.1%), edema peripheral (28.4%), myalgia (26.2%) and nausea (24.0%). Despite the longer treatment duration (median 48.6 weeks), alectinib demonstrated a tolerable safety profile consistent with previous studies; 14.7% of patients experienced AEs leading to dose reductions, 37.3% of patients experienced AEs leading to dose interruptions or modifications and 6.2% of patients experienced AEs leading to withdrawal. **Conclusions:** This pooled phase II analysis demonstrated a median OS of >2 years in patients with pretreated ALK+ NSCLC receiving alectinib. In addition, alectinib was well tolerated over a median treatment duration of almost one year (48.6 weeks). Clinical trial information: NP28673; NCT01801111; NP28761; NCT01871805.

9073 Poster Session (Board #396), Sun, 8:00 AM-11:30 AM

Comparative effectiveness of carboplatin-pemetrexed (Carbo-Pem) with vs. without bevacizumab (Bev) in patients with advanced non-squamous (Sq) non-small cell lung cancer (NSCLC). *First Author: Stephen Joseph Bagley, Division of Hematology/Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: The majority of patients with advanced non-sq NSCLC do not have high programmed death ligand 1 (PD-L1) expression or a targetable genetic alteration. Carbo-pem-bev is commonly used as first-line therapy in these patients, but it is unknown whether the addition of bev to carbo-pem improves overall survival (OS). **Methods:** Using nationally representative electronic health record data from Flatiron Health, we performed a retrospective cohort study of patients diagnosed with advanced non-sq NSCLC from 2011-2017 who received ≥1 cycle of carbo-pem, with/without bev, as initial systemic therapy for metastatic disease. Patients with alterations in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) were excluded. The survival impact of adding bev to carbo-pem was assessed using a Cox proportional hazards model. **Results:** Patient characteristics are listed in Table 1 (n = 5,264). Median follow-up time and OS were 31 (IQR 16-49) and 10.2 (95% CI 9.8-10.8) months (mo), respectively. After adjusting for the covariates in Table 1, the addition of bev was associated with improved OS (median 12.1 vs 8.8 mo; HR 0.80, 95% CI 0.74-0.85, $p < 0.001$). In a sensitivity analysis of patients with known Eastern Cooperative Oncology Group Performance Status (ECOG PS) (N = 2,708), the effect of bev was similar (HR 0.79, 95% CI 0.72-0.88, $p < 0.001$). **Conclusions:** In this large, real-world dataset, the addition of bev to first-line carbo-pem for metastatic non-sq NSCLC was associated with improved OS. To our knowledge, this is the first study to address whether bev improves outcomes when added to carbo-pem.

	Carbo-pem (n = 3108)	Carbo-pem-bev (n = 2156)
Median Age (IQR)	**69 (61-75)**	**67 (60-73)**
Sex	-	-
Male	1611 (52%)	1084 (50%)
Race	-	-
Caucasian	2062 (66%)	1429 (66%)
Black	227 (8%)	136 (6%)
Asian	41 (1%)	32 (2%)
Other	254 (8%)	206 (10%)
Unknown	524 (17%)	353 (16%)
Stage	-	-
IV (*de novo* metastatic)	2558 (82%)	1839 (85%)
Metastatic recurrence of stage I-III	550 (18%)	317 (15%)
Median # days from metastatic diagnosis to chemo start (IQR)	34 (22-52)	32 (21-49)
ECOG PS	-	-
0-1	1208 (39%)	931 (43%)
2	319 (10%)	160 (7%)
3-4	58 (2%)	32 (2%)
Unknown	1523 (49%)	1033 (48%)

9074 Poster Session (Board #397), Sun, 8:00 AM-11:30 AM

Therapeutic and prognostic impact of genetic alterations identified in nationwide genome screening for squamous cell lung cancer (LC-SCRUM-Japan). *First Author: Tomohiro Sakamoto, Tottori University, Yonago, Japan*

Background: A variety of genetic alterations have been identified in squamous cell lung cancer (SqLC), but the clinical relevance of them remains poorly understood. We have prospectively analyzed advanced SqLC patients for multi-gene alterations and have followed up clinical course of the patients, establishing a large-scale clinico-genomic database in our nationwide genome screening project (LC-SCRUM-Japan). **Methods:** Since March 2015 to December 2017, 3316 advanced non-small cell lung cancer patients from 251 institutions had been enrolled in the LC-SCRUM-Japan, and 470 of them were histologically SqLC. Submitted tumor samples were subjected to a next-generation sequencing system, Oncomine Comprehensive Assay, enabling the analysis of < 160 cancer-related genes. **Results:** Among 409 available SqLC samples, potentially targetable gene alterations were detected in 196 (48%). Based on the gene alterations, the patients were categorized into 4 types, consisting of 40 (10%) with genetic alterations of FGFR family (FGFR type; 26 *FGFR1* amp, 12 *FGFR1/2/3/4* mut, 1 *FGFR3* amp and 1 *FGFR3* fus), 67 (16%) with those of the PI3K pathway (PI3K type; 46 *PIK3CA* mut/amp, 18 *PTEN* mut and 3 *AKT* mut), 49 (12%) with other oncogene alterations (AdC-like type; 24 *EGFR* mut/amp, 14 *KRAS* mut, 6 *ALK* mut/fus and 5 *ERBB2* amp) and others. Mutations in *TP53*, *CDKN2A*, *STK11* and *RB1* were also detected in 57/13/7/5%, respectively, but these were not significantly correlated between the 4 types. The overall survival (OS) of the patients with FGFR type tended to be shorter than that of PI3K and AdC-like types (median OS, 8.8 vs 18.8 months; p = 0.09). The efficacy of platinum-containing chemotherapies or immune checkpoint inhibitors was not significantly different among the 4 types in the current follow-up data. **Conclusions:** Through the nationwide screening, a series of genetic alterations have been identified in advanced SqLC and *FGFR* gene alterations were related to poor prognosis. Our large-scale integrative clinico-genomic database enables us to elucidate the clinical significance of genetic alterations, contributing the development of genotype-directed therapeutic strategy for SqLC patients.

9075 Poster Session (Board #398), Sun, 8:00 AM-11:30 AM

Hyperprogression after immunotherapy: Clinical implication and genomic alterations in advanced non-small cell lung cancer patients (NSCLC). *First Author: Youjin Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)*

Background: Hyperprogressive disease (HPD) emerges as a new subset of patients treated with immune-oncology (IO) agent. The definition of HPD is not yet clearly established, and it is unclear which patient is rapidly progressing after IO treatment. We investigated clinical features and potential genomic markers associated with HPD after IO therapy. **Methods:** We performed a retrospective clinical and radiological analysis of advanced NSCLC patients treated with single IO at Samsung Medical Center(July 2014 to December 2017). CT scans were quantitatively analyzed in terms of tumor volume and tumor growth rate (TGR) by comparing prior vs upon IO. We extracted tumor volume for each metastatic organ, classifying into HPD and non-HPD by volume-based growth kinetics. We also performed deep targeted sequencing of 375 of genes. **Results:** Of 220 evaluable patients37 patients (17%) were classified as HPD. 26 (70%) were male, 24 (65%) smoker, 25 (68%) ≧ 65 years, 10 (27%) ECOG PS ≧ 2, 31(84%) adenocarcinoma. Compared to non-HPD population, HPD was not associated with higher tumor burden at baseline, nor with gender, smoking status, PD L1 status, line of chemotherapy, prior radiotherapy. With median follow up of 20 months(m), mPFS and mOS were 4.4m (95% CI: 2.8-6.0), 12m (95% CI: 9.4, 16.0), respectively. HPD patients had significantly lower mPFS (1.2 vs 4.1m, p = < .000), mOS (7.1 vs.15.9m, p = 0.09). Further details with genomic profiling will be presented. **Conclusions:** HPD(defined by tumor growth kinetics) occurs in 17% of 220 advanced NSCLC patients after single-agent checkpoint inhibitors. Genomic profiles may help to identify patients at risk for HPD on IO.

9076 Poster Session (Board #399), Sun, 8:00 AM-11:30 AM

Rare targetable drivers (RTD) in NSCLC: PD-L1 expression, tumor mutation burden (TMB), microsatellite instability (MSI) and outcomes with immune check-point inhibitors (ICPi). *First Author: Elizabeth Dudnik, Thoracic Cancer Unit, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel*

Background: The efficacy of ICPi in NSCLC with RTD is unknown. **Methods:** 82 consecutive patients (pts) with RTD (non-EGFR/ALK) were selected from the Davidoff Cancer Center database. The correlation between RTD type and TMB, MSI (by FoundationOne™ algorithm), and PD-L1 was analyzed. ORR, PFS with ICPi (RECIST 1.1) and OS were assessed; uni- and multivariate OS analysis was done. **Results:** Median age 63y (31-97); males 46%; smokers 50%; adenoca 87%. PD-L1, TMB, and MSI were assessed in 61%, 58%, and 57% pts, respectively (Table). Of 77 pts with advanced disease, 44 received ICPi. ORR with ICPi was 16%; median PFS was 3.2 mo (95% CI, 2.6-5). With median follow-up since ICPi initiation of 7.8 mo [IQR 4.2-14], 19/44 (43%) pts died, median OS was 16.2 mo (95% CI, 8.4-NR). No correlation was seen between OS with ICPi and PD-L1 (p-0.6), TMB (p-0.9), or RTD type (p-0.9). With median follow-up since advanced disease diagnosis (AdvDisDx) of 15 mo [IQR 7.2-24], 40/77 (52%) pts died, median OS was 32 mo (95% CI, 19.9-44.9) and 13 mo (95% CI, 6.6-15.9) for pts who were and were not exposed to ICPi, respectively (log rank test-6.3, p-0.01). In the multivariate analysis, ICPi exposure (p-0.04), targeted agents exposure ($p < 0.01$) and ECOG PS ($p < 0.01$) were the only variables which correlated with OS since AdvDisDx. **Conclusions:** Rare targetable drivers in NSCLC are associated with low/intermediate TMB, MSI stable status and variable levels of PD-L1 expression. ICPi outcomes are comparable to those of unselected NSCLC pts and largely unpredictable. ICPi exposure has independent impact on OS.

		PD-L1, n/%				TMB, n/%				TMB, mut/Mb median, range	MSI, n/%	
	Pts	**< 1%**	**1-49%**	**≥50%**	**NA**	**≤5**	**6-19**	**≥20**	**NA**		**MS-S**	**NA**
All	**82**	**15/30**	**19/38**	**16/32**	**32**	**31/65**	**11/23**	**6/12**	**34**	**4, 0-57**	**47/100**	**35**
BRAF V600E	9	2/25	4/50	2/25	1	4/57	1/14	2/29	2	4, 1-42	7/100	2
Non V600E	9	2/40		3/60	4	1/33	2/67		6	7, 2-14	3/100	6
HER2	13	1/11	8/89		4	8/89		1/11	4	2, 0-57	9/100	4
HER2 amp	6	2/67		1/33	3		1/33	2/67	3	38, 12-43	1/100	5
HER3	1				1			1/100		31	1/100	
cMET ex14	14	2/22	1/11	6/67	5	5/83	1/17		8	4, 0-9	6/100	8
cMET amp	5		1/100		4	2/50	2/50		1	7, 0-10	4/100	1
RET	13	4/50	3/37	1/13	5	7/88	1/12		5	2, 0-7	8/100	5
RET	1	1/100							1			1
ROS1	9	1/20	2/40	2/40	4	4/57	3/43		2	5, 1-10	7/100	2
NTRAK	2			1/100	1				2		1/100	1

9077 Poster Session (Board #400), Sun, 8:00 AM-11:30 AM

Identification of osimertinib resistance mechanisms in Chinese NSCLC patients: Analysis from AURA17 trial. *First Author: Min Hu, IMED Asia, AstraZeneca, and Dizal (Jiangsu) Pharmaceutical Co., Ltd, Shanghai, China*

Background: Osimertinib is approved for metastatic NSCLC patients with EGFR T790M mutation after progression from EGFR-TKI therapy. Despite impressive tumor responses, drug resistance usually develops. Mechanisms of resistance to osimertinib are emerging, while resistance studies with large cohorts of Chinese patients are still lacking. Here we reported a resistance profile of osimertinib using plasma samples from 76 Chinese patients who had progressed by DCO2 (Nov. 4, 2016) of AURA17 study (NCT02442349), the pivotal trial for China market approval. **Methods:** Serial plasma cell-free DNA (cfDNA) were collected from baseline until progressive disease (PD) by investigator assessment. Capture-based 75-gene NGS panel was used to identify resistance mechanisms to osimertinib by comparing paired plasma cfDNA at baseline and PD. Droplet digital PCR was used to dynamically monitor EGFR mutation changes during treatment course. Association of cfDNA biomarkers with objective response rate (ORR) and progression-free survival (PFS) was analyzed. **Results:** 61 out of the 76 patients had detectable EGFR sensitizing mutations (L858R or Ex19Del) in their cfDNA samples at PD. Among them, 8 had acquired EGFR C797S, all *in cis* with T790M, with no enrichment for either L858R or Ex19Del (5:3). The median time of C797S detection from plasma was 2.8 (1.4-8.4) months prior to PD. EGFR amplification, L718Q, I744T, C775Y, G796S/D and T854I mutations were found in 13 patients. Aberrations in bypass tracks including ERBB2/3, FGFR3, HRAS, JAK1/2, MET, MTOR, NTRK1, PIK3CA, *etc.* were observed in 35 patients. Clearance of EGFR sensitizing mutations at weeks 3 or 6 of treatment was associated with favorable ORR (69.7% *vs.* 33.3% and 74.3% *vs.* 33.3%) and PFS (6.9 *vs.* 4.0 and 7.1 *vs.* 4.1 months, respectively). Presence of T790M at PD was correlated with longer PFS (8.2 *vs.* 4.2 months). **Conclusions:** Our study revealed diverse mechanisms of resistance to osimertinib in Chinese NSCLC patients. As the current subset has shorter PFS compared to the overall AURA17 population (6.2 *vs.* 9.7 months), analysis of plasma samples from patients who progressed by 24 months after last subject first dose (LSFD) is ongoing for a more comprehensive view. Clinical trial information: NCT02442349.

9078 Poster Session (Board #401), Sun, 8:00 AM-11:30 AM

Early prediction of outcomes to PD1 inhibitors in non-small cell lung cancer (NSCLC) using next generation sequencing (NGS) of plasma circulating tumor DNA (ctDNA). *First Author: Nicolas Guibert, Toulouse University Hospital, Toulouse France*

Background: Patient selection for PD-1 inhibitors in NSCLC is still based on imperfect screening biomarkers, including PD-L1 tumor expression and tumor mutational burden. We hypothesized that pretreatment molecular profile of ctDNA and its early kinetics during treatment could represent a reliable and non-invasive approach to determine response. **Methods:** Up to 4 serial plasma samples were prospectively collected from patients with advanced NSCLC treated with nivolumab as second line therapy: *i)* pretreatment, *ii)* at 1 month, *iii)* at the first CT-scan, *iv)* at progression. Plasma NGS was performed using InVisionSeq, tagged amplicon sequencing of hotspots and coding regions from 36 genes. The early kinetics (1 month) of ctDNA through treatment was analyzed along with specific baseline alterations as early indicators of response to immunotherapy. **Results:** 80 specimens from 33 patients underwent NGS. Alterations in ctDNA were detectable in 25/33 baseline samples. The most frequently detected alterations at baseline were TP53 (54.4%); KRAS (33.3%); STK11 (24.2%); and NFE2L2 (9%). Lack of detectable ctDNA at baseline in 6/8 patients correlated with progressive disease (PD). Studying 23 patients for whom serial specimens were available with ctDNA detected at baseline, plasma response (kinetics of ctDNA between baseline and 1 month specimens) was correlated with clinical outcomes (RECIST) in 18/23 cases (11/13 with overall response (OR) or stable disease (SD) and 7/10 with PD). Furthermore, ctDNA demonstrated potential predictive ability on outcomes by analyzing specific alterations and type of nucleotide change (transversion vs transition). Transversions in KRAS and TP53 were detected in 13/14 baseline cases demonstrating clinical benefit (OR+SD) while 8/11cases from patients who went on to have PD were enriched with transitions or STK11 co-mutations with TP53 or KRAS transversions. **Conclusions:** Plasma cell-free DNA analysis using NGS could be an additional screening assay to identify patients likely to derive benefit from anti-PD-1 therapy, particularly when tissue is unavailable.

9079 Poster Session (Board #402), Sun, 8:00 AM-11:30 AM

Dissecting the prognostic role of common EGFR-mutations of metastatic NSCLC in TKI era: A systematic review and subgroup meta-analysis. *First Author: Feng-Che Kuan, Department of Hematology and Oncology, Chang-Gung Memorial Hospital, Chiayi, Taiwan*

Background: Del19 is a good prognostic factor comparing to L858R regarding progression-free survival (PFS). In TKI era, whether Del19 is also good prognostic factor in overall survival (OS) and these two common mutations respond equally to reversible and irreversible TKIs are not elucidated. **Methods:** A systematic review and subgroup meta-analysis was undertaken to explore the differential efficacy toward frontline reversible and irreversible TKIs between the common mutations. Extracted overall response rate (ORR), PFS or OS were expressed in risk ratio (RR) or hazard ratio (HR) by random-effects model. The pooling of survival curves was expressed in median and interquartile range (IQR). **Results:** From inception to December 30, 2017, total 20 randomized controlled trials (RCT) and 21 retrospective cohort studies (RCS), comprising of 3,380 patients with Del19 and 2,687 patients with L858R were included in this analysis. Under first-generation (1G) TKIs, Del19 had better ORR, PFS and OS ($RR_{Del19/L858R}$= 1.19, 95% CI: 1.10-1.28; PFS $HR_{Del19/L858R}$= 1.25, 95% CI: 1.14-1.37; OS $HR_{Del19/L858R}$= 1.37, 95% CI: 1.19-1.57). Under second-generation (2G) TKIs, Del19 had no significantly better ORR/PFS ($RR_{Del19/L858R}$= 1.04, 95% CI: 0.94-1.16; $HR_{Del19/L858R}$= 1.18, 95% CI: 0.99-1.42). Under 1/2G TKIs, Del19 is good prognostic factor for OS ($HR_{Del19/L858R}$= 1.35, 95% CI: 1.20-1.52). The pooled median PFS of 1G TKIs was 12.53 (IQR: 11.45-13.70) in Del19 and 10.33 months (IQR: 9.51-11.29) in L858R. The pooled median PFS of 2G TKIs was 14.95 (IQR: 12.01-17.69) and 13.55 months (IQR: 11.33-16.31), respectively. In addition, the pooled median OS of 1G TKIs was 29.48 (IQR: 25.88-33.56) in Del19 and 22.95 months (IQR: 20.54-26.32) in L858R. The pooled median OS of 2G TKI was 32.08 (IQR: 27.86-33.40) and 26.63 months (IQR: 21.15-34.14), respectively. **Conclusions:** In comparison with L858R, Del19 is a good prognostic factor for RR/PFS under 1G TKIs and for OS under 1/2G TKIs. Common mutations respond differently to reversible and irreversible TKIs. Further study targeting on L858R are warranted to fulfill this unmet need in TKI era.

9080 Poster Session (Board #403), Sun, 8:00 AM-11:30 AM

Subgroup analysis of histology in ALTER0303: Anlotinib hydrochloride as 3rd line and further line treatment in refractory advanced NSCLC patients (pts). *First Author: Ying Cheng, Jilin Cancer Hospital, Jilin, China*

Background: In the ALTER0303 trial (NCT02388919), anlotinib hydrochloride was used as subsequence therapy for adult IIIB/IV NSCLC pts who progressed after at least 2 lines of prior systemic therapies. It has demonstrated that anlotinib significantly prolonged OS and PFS in advanced NSCLC pts as 3rd line treatment. Here we report the efficacy of anlotinib in pts with different histology, including adenocarcinoma (ACC), squamous cell carcinoma (SCC) and so on. **Methods:** 437 pts were randomised in a 2:1 ratio to receive anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) or placebo till progression or intolerable toxicity. Pts harboring EGFR or ALK mutations must had received previously targeted therapies. Primary endpoint is OS. Histology was the pre-stratified factor. **Results:** For the ACC pts (n=336), PFS and OS were both significantly improved in the anlotinib arm, and the most common grade ≥3 treatment-related AEs were hypertension and hypertriglyceridemia. Furthermore, in the subgroup of pts with SCC (n=76), remarkable advantages in PFS were observed in the anlotinib arm as well. Hypertension, hyponatremia and hemoptysis were the most common AEs in SCC NSCLC. (Data presented in the Table) **Conclusions:** In the ALTER0303 trial, a significant improvement in PFS was found in anlotinib treated pts from both subgroups (ACC and SCC). This is indicating that using anlotinib as subsequence therapy strategy not only led to the improvement in OS and PFS for advanced ACC pts, but also prolonged PFS of the SCC pts. Anlotinib could be an appropriate option for this difficult-to-treat NSCLC pts as subsequence treatment regardless of the histology. Clinical trial information: NCT02388919.

	ACC				SCC			
	Anlotinib n=228	Placebo n=108	HR	P-value	Anlotinib n=47	Placebo n=29	HR	P-value
Efficacy								
mPFS (mos)	5.53	1.37	0.21	<0.0001	5.63	2.70	0.39	0.001
mOS (mos)	9.63	6.93	0.67	0.0051	10.70	6.00	0.63	0.0932
ORR (%)	9.65	0.93		0.002	8.51	0		0.2933
DCR (%)	82.89	33.33		<0.0001	72.34	51.52		0.0866
Grade ≥3 AEs, n (%)								
Hyponatremia	13 (5.70%)	4 (3.70%)			9 (19.15%)	1 (3.45%)		
hand-foot syndrome	8 (3.51%)	0 (0%)			1 (2.13%)	0 (0%)		
Hypertension	28 (12.28%)	0 (0%)			9 (19.15%)	0 (0%)		
Hemoptysis	3(1.32%)	1 (0.93%)			5 (10.64%)	1 (3.45%)		

9081 Poster Session (Board #404), Sun, 8:00 AM-11:30 AM

Frequency of brain metastases and outcomes in patients with *HER2-, KRAS-, and EGFR*-mutant lung cancers. *First Author: Mark G. Kris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *HER2* mutations are oncogenic drivers in 3% of lung cancers. Here we describe the frequency and course of patients with *HER2* mutant lung cancers with spread to brain and compare results to individuals with *KRAS*- and *EGFR*-driven cancers. **Methods:** We compared cohorts of consecutive patients with *HER2*-(n = 98), *KRAS*- (n = 200) and *EGFR*- (n = 200) mutant lung cancers. Multivariate logistical regressions adjusted for follow-up length were performed to evaluate baseline and subsequent development of brain metastases and survival from the date of diagnosis of stage IV disease. **Results:** In total, brain metastases occurred in 41% of 498 patients (95% CI 37 to 45%). At diagnosis of stage IV disease, 19% (19/98) in the *HER2* cohort, 24% (48/200) in *KRAS*, and 31% (62/200) in *EGFR* had brain metastases (p= 0.8). Among those without brain metastases at baseline, 34% (27/79) of patients with *HER2* vs 11% (16/152) with *KRAS* ($p < 0.001$), vs 23% (32/138) with *EGFR* (p= 0.048) developed brain metastases during treatment. The overall incidence of brain metastases was 47% (46/98) in patients with *HER2*, 32% (64/200) with *KRAS)*, and 47% (94/200) with *EGFR* (p = 0.73). The occurrence of any brain metastases imparted a shorter median survival in patients with *HER2-* (25 vs 30 months, $p< 0.001$) and *EGFR-* (29 vs 92 months, $p < 0.001$) driven cancers but not with *KRAS* (14 vs 21 months, p= 0.44). The median overall survival was 1.6 years (range 1.3 – 2.2 years) for *HER2*, 1.1years (range 0.8 – 1.3 years) for *KRAS*, and 3.0 years (range 2.5 – 4.0 years) for *EGFR* ($p< 0.0001$). **Conclusions:** In our patients with lung cancers driven by *HER2, KRAS*, and *EGFR*, brain metastases occurred in 41% overall. The risk is numerically higher with *HER2* and *EGFR* than *KRAS*. While the incidence of brain metastases in patients with *HER2* mutant lung cancers is numerically lower than *EGFR* at diagnosis, it rises over the disease course to 47%, equal that of *EGFR*. Among those without brain metastases at baseline, a greater number of patients with *HER2*-mutant tumors subsequenty developed brain metastases during treatment compared to the *EGFR* and *KRAS* cohorts. With one third of patients with *HER2* mutant lung cancers developing brain metastases during treatment, close surveillance is critical.

9082 Poster Session (Board #405), Sun, 8:00 AM-11:30 AM

Can duration of response be used as a surrogate endpoint for overall survival in advanced non-small cell lung cancer? *First Author: Boris M Pfeiffer, Merck KGaA, Darmstadt, Germany*

Background: Surrogate endpoints for overall survival (OS) in advanced non-small cell lung cancer (NSCLC), such as overall response rate (ORR) and progression-free survival, are prone to bias due to crossover and unbalanced post-progression therapy or inconsistent response assessment criteria. This study aimed to evaluate the surrogacy of duration of response (DoR) for OS in phase III trials adjusted for crossover, unbalanced post-progression treatment, insufficient information and inconsistent response criteria. **Methods:** The analysis was based on systematic literature review and data extraction. The relationship between absolute differences in median DoR and in median OS was assessed using the correlation coefficient (R). Additionally, the relationship of the combination of ORR and DoR, which may be a better surrogate for OS because it captures both the frequency and duration of response, with OS was evaluated. The bias arising from different definitions of ORR and DoR was addressed in a subset analysis on RECIST-based trials and WHO-based trials. Further stratification by reported definition of DoR, either from start of treatment (randomization) or onset of response, was performed. **Results:** ORR, DoR, and OS values were reported in 20 trials (8,382 patients). The correlation coefficient of DoR with OS was 0.356 (95% CI: 0.000-0.690). 8 trials defined response according to RECIST criteria and 11 trials defined DoR from the first documented response. In these subsets, the correlation was 0.630 (95% CI: 0.000–0.924) and 0.572 (95% CI:0.000–0.873), respectively. The correlation coefficient of the combination of DoR and ORR with OS was 0.790 (95% CI: 0.535–0.913). In the RECIST-based trials and trials defining DoR from first documented response, the correlation coefficients of the combination of ORR and DoR with OS were 0.742 (95% CI: 0.079–0.950) and 0.887 (95% CI: 0.614–0.971), respectively. **Conclusions:** Evaluation of DoR as a surrogate for OS should take into consideration both response assessment criteria and ORR. The adjustment with ORR gives a better estimate of the treatment effect and can be used jointly with DoR as a surrogate endpoint to predict OS benefit.

9083 Poster Session (Board #406), Sun, 8:00 AM-11:30 AM

Concurrent genomic alterations in lung adenocarcinoma with a *MET* exon 14 skipping mutation. *First Author: Julia Rotow, University of California, San Francisco, San Francisco, CA*

Background: *METex14* oncogenic driver mutations are present in 2-4% of lung adenocarcinoma. While second-site *MET* mutations have been reported at MET TKI resistance, the factors influencing response to MET TKI therapy are not yet fully characterized. The landscape of co-occurring genetic alterations, which correlates with treatment response in EGFR-mutant NSCLC, is incompletely understood in *METex14* NSCLC. **Methods:** Targeted exome sequencing of cell-free DNA (cfDNA) obtained via the clinical Guardant360 assay for co-occurring alterations (somatic variants, copy-number alterations) in 68 cancer-associated genes within 70 samples from 65 patients with advanced stage *METex14* NSCLC. Synonymous mutations and those with predicted neutral or unknown functional impact were excluded. **Results:** 81.4% of *METex14*-positive samples contained concurrent genomic alterations, with a mean of an additional 2.6 (range 0-20) alterations/sample. Mutations or amplifications in *TP53* (44.6% of patients), CDK4 (13.8%), EGFR (12.3%), and NF1 (12.3%) were most common. Pathway analysis identified receptor tyrosine kinases (40%), cell cycle mediators (29.2%), and the MAPK pathway (26.2%) as frequently altered. Alterations in the MAPK pathway have not yet been implicated in TKI resistance in *METex14* NSCLC. We identified two patients with newly acquired MAPK pathway alterations (*KRAS* amplification, *KRAS G12D* mutation) at MET TKI resistance. **Conclusions:** The cfDNA from patients with *METex14* NSCLC frequently contains additional oncogenic co-alterations. Among downstream *MET* signaling mediators there is a high rate of concurrent MAPK pathway alterations in *METex*14 NSCLC, as well as newly acquired MAPK pathway alterations at resistance to MET TKI therapy. The MAPK pathway is a potential therapeutic target to enhance treatment responses in *METex14* NSCLC.

9084 Poster Session (Board #407), Sun, 8:00 AM-11:30 AM

Immune-related adverse events to predict survival in patients with advanced non-small cell lung cancer treated with nivolumab: A multicenter analysis. *First Author: Biagio Ricciuti, Clinical Oncology, S. Maria della Misericordia Hospital, Perugia, Italy*

Background: Anti-PD1 or anti-PD-L1 are the current standard of care for platinum-pretreated advanced non-small cell lung cancer (NSCLC) patients (pts), having shown to prolong survival as compared to chemotherapy in second line setting. Pts treated with these drugs not infrequently experience the so-called immune-related adverse events (irAEs), which we hypothesize reflect antitumor responses. In this study we investigated whether irAEs were associated with nivolumab efficacy in pts with advanced NSCLC. **Methods:** We conducted a retrospective study of pts with advanced NSCLC treated with nivolumab between Oct 2013 and Sept 2017. IrAEs were defined as AEs having immunological basis that required monitoring and interventions. We identified two groups according to the development of irAEs and evaluated the ORR, PFS and OS. **Results:** In a cohort of 127 pts, (median [range] age, 63 [30-81] years; 84 men [66.1%], 43 women [33.9%]; 34 [26.8%] with squamous (Sq) histology, 93 [73.2%] with Nsq histology), irAEs occurred in 57 of 127 study pts (44.8%). Six of them (10.5%) experienced grade 3 or higher irAEs. ORR and DCR were significantly higher in pts with irAEs (68.8% versus 4.8%, $P < 0.0001$ and, 79.6% versus 20.3% $P < 0.0001$, respectively). The median PFS was significantly longer in the irAEs group (8.6 [95%CI 4.3-11.7] versus 2.1 [95%CI 1.7-2.4] months, $P < 0.001$). Median OS was also significantly longer in pts with irAEs (17.4 [95%CI 8-28.8] versus 3.7 months [95%CI 2.7-4.6], $P < 0.0001$). Importantly, pts with ≥ 2 irAEs had a significantly prolonged OS as compared to those who developed 1 irAE (median NR versus 11.9 months, P = 0.04). Multivariate analysis confirmed that irAEs were significantly associated with improved survival outcomes, with HR of 0.27 (95% CI, 0.17-0.43; $P < 0.001$) for PFS and 0.36 (95% CI, 0.22 to 0.59; $P < 0.001$) for OS. **Conclusions:** In this multicenter study the development of irAEs was a strong predictor of prolonged OS in NSCLC pts treated with nivolumab. Of note, pts who developed ≥ 2 irAEs had a more pronounced survival benefit as compared to pts with only one event. Further studies are required to investigate the molecular mechanisms underlying this association.

9085 Poster Session (Board #408), Sun, 8:00 AM-11:30 AM

Contribution of nationwide genome screening in Japan (LC-SCRUM-Japan) to the development of precision medicine for non-small cell lung cancer. *First Author: Takashi Seto, Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka, Japan*

Background: A nationwide genome screening project in Japan (LC-SCRUM-Japan) has been established for the development of lung cancer precision medicine. **Methods:** Since 2013, non-squamous non-small lung cancer patients have been screened for ALK/ROS1/RET fusions using RT-PCR and FISH, and since 2015, they have also analyzed for 143 gene alterations using a next-generation sequencing (NGS) system, Oncomine™ Comprehensive Assay. Based on the molecular screening and the monitoring of clinical course and patient survival, a large-scale integrative clinico-genomic database has been established. **Results:** As of December, 2017, 251 institutions were participating and 4371 patients had been enrolled. The success rates of RT-PCR and NGS were 95% and 92%, respectively. Of 3919 available samples, a total of 1568 actionable gene alterations (382 KRAS mut, 193 ERBB2 mut/amp, 142 ROS1 fus, 100 RET fus, 98 MET skip/amp, 97 BRAF mut, 97 ALK fus, 96 PIK3CA mut, 54 FGFR1 amp, 13 NRAS mut, 6 AKT1 mut, 6 FGFR2/3 fus, 4 NRG1 fus, 2 NTRK3 fus and others) were detected in 1505 samples (38%). The concordance rates of the results in ALK, ROS1 and RET fusion detection between NGS and the corresponding RT-PCR were 0.98, 0.99 and 0.99, respectively. Through this screening, a total of 793 genotype-matched patients to molecular-targeted clinical trials were identified, and 136 of them (17%) were enrolled into the trials. Of the 2345 patients analyzed by NGS, the survival data were available in 1298 (55%). The patients with actionable gene alterations who were treated with targeted agents (n = 136) had significantly longer overall survivals than those not treated with targeted agents (n = 401) or the patients without actionable gene alterations (n = 761) (median survival [95%CI], 4.2 [2.4-8.2.] vs. 3.4 [2.3-5.8] vs. 2.3 [1.9-2.8] years, respectively; p = 0.01). **Conclusions:** LC-SCRUM-Japan contributes to the development of precision medicine, especially for ROS1, RET, ERBB2, BRAF and MET-positive lung cancers. In addition to the tissue-based molecular screening, a NGS assay with liquid biopsy was started in December 2017 and is now ongoing in the LC-SCRUM-Japan.

9086 Poster Session (Board #409), Sun, 8:00 AM-11:30 AM

Early determination of benefit or futility in treating NSCLC using the LCSS 3-Item Global Index (3-IGI). *First Author: Richard J. Gralla, Albert Einstein College of Medicine - Jacobi Medical Center, Bronx, NY*

Background: Early assessment of the effect of treatment for advanced NSCLC can prevent unnecessary exposure to toxic and costly therapy while aiding in decision making to change treatment if necessary. Analysis in mesothelioma (Symanowski *JCO* 2014) suggested that a 20% decline from baseline after 2 cycles of chemotherapy in the 3-Item Global Index of the LCSS identified patients unlikely to benefit. The 3-IGI (global distress, activities, QL) takes < 2 minutes to assess. **Methods:** 164 patients with NSCLC receiving chemotherapy or check point inhibitors were prospectively evaluated with the LCSS at baseline and every 3 weeks using electronic media. Patients were also randomized 1:1 so that their physicians knew the results of the LCSS immediately in half of the patients. **Results:** Patients: Stage IV 92%; first line 73%; female 43%; median PS 1; mean age 63. The LCSS was completed after 2 cycles of treatment and prior to planning for the next cycle (generally 6 weeks after baseline; representing 91% of the 148 patients living). Patients with a 20% decline in the 3-IGI compared with baseline had a median survival of 7.6 months, contrasted to 15.8 months for those without this degree of 3-IGI decline (p = 0.01); 1 year survivals = 26% versus 62%. Even with the marked PRO decline after 2 treatment cycles, patients in the 20% decline group received a median of 2.3 more cycles of the same chemotherapy (median cost = $10,712 / patient). In the 50% of patients for which their physicians knew the ongoing LCSS results, fewer chemotherapy cycles and imaging studies were performed, but the differences were not significant (p = 0.8). **Conclusions:** Assessing change from baseline with the 3-IGI of the LCSS identifies after only 2 cycles of treatment those patients who have poor response and survival outcomes if continued on the same therapy. This PRO assessment is rapid, easy and inexpensive. Physicians need to consider the impact of change on decision options given that even when physicians were aware of the worsening PRO they often did not act on the findings. Responding to 3-IGI changes can result in better decisions concerning continuing or changing treatment, lessening toxicity, and savings in cost of unhelpful treatment. Support: NIH/NCI R01 CA157409 Clinical trial information: NCT01924416.

9087 Poster Session (Board #410), Sun, 8:00 AM-11:30 AM

Landscape of EGFR-dependent and independent mechanisms of osimertinib resistance in EGFR-mutant NSCLC patients. *First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Osimertinib is a third generation EGFR TKI, however, the mechanisms of resistance to osimertinib have been incompletely described, and there are currently no targeted regimens known to be effective for these patients. We evaluated clinical and genetic characteristics of patients who received osimertinib for *EGFR*-mutant NSCLC. We also provide treatment experience after progression on osimertinib. **Methods:** Using the MD Anderson GEMINI database and Moffitt Cancer Center dataset, we identified patients treated with osimertinib and performed clinical outcome analysis. Molecular profiling analysis was performed at the time of progression when available. **Results:** 118 patients were identified. Median PFS on osimertinib was 8.8 months (95% CI, 6.5 to 11). Overall survival from diagnosis was 76.7 months (95% CI, 42.5 to 111). 71 patients had disease progression. Upon progression, osimertinib was continued in 44 of 71 patients with 21 (48%) received local consolidation radiation. The osimertinib continued patients had longer second PFS compared to the ones discontinued. For patients who progressed on osimertinib, 42 had molecular profiling upon progression. A total of 22 genes/pathways were observed to have recurrent alterations. In addition to two cases with germline T790M, 19 cases retained and 21 cases lost detectable T790M mutation. Among T790M-retained cases, tertiary EGFR mutations of C797S/G and L792H (11 cases) in EGFR gene, and MET amplification (5 cases), were the most common mechanisms of resistance. In T790M-lost cases, PIK3CA mutation (2 cases), MET amplification, and small cell transformation, but not additional EGFR resistance mutations, were observed. Other resistance- associated alterations included FGFR amplification and RET fusion. Preclinical studies verified that osimertinib resistance could be reversed by targeting a subset of these alterations. **Conclusions:** We found continuation of osimertinib beyond first progression may offer clinical benefit. Osimertinib resistance is associated with diverse mechanisms. The loss of T790M was common, and the majority of resistance was associated with EGFR-independent, as in some cases targetable, mechanisms.

9088 Poster Session (Board #411), Sun, 8:00 AM-11:30 AM

Demographic composition of lung cancer trials: FDA analysis. *First Author: Lola A. Fashoyin-Aje, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Lung cancer is the leading cause of cancer death; in the US non-small cell lung cancer (NSCLC) accounts for 80% of the lung cancer diagnoses. Enrollment of a diverse population in clinical trials (CTs) of new cancer drugs may provide information regarding the safety and efficacy of treatments in demographic subgroups that are disproportionately represented among new cases of, and deaths from, cancer. This analysis characterizes the demographics of patients enrolled in CTs submitted to FDA in support of marketing applications for FDA-approved NSCLC drugs. **Methods:** Reviewed datasets in the applications of original approval for new NSCLC drugs (2011- 17), and pooled demographic data from CTs that provided primary safety and efficacy data for drug approval. **Results:** This table illustrates enrollment by demographics at all sites and in the US. **Conclusions:** Enrollment of females is slightly higher (54%) than predicted based on corresponding incidence rates (48%) for this subgroup in the Surveillance, Epidemiology, and End Results database. Enrollment of younger patients is also higher than predicted based on incidence rate; patients < 65 years comprise 68% of all enrolled patients compared to 28% of new cases. These differences may be attributable, in part, to the number of CTs for new drugs for biomarker-defined NSCLC subtypes that occur more frequently in females and younger patients than in NSCLC in general. In contrast, there is lower representation of racial/ethnic minority patients (< 1%) and patients ≥ 65 years of age (32%) in these CTs than predicted by incidence rates (65.9, 83.7, 312 and 15 cases per 100,000 in patients who are White male, Black male, > 65 years, and < 65 years, respectively). Targeted enrollment of racial/ethnic minorities and older patients is needed to improve their access to CTs; such efforts may facilitate an assessment of safety and efficacy in these subgroups.

	All n = 9711%	US n = 1149%
Age		
< 65 years	68	72
65-80 years	31	25
> 80 years	2	2
Sex*		
Female	54	55
Race#		
American Indian/ Alaskan Native[a]	< 1	< 1
Asian	43	10
Black/African American	< 1	2
Native Hawaiian / Other Pacific Islander[a]	< 1	< 1
Other	2	4
White	50	82
Ethnicity		
Hispanic	2	3
Not Hispanic	19	21
Other	3	12
Missing/Not Collected	76	65

*Missing 'Sex' (n = 2); #Missing 'race'(n = 484). [a] (n = 3).

9089 Poster Session (Board #412), Sun, 8:00 AM-11:30 AM

Phase I/II study of the A2AR antagonist NIR178 (PBF-509), an oral immunotherapy, in patients (pts) with advanced NSCLC. *First Author: Alberto Chiappori, Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL*

Background: ATP is catabolized to adenosine in the tumor microenvironment, leading to excess adenosine and immunosuppressive effects via immune checkpoint protein adenosine 2A receptor (A2AR). NIR178 is an oral A2AR antagonist that selectively binds and inhibits A2AR, reactivating T cell-mediated antitumor immune response. This Phase I/II study evaluated NIR178 in previously treated pts with advanced NSCLC (NCT02403193). **Methods:** Pts (ECOG PS 0–1) had received ≥1 prior line of therapy; EGFR/ALK pts had failed prior TKI therapy. Objectives: primary – determine MTD of single-agent NIR178; secondary – efficacy endpoints, PK, and evaluation of PD-L1 expression. **Results:** At 13 Dec 2017 data cut-off, 24 pts had been treated: median age 68 yrs, 46% male; 79% received prior immunotherapy; 22/24 (92%) pts had discontinued (due to progression [n = 13], death [n = 2], AEs [n = 2] or other reasons [n = 5]) and 2/24 (8%) pts remained on treatment. Dose levels evaluated: 80 (n = 3), 160 (n = 3), 320 (n = 7), 480 (n = 6), 640 mg BID (n = 5). There was 1 DLT: Gr 3 nausea (640 mg). The most frequent (≥20%) any-Gr AEs regardless of causality were nausea (67%), fatigue (63%), dyspnea (46%), vomiting (33%), chest pain and other (29%), gastroesophageal reflux disease, anemia, diarrhea (all 25%), anorexia, back pain, generalized muscle weakness and cough (all 21%). Drug-related Gr 3 AEs were pneumonitis (8%) and nausea (4%); no Gr 4 AEs were reported. Potential immune-related any-Gr AEs were rash (8%), pneumonitis (8%), hypothyroidism, increased ALT/AST (all 4%). NIR178 systemic exposure (Cmax, AUC) increased more than proportionally with dose. Efficacy data for 17/24 treated pts demonstrated responses and SD across the dose range, including 1 confirmed CR (480 mg) and 1 PR (80 mg), both in immunotherapy-naïve pts. Durable SD > 44 wks with tumor shrinkage was observed in 2 ongoing immunotherapy-exposed pts. Disease control was seen in pts with both high and low baseline PD-L1 expression. **Conclusions:** NIR178 was well tolerated; AEs were manageable and there were no Gr 4 drug-related AEs. Immune-related AEs may indicate immune stimulation. Clinical benefit was observed in immunotherapy-exposed and -naïve pts irrespective of PD-L1 status. Clinical trial information: NCT02403193.

9090 Poster Session (Board #413), Sun, 8:00 AM-11:30 AM

Avelumab (anti–PD-L1) in patients with platinum-treated advanced NSCLC: 2.5-year follow-up from the JAVELIN Solid Tumor trial. *First Author: Arun Rajan, Thoracic and Gastrointestinal Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Avelumab, a human anti–PD-L1 IgG1 monoclonal antibody, is an approved treatment for metastatic Merkel cell carcinoma in various countries and platinum-treated advanced urothelial carcinoma in the US. In phase 1b studies, avelumab has shown antitumor activity and acceptable safety in patients with advanced NSCLC. Here, we report long-term data for avelumab in patients (pts) with platinum-treated NSCLC. **Methods:** In a phase 1b cohort of JAVELIN Solid Tumor (NCT01772004), pts with stage IIIB–IV NSCLC unselected for PD-L1 status, with progression after platinum doublet therapy, received avelumab 10 mg/kg Q2W as second-line (2L) or later treatment until confirmed progression, unacceptable toxicity, or withdrawal. PD-L1 expression was assessed using PD-L1 IHC 73-10 assay. Time-to-event endpoints were estimated using Kaplan-Meier methods. **Results:** 184 pts received avelumab. At data cutoff on Feb 15, 2017, median follow-up was 33.9 months (range, 31.0-40.7) and 9 pts (4.9%) remained on treatment. 58 pts (31.5%) had received ≥2 prior lines of therapy for advanced disease. The objective response rate (ORR) was 14.1% (95% CI, 9.4-20.0), including complete response in 1.1%, and median duration of response was 17.5 months (95% CI, 6.9-21.4). Progression-free survival (PFS) rates at 6 months and 1 yr (95% CI) were 24.2% (18.1-30.8) and 16.5% (11.3-22.5). Overall survival (OS) rates at 1 and 2 yrs (95% CI) were 42.5% (35.1-49.7) and 25.0% (18.7-31.8). In evaluable pts with PD-L1+ (n = 122) and PD-L1− (n = 20) tumors (> 1% tumor cell cutoff), ORR (95% CI) was 16.4% (12.1-21.5) vs 10.0% (2.7-24.5), the 1-yr PFS rate was 19.1% (12.3-27.0) vs 5.0% (0.3-20.5), median OS was 11.1 (8.4-17.3) vs 4.6 (2.8-12.5) months, and the 2-yr OS rate was 30.0% (21.7-38.7) vs 17.1% (4.4-37.0), respectively. Safety findings were consistent with earlier analyses; 14.7% had a grade ≥3 treatment-related adverse event, most commonly (> 1%) infusion-related reaction (2.2%), lipase increase (1.6%), and pneumonitis (1.1%), and no treatment-related deaths occurred. **Conclusions:** Avelumab as 2L or later therapy is associated with durable responses and long-term OS in pts with platinum-treated advanced NSCLC. Clinical trial information: NCT01772004.

9091 Poster Session (Board #414), Sun, 8:00 AM-11:30 AM

Association of pre-existing thyroid autoimmunity with the development of thyroid dysfunction induced by nivolumab. *First Author: Shiro Kimbara, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Thyroid dysfunction (TD) induced by immune checkpoint inhibitors is not sufficiently understood. The purpose of this study was to identify risk factors and the clinical course of TD induced by nivolumab. **Methods:** Patients with advanced solid tumors who were treated with nivolumab from March 2009 through March 2016 at the National Cancer Center Hospital were eligible. Thyroid function and anti-thyroid antibodies from the preserved serum samples among patients treated with nivolumab were evaluated retrospectively. The biochemical diagnosis of TD was determined in accordance with the guidelines of ATA, AACE, and the Endocrine Society. We defined thyroid autoimmunity as presence of anti-thyroid antibodies including anti-thyroid peroxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb) before nivolumab. **Results:** One-hundred and eighty-nine patients with advanced solid tumors who were treated with nivolumab from March 2009 through March 2016 at the National Cancer Center Hospital were eligible for this study. Twenty-three (12%) of 189 patients developed TD, including 17 cases of hypothyroidism and 20 of thyrotoxicosis. Thyrotoxicosis followed by hypothyroidism occurred in 14 cases. There were significant difference between patients who developed TD (n = 23) and who did not (n = 166) in thyroid autoimmunity ($p < 0.001$) and elevated TSH ($p = 0.01$) at baseline. Next, we performed further analysis among 168 patients with sufficient assessment of anti-thyroid antibodies. Fourteen of 35 patients (40%) with thyroid autoimmunity developed TD, versus nine of 133 (7%) without (odds ratio 9.19; 95% confidence interval [CI]: 3.53-23.9). In multivariate analysis, elevated TSH and TgAb at baseline were significantly associated with the development of TD, with odds ratios of 7.36 (95% CI: 1.66-32.7) and 26.5 (95% CI: 8.18-85.8), respectively. Interestingly, thyrotoxicosis followed by thyrotoxicosis did not develop in 5 of 6 patients who received steroid therapy on the onset of thyrotoxicosis due to any reasons such as other irAEs and a symptom relief for brain metastasis. **Conclusions:** Patients with preexisting TgAb and elevated TSH before nivolumab treatment were at high risk for TD.

9092 Poster Session (Board #415), Sun, 8:00 AM-11:30 AM

Genetic aberrations related to increased risks of brain metastasis in non-small cell lung cancer (GASTO-1036). *First Author: Delan Li, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Metastatic cancer to the brain has a poor prognosis and subject patients to limited therapeutic options. Lung cancer represents the most common primary tumor giving rise to brain metastasis (BM). Understanding molecular alterations that are associated with increased risks of BM is of great importance to develop more effective intervention and therapeutic strategies for patients. **Methods:** Sixty-one non-small cell lung cancer (NSCLC) patients who underwent surgery for BM removal between 2000 and 2016 were retrospectively studied. Twenty-five patients had synchronous brain metastatic tumors at diagnosis, while the rest had metachronous presentation of BM during the course of their disease progression. We performed mutation profiling using targeted next-generation sequencing for 416 cancer-relevant genes on resected FFPE tumor samples of both lung and brain lesions of these patients. BM-free survival and disease-free survival were assessed in the metachronous cohort by using Kaplan-Meier test and Cox regression model. **Results:** Mutations of oncogenes and tumor suppressors, such as *EGFR*, *TP53, KRAS, PIK3CA,* and gene fusions *(ALK* and *RET)*, were identified in a total of 85% (52/61) of the patients, which were highly concordant between BM and primary lung tumors, albeit discordance was also observed suggesting a unique genetic evolution. Mutations targeting CDKs/CDK inhibitors, PI3K pathway, *MET* and *ERBB2* are more enriched in the metastatic brain foci than the primary lung tumor, suggesting the association of those genes with increased risks of developing BM. Indeed, patients with activated PI3K pathway were found to have significantly shorter BM-free survival (hazard ratio = 8.77, $p < 0.001$) as well as shorter disease-free survival (hazard ratio = 7.43, $p < 0.001$). In addition, activation of WNT pathway, in particular, missense mutations of *CTNNB1*, also tends to be associated with higher risks for disease spread and developing BM from NSCLC. **Conclusions:** Our findings shed lights on genetic concordance and divergence of primary lung and brain metastatic tumors, and also show that activated PI3K and WNT pathways are significantly associated with increased risks of brain metastasis in NSCLC.

9093 Poster Session (Board #416), Sun, 8:00 AM-11:30 AM

Long-term efficacy and outcomes with sequential crizotinib followed by alectinib in *ALK*+ NSCLC. *First Author: Jessica Jiyeong Lin, Massachusetts General Hospital, Boston, MA*

Background: Alectinib was recently approved for first-line treatment of advanced ALK+ NSCLC based on the ALEX trial, which demonstrated improved PFS with first-line alectinib compared to crizotinib. However, crossover was not allowed in ALEX. As standard therapy for ALK+ patients relapsing on crizotinib is treatment with a second-generation ALK inhibitor, such as alectinib, a more appropriate control arm would have been sequential crizotinib and alectinib, rather than crizotinib alone. We therefore evaluated outcomes of patients sequentially treated with crizotinib and alectinib. **Methods:** We identified 94 *ALK*+ NSCLC patients treated with crizotinib followed by alectinib. Medical records were reviewed to determine clinical outcomes and post-alectinib resistance mechanisms. **Results:** The median PFS on crizotinib and alectinib were 8.1 months (95% CI, 6.4-10.6) and 13.1 months (95% CI, 8.2-19.4), respectively. The median interval from crizotinib discontinuation to initiation of alectinib was 8 days (range, 1-304). Five patients (5.3%) switched to alectinib due to toxicity, 1 (1.1%) due to patient preference, and 88 (93.6%) due to progression (pattern: CNS only, n = 39; extracranial only, n = 37; both CNS/extracranial, n = 12). The median combined PFS for sequential crizotinib and alectinib was 22.9 months (95% CI, 17.1-30.5). Of note, among 68 patients who received crizotinib as first-line and alectinib as second-line therapy, the median combined PFS was shorter at 17.1 months (95% CI, 13.3-23.6). The 5-year OS for the overall cohort from the diagnosis of metastatic disease or from initiation of crizotinib was 66% (95% CI, 51-77%) and 59% (95% CI, 44-72%), respectively. Twenty-nine patients underwent a tumor biopsy following progression on alectinib. Of these, 20 (69%) had an *ALK* resistance mutation, including: 10 (50%) G1202R, 6 (12%) I1171N, 1 (5%) I1171S, 1 (5%) I1171T, and 2 (10%) V1180L. **Conclusions:** These findings serve as a historical comparator for first-line alectinib trials including ALEX. While sequential therapy with crizotinib and alectinib can provide significant benefit, this analysis suggests patients may derive greater benefit from first-line alectinib, supporting upfront use of alectinib.

9094 Poster Session (Board #417), Sun, 8:00 AM-11:30 AM

Preliminary Phase II results of a multicenter, open-label study of nazartinib (EGF816) in adult patients with treatment-naïve *EGFR*-mutant non-small cell lung cancer (NSCLC). *First Author: Dong-Wan Kim, Seoul National University Hospital, Seoul, Korea, Republic of (South)*

Background: Nazartinib (EGF816) is a third-generation EGFR-TKI selective for activating and T790M mutations while sparing wild-type EGFR. In the Phase I part of a Phase I/II multicenter study of nazartinib in *EGFR*-mutant NSCLC (NCT02108964), the recommended Phase II dose was 150 mg QD. Preliminary safety and efficacy results are presented from the Phase II expansion in treatment-naïve patients (pts) with *EGFR*-mutant NSCLC. **Methods:** Pts (ECOG PS 0−1) received nazartinib 150 mg QD. Primary objective: evaluation of antitumor activity (overall response rate [ORR]) per blinded independent review committee (BIRC). Secondary objectives: characterization of safety/tolerability, and further efficacy endpoints (including time to response and progression-free survival [PFS]). **Results:** At the data cut-off 31 Aug 2017, 40 pts had been enrolled; median age 63.5 years, 70% Asian, 65% female, 52.5% ECOG PS 1, 16/40 (40%) pts had brain metastases at screening; 3/40 (7.5%) pts had discontinued (2 due to progressive disease and 1 due to AE) and 37/40 (92.5%) pts remained on treatment. Median duration of exposure was 16.1 wks. The most frequent (≥20%) any-grade (Gr) AEs were maculopapular rash (30%), diarrhea (28%), and stomatitis (23%). Gr 3 AEs occurred in 10/40 (25%) pts, most commonly (≥5%) maculopapular rash in 4/40 (10%) pts and hypokalemia in 2/40 (5%) pts; there were no Gr 4 AEs. Pts (n = 24) who were enrolled ≥15 weeks before the data cut-off date were considered evaluable. In these pts, the confirmed ORR by BIRC was 67% (1 CR/15 PRs); the unconfirmed ORR by BIRC was 75% (1 CR/17 PRs, including 2 pts with unconfirmed PRs still ongoing at the data cut off); disease control rate was 96%. Duration of response and PFS data were still immature at the data cut-off. **Conclusions:** Oral nazartinib demonstrated a tolerable safety profile; maculopapular rash, atypical of EGFR-TKIs, was managed with minimal dose adjustment. Promising efficacy in treatment-naïve pts with *EGFR*-mutant NSCLC was seen despite a high number of pts with brain metastases. At the data cut-off, 37/40 pts were still on treatment. Clinical trial information: NCT02108964.

9095 Poster Session (Board #418), Sun, 8:00 AM-11:30 AM

An amplicon-based liquid biopsy for detecting *ALK* and *ROS1* fusions and resistance mutations in advanced non-small cell lung cancer (NSCLC) patients. *First Author: Laura Mezquita, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Villejuif, France*

Background: Circulating tumor DNA (ctDNA), is a surrogate material for somatic mutation (mut) detection, such as *EGFR* in NSCLC patients (pts). However, the applicability for the detection of *ALK*/*ROS1* fusions and resistance mut. is poorly described. The aim of this study was to evaluate an amplicon-based *ctDNA* assay for detecting *ALK*/*ROS1* fusions and mut. in a cohort of *ALK*/*ROS1*+ NSCLC pts. **Methods:** Advanced *ALK*/*ROS1*+ NSCLC pts were prospectively enrolled from Dec 2016 to Dec 2017 in our institution. The analysis of *ALK*/*ROS1* mut, *EML4-ALK* (variant 1,2,3) and *ROS1* fusions (with partner genes *CD74*, *SLC34A2*, *SDC4* and *EZR*) in ctDNA were performed using InVisionFirst™ **Results:** 51 pts were included (43 *ALK*, 8 *ROS1); ALK/ROS1* status was confirmed by *ALK* IHC (26) and FISH (40). The median prior tyrosine kinase inhibitors (TKI) received was 2 (0-4). Blood samples (n = 127) were collected before TKI (n = 9), during (n = 120) or at progression (PD) (n = 25) in 45 pts that received TKI (13 crizotinib, 32 next-gen. TKI) or other therapies (n = 6). Before TKI, *ALK*/*ROS1* ctDNA fusions were detected in 86% of pts (5/6 *ALK*; 1/1 *ROS1*). In samples at PD, 64% had fusions detected (15/22 *ALK*; 1/3 *ROS1*). Overall, 16 pts had a positive fusion in blood (5 *EML4-ALK* variant 1-2, 8 variant 3, 2 *CD74-ROS1*, and 1 *SLC34A2-ROS1* (13 *ALK*, 3 *ROS1*). By contrast, a minority (13%) of samples collected during clinical response, were positive (8/69 *ALK*; 2/11 *ROS1). ALK* mut were detected in 30% of blood samples at PD to TKI (6/17): 17% (1/5) post-crizotinib (*G1269A*, *R1264K*, *L1196Q*, *F1164L*, *C1156Y*), and 45% (5/11) post next-gen. TKI (all *G1202R*), all of them associated with the *ALK* variant 3. No *ROS1* mut were detected. Complex *ALK* mut were observed in 2 pts variant 3 (post crizotinib and lorlatinib). Other *non-ALK* mut were found in 47% of samples at PD: *TP53* (5), *NFE2L2* (4), *PTEN* (2), *KRAS* (1) and *PI3KCA* (1). Complex *ALK* mut + *non-ALK* mut were found in 4 (24%) samples; exclusively others *non-ALK* mut were found in 4 samples. This could explain TKI resistance in 24%. **Conclusions:** Routine liquid biopsy detects *ALK/ROS1* fusions in untreated NSCLC pts and reflects treatment sensitivity in TKI exposed pts. It is also an accurate tool to assess TKI resistance.

9096 Poster Session (Board #419), Sun, 8:00 AM-11:30 AM

Real-world treatment patterns and survival of BRAF V600-mutated metastatic non-small cell lung cancer patients. *First Author: Leora Horn, Vanderbilt University Medical Center, Nashville, TN*

Background: There is limited evidence on clinical outcomes in patients with BRAF-mutated non-small cell lung cancer (NSCLC) treated outside the controlled environs of clinical trials. To address this gap, we described treatment patterns and survival in such patients evaluated and treated at selected US academic cancer centers in 2009 -2016. **Methods:** This was a cross-sectional, retrospective medical record review of BRAF V600-mutated metastatic NSCLC patients from 7 centers. Participants in current/ previous BRAF-related clinical trials were excluded. Onset of metastatic NSCLC defined the index date, which was required to occur ≥6 months before the record abstraction date. We described treatment patterns and used Kaplan-Meier analyses for overall survival (OS). **Results:** The study included 72 patients. At index, median age [range] was 65 [44 to 90] years, 61.1% were female, 66.7% were current/former smokers, and 70.8% had Stage IV NSCLC at diagnosis. Fifty-two patients received ≥1 line of systemic therapy for metastatic disease. Platinum-based doublet chemotherapy was the most common first-line (1L) regimen (76.9% of 1L recipients); no patient received 1L targeted therapy (TT). Of the 33 second-line (2L) treatment recipients 30.3% received TT, and 10 patients received TT in ≥3 lines. At time of review, 38 patients were deceased. Median (95%CI) OS from the index date was 31.0 (14.5, 63.8) months for all patients, and 45.9 (16.1, 62.4) months from 1L initiation among 1L recipients. Median (95%CI) OS was 56.5 (13.4, 89.1) months from metastatic onset for TT recipients and 27.2 (10.6, 64.6) months in those not treated with TT. Patients (26) who had a BRAF test result < 3 months from metastatic onset had substantially shorter median survival (14.1 months) than patients (21) who had a test result ≥3 months after onset (52.7 months). **Conclusions:** These findings indicate that survival expectations of BRAF V600-mutated metastatic NSCLC patients may be higher than metastatic NSCLC patients without an oncogenic driver. The data also show patients who received TT had numerically longer OS from metastatic onset than patients receiving usual care, adding to the evidence on the importance of TT in BRAF V600-mutant NSCLC.

9097 Poster Session (Board #420), Sun, 8:00 AM-11:30 AM

Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-estrogen in women with non-squamous advanced stage NSCLC: IFCT-1003 LADIE trial. *First Author: Julien Mazieres, Hôpital Larrey, Centre Hospitalier Universitaire Toulouse, Toulouse, France*

Background: The incidence of lung cancer is increasing dramatically in women with recent findings as the preferential involvement of the EGFR pathway and the potential impact of hormonal factors in women. Preclinical data have shown that the combination of an EGFR-TKI with an anti-estrogen could overcome resistance to EGFR-TKI. **Methods:** IFCT-1003 LADIE Trial was a 2x2 arms parallel open-label randomized phase II trial. PS 0-2 post-menopausal women with advanced stage lung adenocarcinoma were treated with gefitinib (G 250 mg/day) vs. G + fulvestrant 500 mg / month with a supplementary dose at day 15 (G+F) in the EGFR mutated group (EGFR+) in 1st or 2nd line setting or with erlotinib (E 150 mg/day) vs. E + fulvestrant (E+F) in the EGFR wild-type group (EGFR WT) in 2nd or 3rd line setting until progression or unacceptable toxicity. Primary objective was progression-free survival (PFS) at 3 and 9 months for EGFR WT and EGFR+ patients, respectively. **Results:** From 02/2012 to 03/2017, 204 pts (G 104, G+F 100) and 175 (E 87, E+F 88) were enrolled in the EGFR+ and EGFR WT cohorts respectively. The median number of fulvestrant injections was 10 in the G+F group and 3 in the E+F group. The tolerance was correct (grade 3/4: 24.2% in the G+F group *vs* 21.3% in the G group, 16.0% in the E+F group *vs* 13.8% in the E group) and no treatment-related death. In the EGFR+ cohort, the primary endpoint was reached as 54 pts in the G+F group were non-progressive at 9 months. Nevertheless, addition of F to G was not associated with significant better PFS (9.9 *vs* 10.1 months) or OS (22.1 *vs* 29.9 months). In the EGFR WT cohort, the primary endpoint was not reached as 29 patients were non-progressive at 3 months. Here also, addition of F to E was not associated with better outcome (PFS 1.8 *vs* 2.0 and OS 10.0 *vs* 7.3 months). No PFS difference was observed in the subgroup of patients with positive staining for REα. **Conclusions:** Addition of fulvestrant to EGFR-TKI is feasible and is associated with good PFS in the EGFR mutated group. Nevertheless, the lack of benefit associated with the combination of fulvestrant to EGFR-TKI does not support its future development in a phase 3 trial in women with NSCLC. Clinical trial information: NCT01556191.

9098 Poster Session (Board #421), Sun, 8:00 AM-11:30 AM

Targeting NFE2L2 mutations in advanced squamous cell lung cancers with the TORC1/2 inhibitor TAK228. *First Author: Paul K. Paik, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite efforts over the past decade, no targeted treatments exist for pts w/ SQCLC. Analyses by TCGA and others (Paik Cancer Disc 2015) have identified a heretofore untargeted, frequently mutated oncogene (NFE2L2)/tumor suppressor (KEAP1) pair, each mutated in ~20% of pts w/ SQCLC. NFE2L2 encodes Nrf2, a transcription factor involved in the oxidative stress response which is targeted for degradation by Keap1. NFE2L2 mutations occur exclusively in an exon 2 hotspot that encodes the Neh2 domain (aa.1-86), which is the binding site for Keap1. Mutations in this region disrupt Keap1 binding, leading to Nrf2 nuclear translocation and increased mTOR signaling through regulation of RagD (Shibata Cancer Res 2010). We now report translational studies and prelim results from a phase 2 trial of the oral TORC1/2 inhibitor TAK228 in SQCLC pts with these mutations. **Methods:** Cytotoxicity, signaling, and xenograft experiments were performed using LK-2 SQCLC cells harboring an NFE2L2 E79K mutation treated with TAK228, everolimus, rapamycin, or deforolimus. Pts w/ prev treated stage IV SQCLC w/ NFE2L2 mutations are eligible for an NCI CTEP single-institution phase 2 study of TAK228 3mg po qd (continuous 28 day cycles; NCT02417701). 1^0 endpoint: ORR. 2^0 endpoint: PFS. The study utilizes a Simon 2-stage design with H0 = 5% (N≥1/5 responses), HA = 40% (N≥2/10 responses). **Results:** TAK228 exhibited significantly increased anti-tumor activity over TORC1 rapalogs in LK-2 cells. TAK228 alone was cytotoxic at sub-[μM] (IC50 68nM); all other rapalogs had IC50s $>$ 10μM. This was assoc with an 80% decrease in downstream pS6 . Tumor response (-55% shrinkage) was also seen in an LK-2 xenograft treated with TAK228. No anti-tumor/growth inhibitory response was seen with any other rapalog. N = 4 pts have been treated on the clinical trial (exon 2 del, D29H, F37V, W24C). 2 related-SAEs (G3 hyperglycemia, G3 confusion) were seen; no other $>$ G2 AEs reported. ORR = 25% (1 PR, 3 SD, 0 PD). Prolonged response is present, with DOR = 11mo, 8mo, 5.5mo, and 1mo, all ongoing. **Conclusions:** TAK228 is well-tolerated w/ evidence of pre-clinical and clinical activity in NFE2L2 mutant SQCLC. The trial has met its first-stage endpoint and has expanded to N = 10 patients. Clinical trial information: NCT02417701.

9099 Poster Session (Board #422), Sun, 8:00 AM-11:30 AM

Final results of a phase I prospective trial evaluating the combination of stereotactic body radiotherapy (SBRT) with concurrent pembrolizumab in patients with metastatic non-small cell lung cancer (NSCLC) or melanoma. *First Author: Allison M. Campbell, Yale University School of Medicine, Department of Therapeutic Radiology, New Haven, CT*

Background: We report final Phase I results of a Phase I/II prospective trial assessing safety and tolerability of SBRT and concurrent pembrolizumab. **Methods:** Eligible patients had metastatic NSCLC or melanoma and ≥ 2 sites of disease. Patients who had received prior anti-PD1 therapy were eligible if their disease had progressed by RECIST criteria; these patients received SBRT at enrollment. Immunotherapy naïve patients were treated with 200 mg of pembrolizumab q3 weeks until disease progression, then received SBRT. After SBRT, patients received pembrolizumab q3 weeks until disease progression. Patients were assigned to an SBRT dose escalation arm based on target location: either in the lung (arm A) or elsewhere (arm B). **Results:** 24 patients were enrolled (melanoma n=5; NSCLC n=19). 9 patients had received prior anti-PD-1 therapy and therefore got SBRT at enrollment. 15 patients were immunotherapy naïve and received a mean of 8.3 cycles of pembrolizumab before disease progression and SBRT. The target SBRT dose of 30 Gy in 3 fractions was reached for each arm. No dose limiting toxicities (DLTs) were observed within 60 days of SBRT. Non-hematologic toxicities of $>$ grade 2 occurring during the 60 day DLT window or during subsequent pembrolizumab treatment are presented in the table below, with immune-related adverse events noted. 5 of 24 patients (21%) had an immune mediated grade 2 or 3 adverse event during post SBRT immunotherapy. Patients received pembrolizumab for a mean of 19.8 weeks post-SBRT (range 0-52 weeks) before disease progression. **Conclusions:** Dose escalation to 30 Gy in 3 fractions was completed for both arms without dose limiting toxicity. Combination therapy was well tolerated. Preliminary efficacy data indicates that addition of SBRT to a single site resulted in a mean of 19.8 weeks of continued response. Clinical trial information: NCT02407171.

	Pre SBRT	Arm A (Lung Target)		Arm B (Non Lung Target)	
		30 Gy in 5 fx	*30 Gy in 3 fx*	*30 Gy in 5 fx*	*30 Gy in 3 fx*
n	15	7	6	4	7
Gr 2	4 *hypothyroid; n=1* *pneumonitis; n=1*	2	2 *colitis; n=1*	0	3 *pneumonitis; n=1*
Gr 3	1 *hypothyroid; n=1*	1 *pneumonitis; n=1*	2 *enterocolitis; n=1* *pneumonitis; n=1*	0	1 *colitis; n=1*
Gr 4	0	0	0	0	0
Gr 5	0	0	0	0	0

9100 Poster Session (Board #423), Sun, 8:00 AM-11:30 AM

EGFR reporting in stage IV adenocarcinoma of the lung: Demographic predictors of EGFR testing and survival. *First Author: Shagufta Shaheen, Loma Linda University Medical Center, Loma Linda, CA*

Background: Tyrosine Kinase inhibitors (TKI) have changed the treatment paradigm in patients with stage IV adenocarcinoma of the lung (AdenoCa) harboring epidermal growth factor receptor (EGFR) mutation. Currently there are no guidelines for reflex pathologic testing or mandatory reporting of these mutations. **Methods:** Data for age, sex, race/ethnicity, SES, diagnosis year and EGFR mutation status (+/-) in Stage IV lung AdenoCa (2005-2015) were extracted from the population-based California Cancer Registry (CCR). Logistic regression assessed the proportion of AdenoCa patients that received EGFR testing by age, socioeconomic status quintile (SES), gender and race/ethnicity. Proportional hazards analysis evaluated survival by EGFR status. Among EGFR positive patients, demographic factor adjusted, lung cancer specific Cox proportional mortality hazards ratios (HR) were compared for use of TKI (Y/N). **Results:** Of the 23,674 patients, 3,916 (17%) had EGFR results in their report; this percentage increased for ordinally higher SES quintiles (Trend $p < 0.001$). Odds of EGFR testing (Y/N) increased from 2005 to 2015 ($p < 0.001$) and the odds ratio was higher for females vs. males (OR = 1.20;95%CI = 1.11-1.30;$p < 0.001$). Odds of EGFR testing was higher for Asian/Other and lower for non-Hispanic black patients vs. non-Hispanic white (OR = 1.32;95%CI = 1.20-1.45;$p < 0.001$ and OR = 0.86; 95%CI = 0.74-0.99;p = 0.002), respectively. Among EGFR tested patients, 1,173 (30%) were positive, 2,618 (67%) negative and 125 (3%) had unknown status. Median survival time was 858 days and 390 days for TKI (Y/N). Adjusted HR for TKI (Y/N) was 0.61; 95%CI = 0.58-0.64; $p < 0.001$). **Conclusions:** These findings reveal that, in spite of EGFR testing recommendations, only about 17% of patients had evidence of testing. The trend for higher testing prevalence in higher SES quintiles and during recent years is consistent with more comprehensive insurance and improving compliance. These findings reveal remarkably increased survival for EGFR positive patients treated with TKI. These findings underscore the need for reflex pathologic testing for EGFR mutations in advanced lung AdenoCa to improve patient outcomes and avoid delays in treatment.

9101 Poster Session (Board #424), Sun, 8:00 AM-11:30 AM

Clinical utility of plasma-based digital next-generation sequencing (NGS) in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping. *First Author: Jon Zugazagoitia, Medical Oncology Department. Hospital 12 de Octubre, Madrid, Spain*

Background: Approximately 20 % of tumor biopsies from patients with advanced-stage lung adenocarcinomas yield insufficient tissue for successful molecular subtyping. In this study, we have analyzed the clinical utility of NGS of cell-free circulating tumor DNA (ctDNA) in patients with inadequate tumor samples for tissue genotyping. **Methods:** We prospectively selected consecutive patients with advanced-stage lung adenocarcinomas with insufficient tissue for *EGFR*, *ALK* or *ROS1* genotyping across 12 Spanish institutions (January-September 2017). Cases with known alterations in any of these genes were ineligible. ctDNA NGS was performed by Guardant Health (Guardant360, Redwood City, CA), using a hybrid-capture-based 73-gene panel. Variants were deemed actionable if they were part of the OncoKB precision oncology knowledge database, and classified in 4 levels based on their clinical or preclinical evidence for drug response. All patients provided informed consent. **Results:** We included 93 patients; 48 (52 %) were treatment naïve. Eighty-three patients (89 %) had detectable levels of ctDNA, and none of the clinical characteristics predicted ctDNA detection. Level 1-4 actionable drivers were detected in 53 patients (57 %) in the entire cohort and 29 patients (60 %) in the treatment naïve subgroup, of which 13 (14 %) and 7 (15 %) respectively had level 1-2A drivers (FDA-approved and standard-care biomarkers according to lung cancer guidelines). The majority of patients with actionable drivers had clinically relevant co-mutations (n = 46, 87 %), without significant differences across the 4 actionable subgroups. Thirteen patients (14 %) received genotype-matched therapies, the majority of which achieved clinical benefit. Seven treatment-naïve patients (15 %) received targeted drugs as their first-line therapy. Most patients with level 1-2A (85 %), but a minority with level 2B-4 drivers (5 %), received targeted therapies. **Conclusions:** ctDNA NGS (Guardant360) detects actionable drivers and allows timely initiation of genotype-matched therapies in lung adenocarcinoma patients with insufficient tumor for tissue genotyping.

9102 Poster Session (Board #425), Sun, 8:00 AM-11:30 AM

Association of CDKN2A gene alteration with high expression of PD-L1. *First Author: Yan Zhang, Department of Cancer Biology, Mayo Clinic, Jacksonville, FL*

Background: Gene CDKN2A, which encodes for p16INK4a/p14ARF is known to be important growth suppressor gene. CDKN2A gene alteration has been reported in non-small cell lung cancer (NSCLC). However, the demographic and clinical features of NSCLC with CDKN2A, coexisting gene alteration and association with immunotherapy biomarkers such as PD-L1 and tumor mutation burden are unknown. **Methods:** Tumor next-generation sequencing data from 197 NSCLC patients who are diagnosed at Mayo Clinic FL are retrospectively analyzed. Patients with CDKN2A gene alterations are identified. Data including demographic feature, clinical feature, coexisting gene alteration and association with immunotherapy biomarkers such as PD-L1 and tumor mutation burden are investigated. **Results:** One hundred ninety-seven patients with NSCLC were identified, and 49 (24.8%) had CDKN2A gene alteration, including 32 gene loss, 4 somatic mutations and 3 deletions. The medium age of patients with CDKN2A gene alteration was 66.7. It was slightly more predominant in male than female (53.1% versus 46.9%) and more in smoker than never-smoker (65.3% versus 34.7%). Among patients with CDKN2A gene alteration, 83.7% (41/49) were found in lung adenocarcinoma, 10.2% were found in lung squamous cell carcinoma and 6.1% were found in other histology. The most common coexisting gene alterations associated with CDKN2A are CDKN2B (61%) followed by TP53 (51%), KRAS (35%), EGFR (14.2%), STK11 (12.2%), MET (10%), PI3KCA (10%), HER-2 (8%), ALK (4%), BRAF (2%). Interestingly, 65% of patients with CDKN2A gene alteration were found to have expression of PD-L1 (defined by $>$ 1% PD-L1). Among them, 61.5% patients have high expression of PD-L1 (defined by $>$ 50% PD-L1). Patients with CDKN2A gene alteration are also associated with high tumor mutation burden (8.77mutation/mb). **Conclusions:** CDKN2A gene alteration is commonly seen in NSCLC. Co-existing driver mutations such as EGFR, MET, HER-2, ALK, BRAF are found. Immunotherapy related biomarkers such as high expression level of PD-L1 and tumor mutation burden are found common in patients with CDKN2A gene alteration, indicating the likelihood of clinical benefit to immunotherapy and warrant further investigation in a larger, prospective study.

9103 Poster Session (Board #426), Sun, 8:00 AM-11:30 AM

The effect of thoracic radiation on overall survival and their association with systemic immune therapy in stage IV NSCLC: Findings from the National Cancer Database. *First Author: Feng-Ming Spring Kong, Indiana University School of Medicine, Dept of Radiation Oncology, Indianapolis, IN*

Background: The role of thoracic radiation (TRT) is controversial for stage IV non-small cell lung cancer (NSCLC). A prospective study of 29 patients reported superior progression free survival with radical TRT. This study aimed to report the overall survival (OS) effect of TRT and examine whether the OS effect varies with the timing of TRT regarding to systemic therapy. **Methods:** Stage IV patients from the national cancer database (NCDB) 2005-2014 formed the base of the study population. TRT, dose and time effects were analyzed individually in patients treated with non-immune systemic therapy or immune therapy. The primary endpoint was OS. Kaplan-Meier test was used for the OS analysis. **Results:** A total of 334,702 patients were eligible. Median survival time (MST) was 5.2 months (mo). Younger age, female gender, non-African American, lower Charlson comorbidity score, and any TRT were all significantly associated with favorable OS (all $P < 0.001$). In 326,287 patients receiving non-immune systemic therapy, TRT was a significant factor for favorable OS (HR = 0.964, 95%CI 0.955-0.974, $P < 0.001$). Comparing to those receiving TRT before non-immune systemic therapy (n = 5,500, MST = 8.8 mo), patients with concurrent TRT-systemic treatments (within 30 days of systemic therapy) had significantly worse OS (n = 20,099, MST = 7.2 mo, $P < 0.001$), while patients receiving TRT after systemic therapy had the best OS (n = 6,064, MST = 11.2 mo, $P < 0.001$). In 4,639 patients treated with immune therapy, TRT was associated with significantly worse OS (n = 512, MST = 11.1 mo, $P < 0.001$), comparing to immune therapy alone (n = 4,127, MST = 14.1 mo). Patients received concurrent TRT had worst OS (n = 177, MST = 7.4 mo, $P < 0.001$), comparing to TRT before immune therapy (n = 165, MST = 12.2 mo) and TRT after immune therapy (n = 138, MST = 13.2 mo, P = 0.086). **Conclusions:** In patients with stage IV NSCLC, TRT seemed to be associated with better OS in those treated with non-immune systemic therapy but worse overall survival in patients receiving immune therapy. Concurrent TRT with any systemic therapy including immune therapy was associated with worse survival.

TPS9104 Poster Session (Board #427a), Sun, 8:00 AM-11:30 AM

ECHO-306/KEYNOTE-715: A phase 3 study of first-line epacadostat plus pembrolizumab with or without platinum-based chemotherapy vs pembrolizumab plus platinum-based chemotherapy plus placebo for metastatic non–small cell lung cancer (mNSCLC). *First Author: Rina Hui, Westmead Hospital, Westmead, Australia*

Background: Novel combination treatments targeting broad immunosuppression in the tumor microenvironment may improve survival. The indoleamine 2,3-dioxygenase 1 (IDO1) intracellular enzyme and PD-1 receptor both suppress T-cell–mediated antitumor immunity, are co-expressed in multiple tumor types, and are correlated with poor prognosis. Epacadostat (E) is a potent and highly selective oral inhibitor of IDO1. Pembrolizumab (P) ± chemotherapy is a first-line treatment option for mNSCLC. Because promising efficacy and minimal additive toxicity were observed with E + P in mNSCLC in the phase 1/2 ECHO-202/KEYNOTE-037 study, this phase 3 global study (NCT03322566) was initiated to evaluate first-line E + P, E + P + chemotherapy, and E-matched placebo + P + chemotherapy in patients with mNSCLC unselected by PD-L1. **Methods:** Eligible patients: aged $\geq$18 years, stage IV NSCLC (no *EGFR* mutation or *ROS1*/*ALK* translocations), ECOG PS $\leq$1, no untreated brain metastases, no prior systemic therapy for mNSCLC, and no prior IDO1 inhibitors or immune checkpoint therapies. Patients (~1062) will be randomized 1:1:1 and stratified based on ECOG PS (0 vs 1), PD-L1 status (tumor proportion score $<$ 50% vs $\geq$50%), tumor histology (squamous vs nonsquamous), and region (East Asia vs non-East Asia). Treatment includes E 100 mg BID, P 200 mg Q3W, paclitaxel 175–200 mg/m^2 + carboplatin AUC 5–6 Q3W $\times$ 4 cycles (squamous), or pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC 5 Q3W $\times$ 4 cycles followed by pemetrexed 500 mg/m^2 Q3W (nonsquamous). Patients receive treatment up to 2 years (35 cycles of P), or until disease progression, intolerable toxicity, or investigator/patient decision to withdraw. Primary endpoints: OS and PFS. Secondary endpoints: ORR, duration of response, safety, and tolerability. Exploratory endpoints: patient reported outcomes, E pharmacokinetics, pharmacodynamics, and potential correlations between baseline biomarkers and clinical activity (OS, PFS, ORR). Tumor response will be assessed centrally per RECIST v1.1. Adverse events will be graded per CTCAE v4.0. Clinical trial information: NCT03322566.

TPS9105 Poster Session (Board #427b), Sun, 8:00 AM-11:30 AM

MORPHEUS: A phase Ib/II multi-trial platform evaluating the safety and efficacy of cancer immunotherapy (CIT)-based combinations in patients (pts) with non-small cell lung cancer (NSCLC). *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: CIT has demonstrated a significant survival benefit in multiple cancers. Despite this, only subsets of pts experience durable response with CIT monotherapy. Thus, CIT combinations may be needed to address the mechanisms that allow cancers to escape anti-tumor immunity. However, a large number of potential combinations would have to be tested in order to identify an effective CIT combination. The MORPHEUS platform consists of multiple, global, open-label, randomized, Phase Ib/II trials designed to assess the impact of CIT combinations in pts with different tumor types. The randomized trial designs allow comparison of a single control arm vs multiple CIT combination arms. These trials will aid development of CIT combinations by identifying early signals and will have the flexibility to open new treatment (Tx) arms with novel CIT combinations and to close arms that show minimal clinical activity or unacceptable toxicity. Various CIT combinations that simultaneously enhance immune cell priming and activation, tumor infiltration and/or recognition of tumor cells for elimination will be evaluated. Here we describe a MORPHEUS Phase Ib/II trial in pts with metastatic NSCLC, a population likely to benefit from CIT-based combinations. **Methods:** MORPHEUS-Lung (NCT03337698) will enroll 2 cohorts (C): C1 will enroll pts who are Tx naive for metastatic NSCLC and have high tumor PD-L1 expression (TPS $\geq$ 50% per Dako 22C3 or VENTANA SP263); C2 will enroll pts who have progressed on prior platinum and anti–PD-L1/PD-1 Tx given concurrently or sequentially, regardless of tumor PD-L1 expression levels. Pts with non-squamous and squamous NSCLC will be included; those with an *EGFR* mutation or *ALK* gene rearrangement will be excluded. Pts will be randomized to the control arm or one of several experimental arms (2 for C1; 5 for C2). Pts experiencing loss of clinical benefit or unacceptable toxicity may be eligible to switch to a different CIT combination arm. Safety measures and investigator-assessed ORR (RECIST v1.1) are primary endpoints. PFS, OS, DCR and DOR are among the secondary endpoints. Exploratory biomarkers will also be examined. Clinical trial information: NCT03337698.

TPS9106 Poster Session (Board #428a), Sun, 8:00 AM-11:30 AM

A phase 2 study of poziotinib in patients with EGFR or HER2 exon 20 mutation-positive non-small cell lung cancer. *First Author: Zandong Yang, Inovio Pharmaceuticals, Plymouth Meeting, PA*

Background: Poziotinib is a novel, oral, quinazoline-based pan-HER inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors, including human epidermal growth factor receptor (HER1/ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4), which leads to inhibition of the proliferation of tumor cells that overexpress these receptors or activated by EGFR or HER2 exon 20 mutations. There is no FDA approved targeted therapy for EGFR or HER2 exon 20 insertion mutant NSCLC. Chemotherapy remains the standard of care for metastatic disease with severe side effects and modest efficacy. Preclinical testing indicates that poziotinib is more active than currently approved tyrosine kinase inhibitors against cell lines with a range of *EGFR* exon 20 mutations *in vitro* when using the standard Ba/F3 model. An ongoing investigator-initiated study at MD Anderson is showing that poziotinib is effective at reducing tumor size in patients with EGFR or HER2 exon 20 mutations. The primary endpoint of this Phase 2 study is to evaluate the Objective Response Rate (ORR) to poziotinib in patients with EGFR or HER2 positive non-small cell lung cancer (NSCLC). Secondary endpoints are to evaluate the Disease Control Rate (DCR) and Duration of Response (DoR) in this group of patients. **Methods:** This is an open-label, multicenter study evaluating the efficacy and safety of poziotinib in patients with histologically or cytologically confirmed NSCLC with a documented EGFR or HER2 exon 20 insertion mutation. Patients with T790M point mutations will be excluded. Patients will be enrolled into one of two cohorts based on documented EGFR (Cohort 1; n = 87) or HER2 (Cohort 2; n = 87) exon 20 mutations. Both cohorts are enrolling simultaneously. Patients must be 18 years of age, have an ECOG score $\leq$2, and have adequate tumor tissue from biopsy or surgical procedure to enable molecular profiling. The starting dose of poziotinib is 16 mg PO daily with possible dose reductions to 14 mg and 12 mg for tolerability issues. Patients will be treated until either progression or intolerable adverse events. Response will be assessed by an Independent Image Review. Study enrollment began in October 2017. Clinical trial information: NCT 03318939.

TPS9107 Poster Session (Board #428b), Sun, 8:00 AM-11:30 AM

Phase 1/2 study of mRNA vaccine therapy + durvalumab (durva) $\pm$ tremelimumab (treme) in patients with metastatic non-small cell lung cancer (NSCLC). *First Author: Leena Gandhi, NYU Perlmutter Cancer Center, New York, NY*

Background: Vaccine therapies stimulate the immune system to attack cancer cells (active immunotherapy), whereas checkpoint inhibitors block immune inhibition (passive immunotherapy). Several PD-1 and PD-L1 blocking antibodies are approved for NSCLC. This study combines active and passive immunotherapies to determine if the addition of a mRNA vaccine can enhance the activity of checkpoint blockade. The vaccine BI 1361849 (comprising 6 mRNAs encoding for selected tumor-associated antigens: MUC1, survivin, NY-ESO-1, 5T4, MAGE-C2 and MAGE-C1) is combined with 1 or 2 checkpoint inhibitors (durva [anti-PD-L1] $\pm$ treme [anti-CTLA-4]). **Methods:** This ongoing Phase 1/2, open-label study (NCT03164772) evaluates the safety and efficacy of BI 1361849 when administered with durva (Arm A) or durva + treme (Arm B) in NSCLC patients. In arm A, an initial dose-evaluation phase follows a 3+3 design to determine the dose of durva (1500 or 750 mg) to be given with the vaccine. Arm B uses the durva dose from Arm A, with the addition of 75 mg treme. In the expansion phase, 20 patients are treated in each arm. To aid in the evaluation of immune responses, there is an additional control group (n = 10), which receives the checkpoint inhibitors only. Study treatment is administered over 12 (28-day) cycles. Durva (x 12 doses) and treme (x 4 doses) are administered intravenously every 28 days. The vaccine is administered on 1 to 3 days over each of the 12 cycles using a device that provides a needle-free intradermal administration. The primary endpoint is safety/tolerability per CTCAE, including dose-limiting toxicity during dose evaluation. Secondary endpoints are progression-free survival and objective response rate at 8 and 24 weeks, disease control rate, response duration, and overall survival, with tumor response evaluated by RECIST and immune-related RECIST. Exploratory objectives include effects on tumor microenvironment and evaluation of immune responses. Enrollment opened 20Dec2017. Clinical trial information: NCT03164772.

TPS9108 Poster Session (Board #429a), Sun, 8:00 AM-11:30 AM

A trial of CV301 in combination with anti-PD-1 therapy versus anti-PD-1 therapy in subjects with non-small cell lung cancer. *First Author: Arun Rajan, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: Despite recent therapeutic advances in non-small cell lung cancer (NSCLC), an unmet medical need remains for most patients. Pembrolizumab (pembro) is approved in first-line treatment of patients with NSCLC as a single agent when PD-L1 expression is $>$ 50% and in combination with chemotherapy when PD-L1 expression is $<$ 50%. It is believed that a fraction of non-responders to pembro lack an adequate tumor-directed immune response. CV-301 is a poxviral-based vaccine comprising a prime-boost strategy with Modified Vaccinia Ankara (MVA) prime and fowlpox boost. The viral vectors encode 2 tumor associated antigens, CEA and MUC-1, as well as 3 costimulatory molecules (B7.1, ICAM-1 and LFA-3, called TRICOM). Current preclinical and mechanistic evidence suggests that CV-301 can generate a tumor-directed immune response in NSCLC, potentially increasing the clinical benefit associated with pembro. **Methods:** This open-label, multi-center trial will evaluate the combination of CV301 and pembro. The phase 1 trial, an evaluation of safety of ascending doses of CV301, has been completed. The vaccine was well tolerated with no DLTs. The phase 1b portion is currently enrolling at least 6 patients with NSCLC in the maintenance setting of pembro and will continue pembro in combination with CV301 with a goal to establish safety of the combination. Safety monitoring will occur every two weeks. If safety is established, the randomized Phase 2 portion will enroll 176 subjects, randomized 2:1 to receive maintence pembro in combination with CV301 (2) or alone (1). Maintenance setting is defined as the period following 11 weeks of initial treatment, after which chemotherapy would be complete in the $<$ 50% PD-L1 expression group. To be eligible, patients must have stable disease or objective response at the time of radiographic evaluation (approximately 11-12 weeks after initiation of first line therapy). Preliminary efficacy will be analyzed during the Phase 2 cohort based on the Intent-to-Treat population, comprising overall survival (primary), progression-free survival and overall response rate (secondary). Clinical trial information: NCT02840994.

TPS9109 Poster Session (Board #429b), Sun, 8:00 AM-11:30 AM

ECHO-305/KEYNOTE-654: A phase 3, randomized, double-blind study of first-line epacadostat plus pembrolizumab vs pembrolizumab plus placebo for metastatic non–small cell lung cancer (mNSCLC) with high PD-L1 levels. *First Author: Mark M. Awad, Dana-Farber Cancer Institute, Boston, MA*

Background: The indoleamine 2,3-dioxygenase 1 (IDO1) intracellular enzyme and PD-1 receptor both suppress T-cell–mediated antitumor immunity, are coexpressed in multiple tumor types, and are correlated with poor prognosis. Epacadostat (E) is a potent and highly selective oral inhibitor of IDO1. Pembrolizumab (P; PD-1 inhibitor) is the standard of care for treatment-naive mNSCLC with high PD-L1 expression (tumor proportion score [TPS] ≥50%) and no *EGFR* or *ALK* genomic aberrations. Because encouraging activity and minimal additive toxicity were previously observed with E + P in mNSCLC in the phase 1/2 ECHO-202/KEYNOTE-037 study, this phase 3 global trial (NCT03322540) was initiated to compare E + P vs P + E-matched placebo as first-line treatment for patients with PD-L1 high mNSCLC. **Methods:** Eligible patients: aged ≥18 years, stage IV NSCLC (no *EGFR*-sensitizing mutation or *ROS1*/*ALK* translocations), TPS ≥50%, ECOG PS ≤1, no prior systemic therapy for mNSCLC, and no prior IDO1 inhibitors or immune checkpoint therapies. Approximately 588 patients will be randomized 1:1 to E 100 mg oral BID + P 200 mg IV Q3W or P + E-matched placebo, and stratified by tumor histology (squamous vs nonsquamous), ECOG PS (0 vs 1), and geographical location (East Asia vs non–East Asia). Patients receive treatment until disease progression, intolerable toxicity, investigator/patient decision to withdraw, or until they have received up to 35 cycles of E + P or P + placebo (~2 years). Eligible patients may continue study treatment beyond initial radiographic progression. Patients may discontinue treatment after confirmed complete response. Primary endpoints include PFS and OS. Secondary endpoints include ORR, duration of response, safety, and tolerability. Exploratory endpoints include patient-reported outcomes, E pharmacokinetics, pharmacodynamics, and potential relationship between baseline biomarkers and clinical activity (PFS, OS, ORR). Tumor response will be assessed by a blinded central review, per RECIST v1.1 criteria. Adverse events will be monitored throughout the study and graded per CTCAE v4.0. Clinical trial information: NCT03322540.

TPS9110 Poster Session (Board #430a), Sun, 8:00 AM-11:30 AM

Phase 1 study of the anti-HER3 antibody drug conjugate U3-1402 in metastatic or unresectable EGFR-mutant NSCLC. *First Author: Pasi A. Janne, Dana-Farber Cancer Institute, Boston, MA*

Background: While outcomes for patients with EGFR-mutant NSCLC have significantly improved with the use of EGFR tyrosine kinase inhibitors, there remain limited treatment options for many patients once they develop resistance to these agents. The HER3/ERBB3 oncogene is overexpressed in many cancers, including NSCLC, and higher expression is correlated with poorer outcomes. U3-1402 is a HER3-targeting antibody-drug conjugate (ADC) of high drug-to-antibody-ratio (DAR = 7 to 8) with a novel linker and topoisomerase I inhibitor payload. **Methods:** This is a multicenter Phase 1, Dose Escalation, and Dose Expansion study of U3-1402 in metastatic or unresectable adenocarcinoma NSCLC subjects harboring EGFR-activating mutation who (a) are T790M mutation-negative after disease progression during treatment with erlotinib, gefitinib, or afatinib or (b) develop disease progression while on osimertinib. Eligible subjects are at least 18 years of age, have ECOG PS 0 or 1, have radiological documentation of disease progression while receiving continuous treatment with erlotinib, gefitinib, afatinib, or osimertinib, have at least one measurable lesion per RECIST v1.1, have adequate bone marrow and organ function, do not have mean QTc prolongation to > 470 ms for females and > 450 ms for males, and do not have spinal cord compression or clinically active brain metastases. In Dose Escalation, subjects receive U3-1402 via intravenous infusion in 21-day cycles. In Dose Escalation, escalation of U3-1402 dosing is based on dose-limiting toxicity data in subjects, guided by the modified Continuous Reassessment Method (mCRM). In Dose Expansion, subjects receive U3-1402 at the recommended dose for expansion (RDE) determined in Dose Escalation. Primary objectives are to determine the safety, tolerability, and RDE of U3-1402. Secondary objectives are to assess the pharmacokinetic parameters of U3-1402 and its components, and to assess antitumor activity of U3-1402 (RECIST v1.1). Enrollment to cohort 1 began in January 2018. Clinical trial information: NCT03260491.

TPS9111 Poster Session (Board #430b), Sun, 8:00 AM-11:30 AM

A phase 1b trial of RORγ agonist LYC-55716 in combination with pembrolizumab to evaluate safety, efficacy, and immune biomarker profiles in patients with metastatic non-small cell lung cancer. *First Author: D. Ross Camidge, University of Colorado-Denver, Aurora, CO*

Background: LYC-55716 is a first-in-class oral, small-molecule agonist of the retinoic acid receptor–related orphan receptor γ (RORγ) being developed as an immuno-oncology agent for solid tumors. In preclinical studies, LYC-55716 reduces tumor growth and enhances survival by reprogramming immune cell gene expression for improved anti-tumor effector functions and decreased immunosuppressive mechanisms. RORγ agonist treatment decreases expression of PD-1 and other co-inhibitory receptors, which may diminish checkpoint inhibition within the tumor microenvironment (TME). Additionally, in syngeneic tumor models, the addition of RORγ agonists enhances the activity of PD-1/PD-L1 inhibitors, which is associated with increased number and activation of tumor-infiltrating lymphocytes and decreased immune suppression. An open-label, multicenter Phase 1b trial is ongoing to assess the safety and tolerability of combining LYC-55716 and pembrolizumab (L+P) to treat patients with non–small cell lung cancer (NSCLC). **Methods:** The Phase 1b trial (NCT03396497) will evaluate the occurrence of dose-limiting toxicities (DLTs) and determine the recommended Phase 2 dose of L+P in adults with metastatic NSCLC receiving pembrolizumab treatment. Following a screening period, a run-in cohort (n = 3) will receive L+P to monitor for adverse reactions. If no DLTs occur, the main study cohort (n = 15) will receive L+P until disease progression or unacceptable toxicity. Planned pre-/post-treatment tumor biopsies and blood samples will be collected in the main study cohort. Primary endpoints are safety (monitoring of adverse events, physical examination, and lab results) and incidence of DLTs during the run-in period and further treatment. Secondary endpoints for the main cohort include profiling of immune biomarker changes, objective response rate and duration of response, and pharmacokinetics. Patients will be followed for progression-free and overall survival. Clinical trial information: NCT0336497.

TPS9112 Poster Session (Board #431a), Sun, 8:00 AM-11:30 AM

Phase I/II study of nivolumab and ipilimumab combined with nintedanib in advanced NSCLC. *First Author: Sonam Puri, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Combination immunotherapy with nivolumab and ipilimumab has proven clinical activity in NSCLC. There is growing evidence to suggest that the tumor microenvironment (TME) may interfere with effective immune recognition, even in the presence of checkpoint inhibitors. Unpublished preclinical data from our group demonstrates that human lung cancer derived cancer-associated fibroblasts (CAFs) inhibit tumor infiltrating lymphocyte activation and are potentially immunosuppressive. Targeting the TME may represent an important synergistic approach in immunotherapy. Nintedanib is an orally available triple kinase inhibitor that is active against NSCLC, inhibits CAFs, and targets VEGFR, FGFR and PDGFR. Based on these observations a phase IB/II trial of the combination of nintedanib, nivolumab and ipilimumab was initiated in NSCLC patients. **Methods:** This is a single institution, investigational, non-randomized, parallel assignment phase I/II clinical trial of patients with locally advanced or metastatic NSCLC. Eligible patients can be immunotherapy naïve or with disease progression following immunotherapy. Primary objective of phase I is to determine the tolerability of concurrent administration of the proposed regimen. Three dose levels of nintedanib (100mg, 150 mg and 200 mg twice daily) are given with fixed doses of nivolumab (3mg/kg every 2 weeks) and ipilimumab (1mg/kg every 6 weeks). Dose escalation will be done by the modified continuous re assessment method (O, Quigley et al, 1990). Phase II is divided into two single arm cohorts (Arm A: Treatment or immunotherapy naïve; Arm B: Immunotherapy pretreated). Enrollment to phase II will be done by the Bayesian two-stage design method. The primary objective of phase II is to determine the efficacy of the combination regimen in NSCLC. Key secondary objectives are overall survival and progression free survival. The sample size calculation of 18 patients in phase I and 80 patients in phase II assumes 18 months for accrual and 2-3 years for follow up. Enrollment to phase I was started on 29th January 2018 and to date 1 patient has been enrolled. Serial blood and tumor biopsies are obtained to evaluate potential predictive and resistance mechanisms. Clinical trial information: NCT03377023.

TPS9113 Poster Session (Board #431b), Sun, 8:00 AM-11:30 AM

Phase I/II trial of dasatinib and osimertinib in patients with advanced *EGFR*-mutant non-small cell lung cancer. *First Author: Chul Kim, Georgetown University, Washington, DC*

Background: Epidermal growth factor receptor (EGFR) mutations are one of the most common driver oncogenes in non-small cell lung cancer (NSCLC). While the presence of these mutations predicts sensitivity to tyrosine kinase inhibitors (TKIs), a small but non-negligible subset of patients do not respond to EGFR-TKIs, suggesting intrinsic resistance. Moreover, acquired resistance to EGFR-TKIs is inevitable. In preclinical studies, overexpression of Cripto-1, a member of the EGF–Cripto-1/FRL-1/Cryptic protein family, contributes to the development of intrinsic resistance to EGFR-TKIs through the activation of the Src-tyrosine kinase pathway. In EGFR-mutant mouse models, we demonstrated synergy between erlotinib and Src inhibition. *In vitro* experiments showed increased synergy when using osimertinib, a third generation EGFR inhibitor with dasatinib, a SRC inhibitor. Based on these data, we initiated a phase I/II trial to explore the feasibility and benefit of combining osimertinib and dasatinib in patients with EGFR-mutant NSCLC. **Methods:** This is an open-label, single-arm phase I/II trial of osimertinib and dasatinib in treatment-naïve patients with advanced EGFR-mutant NSCLC (NCT02954523). Patients with sensitizing *EGFR* mutations as well as those with T790M mutation are eligible. Patients with pleural or pericardial effusions at study entry are excluded. The primary endpoint of the phase I part is to establish a safe and tolerable phase II dose of osimertinib and dasatinib. The endpoint of the phase II part is the reduction of the proportion of patients who progress or have stable disease lasting 4 months or less (definition of intrinsic resistance). For the phase II portion, a two-stage design with a total of 28 patients will be used. The null hypothesis that the proportion of patients with intrinsic resistance is at least 30% will be tested against the alternative hypothesis that the true proportion of patients with intrinsic resistance is at least 10% (alpha one-sided 5%, power 85%). Accrual is underway at Georgetown University and Hackensack University Medical Center. Using tumor and serum samples, the role of Cripto-1 in mediating resistance to osimertinib will be elucidated. Clinical trial information: NCT02954523.

TPS9114 Poster Session (Board #432a), Sun, 8:00 AM-11:30 AM

Trial in progress: Multicenter observational study to evaluate the relationship between gut bacterial flora and their therapeutic or adverse effects in advanced non-small cell lung cancer patients treated with nivolumab. *First Author: Takashi Yokoi, Department of Thoracic Oncology, Kansai Medical University Hirakata Hospital, Osaka, Japan*

Background: Nivolumab is one of the standard therapies for pretreated advanced non-small cell lung cancer (NSCLC). A correlation between PD-L1 expression on tumor cells and antitumor effects of nivolumab has been shown especially in non-squamous NSCLC. However, PD-L1 expression is an insufficient biomarker because of the weak correlation. It is therefore important to explore better biomarkers. In recent years, the antitumor effects of immune checkpoint inhibitors have been shown to depend on distinct *Bacteroides* species in preclinical mouse models. This multicenter observational study was planned to evaluate the relationship between gut bacterial flora and their therapeutic or adverse effects on advanced NSCLC patients treated with nivolumab. **Methods:** We prospectively collect microbiome samples from patients with NSCLC who will be treated with nivolumab. Gut (fecal) microbiome samples are collected at treatment initiation and after four doses of nivolumab. We will analyze the trend of gut microbiome differences The key inclusion criteria are histologically or cytologically proven NSCLC, pretreated NSCLC without any immune checkpoint inhibitor, ECOG PS 0-2, one or more measurable lesions, and written informed consent. The key exclusion criteria are previous or active interstitial pneumonia, autoimmune disease, exposure to corticosteroids or antibiotics, and previous or active inflammatory bowel disease. Clinical trial information: UMIN000026375.

TPS9115 Poster Session (Board #432b), Sun, 8:00 AM-11:30 AM

eXalt3: Phase 3 randomized study comparing ensartinib to crizotinib in anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) patients. *First Author: Leora Horn, Vanderbilt University Medical Center, Nashville, TN*

Background: Ensartinib (X-396) is a novel, potent ALK small molecule tyrosine kinase inhibitor (TKI) with additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK. Ensartinib is well-tolerated and has shown promising activity in NSCLC patients in a phase 1/2 study in patients that were both ALK TKI naïve and patients that received prior crizotinib, as well as those with CNS metastases. The safety profile of ensartinib appears to be different than other ALK TKIs. **Methods:** In this global, phase 3, open-label, randomized study, approximately 270 patients with ALK+ NSCLC who have received no prior ALK TKI and up to one prior chemotherapy regimen will be randomized with stratification by prior chemotherapy (0/1), performance status (0-1/2), brain metastases at screening (absence/presence), and geographic region (Asia /other), to receive oral ensartinib (225 mg, once daily) or crizotinib (250mg, twice daily) until disease progression or intolerable toxicity. Eligibility also includes patients $\geq$ 18 years of age, stage IIIB or IV ALK+ NSCLC. Patients are required to have measurable disease per RECIST 1.1, adequate organ function, and an ECOG PS of $\leq$2. Adequate tumor tissue (archival or fresh biopsy) must be available for central testing. The primary endpoint is progression-free survival assessed by independent radiology review based on RECIST v. 1.1 criteria. Secondary efficacy endpoints include overall survival, response rates (overall and central nervous system [CNS]), PFS by investigator assessment, time to response, duration of response, and time to CNS progression. The study has $>$ 80% power to detect a superior effect of ensartinib over crizotinib in PFS at a 2-sided alpha level of 0.05. Phase 3 recruitment began in June, 2016 and currently has 98 active sites in 20 countries. The duration of recruitment will be approximately 24 months. This study is registered with. Clinical trial information: NCT02767804.

TPS9116 Poster Session (Board #433a), Sun, 8:00 AM-11:30 AM

A multicenter, randomized, double-blind, placebo-controlled phase III study of apatinib or placebo plus gefitinib as first-line treatment in patients with *EGFR*-mutant advanced non-small cell lung cancer (NSCLC). *First Author: Hongyun Zhao, State Key Laboratory of Oncology in South China, Caner Center, Sun Yat-sen University, Guangzhou, China*

Background: Dual inhibition of epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) pathway is becoming an encouraging strategy in the treatment of advanced NSCLC. Apatinib is a tyrosine kinase inhibitor that selectively inhibits the VEGF receptor-2. Our phase I study of Apatinib plus Gefitinib has shown a manageable tolerability profile and promising antitumor activity with an anticipated progressive-free survival (PFS) $>$ 14 mos. This phase III study aims to evaluate the efficacy and safety of Apatinib or placebo plus Gefitinib as first-line treatment in patients (pts) with stage IIIB-IV NSCLC harboring an activating *EGFR* mutation. **Methods:** Treatment-naïve stage IIIB or IV NSCLC pts with *EGFR* 19 Del or 21 L858R mutation are enrolled. Other inclusion criteria include ECOG PS of 0 or 1, $\geq$1 measurable lesion according to RECIST v1.1 and adequate organ function. Eligible pts will be randomized in a 1:1 ratio to receive either Apatinib or Placebo 500 mg QD plus Gefitinib 250 mg QD until progressive disease or unacceptable toxicity. Stratified randomization is based on *EGFR* mutation status, gender and ECOG PS. The primary endpoint is PFS. Secondary endpoints include overall survival, objective response rate, disease control rate, time to progression, duration of response, quality of life and the safety profile. Independent Data Monitoring Committee and Independent Review Committee will be used in this study. According to previous report (erlotinib plus bevacizumab *vs.* erlotinib alone: 16.0 *vs.* 9.7 mos, HR 0.54, Lancet Oncol, 15(11):1236-1244), it was assumed that the estimated median PFS would be 15 mos in the Apatinib + Gefitinib group and 10 mos in the Placebo + Gefitinib group. To detect a 5-mos improvement of PFS in Apatinib + Gefitinib group at a two-sided significant level of 0.05 and a power of 0.8, allowing for a dropout rate of 20%, the sample size should be 155 patients per group. In total, 310 patients will be enrolled in this trial at 30 sites in China. From August 2017, 100 patients have been enrolled. Clinical trial information: NCT02824458.

TPS9117 Poster Session (Board #433b), Sun, 8:00 AM-11:30 AM

Afatinib in combination with pembrolizumab in patients (pts) with stage IIIB/IV squamous cell carcinoma (SCC) of the lung. *First Author: Benjamin Philip Levy, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Sibley Memorial Hospital, Washington DC, MD*

Background: Afatinib and pembrolizumab have demonstrated improvements in the outcomes of pts with SCC of the lung and are approved as monotherapy. Afatinib is a selective and irreversible ErbB family blocker with activity against all homo- and heterodimers formed by ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4. Pembrolizumab is a humanized IgG4 monoclonal antibody with potent receptor-blocking activity for PD-1. Given the efficacy of these agents as monotherapy in chemo-refractory lung SCC, concurrent inhibition of PD-1 and EGFR pathways represents a promising approach to improve clinical outcomes in lung SCC. **Methods:** Study 1200.283 (NCT03157089; LUX-Lung IO/Keynote 497) is a phase II, single-arm study (n = 5062). Eligible pts have stage IIIB/IV lung SCC, progressed during/after first-line platinum-based chemotherapy, and have an ECOG PS 0/1. Prior immune checkpoint inhibitor or EGFR targeted therapy are prohibited. A safety run-in will be performed in 12 pts, using afatinib (starting dose 40 mg/day, with potential dose de-escalation to 30 mg) with pembrolizumab (200 mg every 3 weeks) to assess the safety and confirm the recommended Phase II dose (RP2D) based on dose limiting toxicities observed during the first cycle. In the main trial, afatinib at the RP2D, in combination with pembrolizumab, may be continued for a maximum of 35 cycles. In case of toxicity, afatinib dose reduction to 30/20 mg will be permitted. Primary endpoint is objective response (OR; complete response [CR] or partial response [PR] [RECIST v1.1]). Further endpoints include disease control (CR, PR, stable disease), duration of OR, PFS, OS, and pharmacokinetics. All pts will provide a fresh or archived tumor tissue sample to measure PD-L1 expression and mRNA expression of genes involved in the immune system. Exploratory biomarkers include the evaluation of immune status by determination of tumor infiltrating cells (e.g. CD8+ cells) or TH1-type cytokines, and blood biomarkers related to the emergence of resistance at progression. This study is conducted in the US, Spain, France, Turkey, and Korea. As of January 2018, enrollment in the safety run-in is complete (n = 12). Clinical trial information: NCT03157089.

9500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

External validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): Effect of adding EORTC sentinel node (SN) tumor burden criteria on prognostic accuracy in stage III. *First Author: Max Fullah Madu, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Now that effective adjuvant therapy has arrived in melanoma, accurate staging and patient selection to optimize a risk/benefit ratio is crucial. The new 8th Edition AJCC staging system for melanoma aims to improve risk stratification. The goal of this study was to externally validate the prognostic and discriminatory ability for survival of the 8th Edition in comparison to the 7th. **Methods:** Analysis of a prospective cohort of patients treated in the Netherlands Cancer Institute for AJCC 7/8th Edition stage III melanoma between 2000 and 2016. Stage III melanoma was defined as regional lymph node metastases, with or without concurrent local recurrence, (micro)satellite or in-transit metastases. Prognostic factors for melanoma-specific survival (MSS) and distant metastasis-free survival (DMFS) were analyzed. Survival differentiation of the 7th and 8th edition was assessed with log-rank tests and Cox proportional hazards models. Discriminatory ability was compared using the area under the curve (AUC) of the receiver operating statistic (ROC) obtained with Cox models. **Results:** 640 patients were included with a median follow-up of 59 months (interquartile range 32-108). Median MSS was 138 months, DMFS 96 months. Age, Breslow thickness, ulceration of the primary tumor and number of positive lymph nodes (N) were significant prognostic parameters for MSS and DMFS. The 8th Edition performed similarly to the 7th in terms of survival discrimination, but failed to differentiate MSS between stage IIIA and IIIB after correction for sex and age. Both in 7th and 8th edition stage IIIA melanoma, patients with an SN metastasis size < 1 had excellent DMFS and MSS. **Conclusions:** The AJCC 8th edition staging system differentiates survival slightly worse than the 7th edition. Survival in both 7th and 8th edition stage IIIA melanoma is heterogeneous and can be sub-classified according to EORTC SN tumor burden, which can aid clinical decision-making concerning adjuvant therapy.

9501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Final analysis of DECOG-SLT trial: Survival outcomes of complete lymph node dissection in melanoma patients with positive sentinel node. *First Author: Ulrike M. Leiter, Department of Dermatooncology, University of Tübingen, Tuebingen, Germany*

Background: The multicenter DeCOG-SLT trial assessed in a randomized phase 3 trial whether complete lymph node dissection (CLND) resulted in increased survival compared with observation in patients with positive sentinel node biopsy (SLNB). This study now gives an update three years after inclusion of the last patient. **Methods:** Outcomes of 473 patients in the intent-to-treat population (ITT) randomly assigned into the DeCOG trial were evaluated with an additional 3 years follow-up observation after randomization has ended. A total of 233 patients was analyzed in the observation group, 240 in the CLND group. The primary endpoint was distant metastasis-free survival (DMFS); recurrence-free (RFS) and overall (OS) survival were secondary endpoints. **Results:** Patient enrolment was performed from January 2006 to December 2014 followed by an observation period from January 2015 to December 2017. The median follow-up time was 72 months (95% CI 67.2;76.8) No significant treatment-related difference was seen in the 5-years DMFS: 68% (90%CI: 62.1%;72.5%, 79 events) in the observation arm and 65% (90%CI: 59.3%;70.5%, 85 events) in the CLND arm (HR1.08 (90%CI 0.83; 1.39), P = 0.65). The 5 years RFS (HR 1.01 (90%CI 0.8; 1.28), P = 0.94) and OS (HR 0.99 (90%CI 0.74; 1.31), P = 0.93), also showed no differences with respect to the treatment arms. The 5-year DMFS differed according to the tumor load in the SLNB, but again not between CLND and observation arm ($\leq$ 1.0 mm: 78.7% vs 72.5%, HR 1.12, P = 0.58 and $>$ 1.0 mm 54.7% vs 51.7%, HR 0.98, P = 0.95) Regional lymph node metastases occurred in 10.8% of the CLND and in 16.3% of the observation arm (P = 0.11) The multivariate proportional hazard regression analysis revealed tumor thickness and tumor load in the SLNB to be independent prognostic factors for RFS, DMFS and OS. **Conclusions:** After a median follow-up time of 72 months there was no survival benefit in melanoma patients with positive SLNB undergoing CLND compared to observation only. Clinical trial information: NCT02434107.

9502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: Updated results from a phase III trial (CheckMate 238). *First Author: Jeffrey S. Weber, New York University Perlmutter Cancer Center, New York, NY*

Background: In the initial report of data from CheckMate 238, at a minimum follow-up of 18 mo, NIVO demonstrated significantly longer recurrence-free survival (RFS) vs IPI in patients (pts) with resected stage III or IV melanoma. Here, we report updated efficacy results from this phase III study with an additional 6 mo of follow-up. **Methods:** Eligible pts included those $\geq$15 yrs of age who underwent complete resection of stage IIIB/C or IV melanoma. 906 pts were randomized 1:1 (stratified by disease stage and PD-L1 status at a 5% cutoff) to receive NIVO 3 mg/kg Q2W (N=453) or IPI 10 mg/kg Q3W for 4 doses, then Q12W (from week 24) (N=453) for up to 1 yr, or until disease recurrence or unacceptable toxicity. The primary endpoint was RFS; distant metastasis-free survival (DMFS) in pts with stage III disease was an exploratory endpoint. **Results:** At a minimum follow-up of 24 mo, RFS continued to be significantly longer for NIVO vs IPI (hazard ratio 0.66, $P<0.0001$), with 171/453 and 221/453 events, respectively. The 24-mo RFS rates were higher for NIVO vs IPI in subgroups defined by disease stage, PD-L1 expression, and *BRAF* mutation status (Table). DMFS also continued to be significantly longer for NIVO vs IPI, with 24-mo rates of 70.5% and 63.7%, respectively (hazard ratio 0.76, P=0.034). Subsequent therapies were received by 31.1% of pts in the NIVO group and 41.1% in the IPI group. Per protocol, there was no additional safety assessment for the current analysis given that all pts had been off study treatment $>$100 days at the time of the previous data cutoff. **Conclusions:** With extended follow-up, NIVO demonstrated a sustained efficacy benefit vs IPI in pts with resected stage III/IV melanoma at high risk of recurrence, regardless of disease stage, PD-L1 expression, or *BRAF* mutation status. Clinical trial information: NCT02388906.

	NIVO	IPI
RFS, 24-mo rates; % (N)		
ITT population	62.6% (453)	50.2% (453)
Stage IIIB	70.8% (165)	60.7% (148)
Stage IIIC	58.0% (203)	45.4% (218)
Stage IV	58.0% (82)	44.3% (87)
PD-L1 ≥5%	75.5% (152)	58.4% (154)
PD-L1 <5%	55.2% (275)	45.5% (286)
***BRAF* mutant**	61.9% (187)	51.7% (194)
***BRAF* wild-type**	63.5% (197)	46.2% (212)

9503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006. *First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, Mater Hospital, and Royal North Shore Hospital, Sydney, Australia*

Background: KEYNOTE-006 (NCT01866319) established superiority of pembro over ipi in advanced melanoma. We provide 4-y outcomes, long-term data for pts who completed 2 y pembro, and data for second course. **Methods:** Eligible pts (N = 834) were randomly assigned 1:1:1 to receive pembro 10 mg/kg Q2W, pembro 10 mg/kg Q3W, or ipi 3 mg/kg Q3W for 4 doses. Treatment was continued for 2 y (pembro only; completed defined as $\geq$94 weeks of pembro and discontinued with at least SD) or until disease progression, intolerable toxicity, or pt/investigator decision to discontinue. End points were OS and ORR per irRC by investigator review. Upon PD, eligible pts could receive an additional 1 y pembro. **Results:** At data cutoff (Dec 4, 2017), median follow-up was 45.9 mo (range, 0.3-50.0). 4-y OS rate was 42% in the pooled pembro arms (n = 556) and 34% in the ipi arm (n = 278); ORR was 42% and 17%. Median DOR was NR for pembro (range, 1.0+ to 46.1+ mo) or ipi (1.1+ to 45.6+ mo); 62% pembro- and 59% ipi-treated pts had a response lasting $\geq$42 mo. In treatment-naive pts, 4-y OS rates were 44% in the pooled pembro arms (n = 368) and 36% in the ipi arm (n = 181); ORR was 47% and 17%. Median DOR was NR for pembro (range, 1.6+ to 46.0+ mo) or ipi (1.1+ to 42.2+ mo); 65% pembro- and 68% ipi-treated pts had a response lasting $\geq$42 mo. Of 556 pts, 103 (19%) completed the protocol-specified 2-y pembro (28 CR, 65 PR, 10 SD). Median follow-up was 20.3 mo after pembro completion; 89 (86%) pts did not progress and 14 pts had PD (prior response 2 CR, 9 PR, 3 SD). Eight pts (prior response 3 CR [including 1 pt who discontinued early with CR and then progressed], 4 PR, and 1 SD) received second-course pembro but 3 discontinued (1 each due to PD, interstitial pneumonia, and infection). Median duration of second-course pembro was 9.7 mo; BOR was 1 CR, 1 PR, 5 SD, and 1 PD. 1 pt with SD had subsequent PD. 5 pts had a TRAE during second-course pembro; there were no grade 3/4 TRAEs or deaths. **Conclusions:** Pembro provides durable antitumor activity in treatment-naive or -experienced pts with advanced melanoma. Of pts who completed 2 y pembro, 86% were progression free at 20 mo. Pembro is safe and provides additional antitumor activity as second-course treatment. Clinical trial information: NCT01866319.

9504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Overall survival in COLUMBUS: A phase 3 trial of encorafenib (ENCO) plus binimetinib (BINI) vs vemurafenib (VEM) or enco in *BRAF*-mutant melanoma. *First Author: Reinhard Dummer, University of Zurich Hospital, Department of Dermatology, Zurich, Switzerland*

Background: Combined BRAF/MEK inhibitor therapy is standard of care in advanced *BRAF*V600-mutant melanoma. COLUMBUS Part 1 evaluated ENCO 450 mg once daily (QD) + BINI 45 mg twice daily (BID;COMBO450) vs VEM 960 mg BID or ENCO 300 mg QD (ENCO300) in patients (pts) with advanced *BRAF*V600-mutant melanoma. The primary study endpoint was progression-free survival (PFS); median PFS was 14.9 vs 7.3 mo for COMBO450 vs VEM; hazard ratio (HR): 0.54 (2-sided $P< 0.001$). Here we report a planned analysis of overall survival (OS), a secondary endpoint of the study. **Methods:** Pts with advanced/metastatic *BRAF*V600-mutant melanoma, untreated or progressed on/after first-line immunotherapy, were stratified by disease stage, Eastern Cooperative Oncology Group Performance Status and prior first-line immunotherapy. Pts in Part 1 were randomized 1:1:1 to COMBO450 (n = 192), ENCO300 (n = 194), or VEM (n = 191). Tumor responses and progression were assessed by blinded independent central review. An analysis of OS was planned after 232 events in the COMBO450 and VEM arms combined. **Results:** As of data cutoff,105, 106, and 127 events contributed to the OS analysis in the COMBO450, ENCO300, and VEM arms, respectively; median follow-up across arms was 21.5 mo. Median OS was 33.6 mo (95% CI, 24.4-39.2) with COMBO450, 23.5 mo (95% CI, 19.6-33.6) with ENCO300, and 16.9 mo (95% CI, 14.0-24.5) with VEM. Risk of death was reduced with COMBO450 vs VEM (HR, 0.61 [95% CI, 0.47-0.79]; nominal 2-sided $P< 0.001$). Updated median PFS was 14.9 mo (95% CI, 11.0–20.2) with COMBO450, 9.6 mo (95% CI, 7.4–14.8) with ENCO300, and 7.3 mo (95% CI, 5.6–7.9) with VEM. PFS was longer with COMBO450 vs VEM (HR, 0.51 [95% CI, 0.39–0.67]). Updated response rates, safety data, and information on 2nd-line therapy will be presented at the meeting. **Conclusions:** The best-in-class median PFS of 14.9 and median OS of 33.6 mo suggest that COMBO450 is a promising new regimen for treatment of *BRAF*-mutant melanoma. SPONSOR: Array BioPharma Inc. Clinical trial information: NCT01909453.

9505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. *First Author: Suzanne Louise Topalian, Johns Hopkins Bloomberg/Kimmel Institute for Cancer Immunotherapy and Kimmel Cancer Center, Baltimore, MD*

Background: MCC is a rare, aggressive skin cancer commonly associated with the oncogenic Merkel cell polyomavirus (MCPyV). The PD-1/PD-L1 immunosuppressive pathway is often upregulated in MCC, and advanced metastatic MCC is responsive to PD-1 blockade. Here we report the first trial of anti–PD-1 in the neoadjuvant setting for resectable MCC. **Methods:** In the phase 1/2 CheckMate 358 trial of nivo anti–PD-1 in virus-associated cancers (NCT02488759), patients (pts) with resectable MCC received nivo 240 mg IV on D1 and D15. Surgery was planned on D29. Tumor regression was assessed radiologically before surgery, and microscopically in the surgical specimen. Immunohistochemistry (IHC) was used to assess tumor MCPyV status and tumor PD-L1 expression. Data were analyzed as of August 7, 2017 with a median follow-up of 54.1 wks. **Results:** 25 pts with resectable MCC, AJCC stage IIA–IV, received ≥1 dose of nivo. Median age was 70 yrs (range 22–88). Among 18 patients' tumors evaluated by IHC, 8 (44%) were MCPyV+, and 6 (30%) were PD-L1+ (1% cutoff). 22 of 25 (88%) pts had surgery at ~D29 without significant delay; 3 pts did not have surgery on trial, 1 due to rapid tumor progression and 2 due to grade 2–3 adverse events (AEs). Among 20 pts with pre/post nivo CT scans, 16 (80%) had tumor regression (range 13%–100% reduction), including 9 (45%) with > 30% reduction. Among 17 resections evaluated for pathologic response by central investigator review, 11 (65%) had a major pathologic response (MPR, defined as ≤10% residual viable tumor cells), including 8 (47%) complete responses. MPRs and radiologic responses were seen in virus+/− tumors and in PD-L1+/− tumors. Treatment-related AEs were reported in 36% (any grade) and 4% (grade 3–4) of pts, with no new safety signals. Among 21 pts followed after surgery, all were progression-free at 6 mo; 2 pts had relapsed at 12 mo. **Conclusions:** Nivo administered for 4 wks before surgery in MCC was safe and induced substantial radiologic and pathologic tumor regressions in 45% and 65% of patients, respectively. In some pts, this obviated the need for more extensive surgery. The majority of operated patients remain tumor-free at 12 mo. Data will be updated per a March 2018 database lock. Clinical trial information: NCT02488759.

9506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Durable tumor regression and overall survival (OS) in patients with advanced Merkel cell carcinoma (aMCC) receiving pembrolizumab as first-line therapy. *First Author: Paul Nghiem, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is an aggressive skin cancer often caused by the Merkel cell polyomavirus (MCPyV). Clinical trials of PD-1-axis blocking agents in aMCC have demonstrated increased progression free survival (PFS) compared to historical data from patients (pts) receiving chemotherapy, but data on response durability and OS are limited. Here we report outcomes from the expanded phase 2 Cancer Immunotherapy Trials Network-09 trial of pembrolizumab (PEM, anti-PD-1) in the first-line setting (NCT02267603). **Methods:** Adults with aMCC, naïve to systemic therapy for aMCC, received PEM (2 mg/kg Q3W) for up to 2 yrs. Responses per RECIST v1.1 were assessed centrally based on CT scans performed at 12 wks and Q9W thereafter. Tumor MCPyV status was assessed by serum antibody titer and/or IHC for MCPyV oncoprotein. Preliminary results from the first 26 pts have been reported (Nghiem NEJM 2016). We now include data from an expansion cohort of 24 pts. **Results:** 50 pts (43 stage IV, 7 unresectable stage IIIB) were enrolled 01/2015 – 05/2017. 80% of pts were ≥65 yrs of age. As of 06/21/17, median follow-up was 8.6 mo (range 0.4 - 29 mo). Among tumors from 49 pts, 65% were MCPyV+. Of 42 pts with ≥21 wk follow-up, confirmed ORR was 50% (95% CI 34.2-65.8; CR 19%, PR 31%). ORR was 52% and 44% in pts with MCPyV (+) and (-) tumors, respectively. Median PFS was not reached (NR; 95% CI 2.9 mo - Not Estimable). OS rate at 18 mo was 68% and median OS was NR, comparing favorably to historical first-line chemotherapy data (18 mo OS rate ~30%; Iyer 2016 & Cowey 2017). Among 21 confirmed responders, median response duration was NR (range 3.9+ to 25.6+ mo). Treatment-related adverse events (TRAE) of any grade (CTCAE v4.0) were seen in 47/50 pts (94%); 15 pts (30%) experienced a grade ≥3 TRAE, including 1 treatment-related death. TRAEs led to discontinuing PEM in 6 pts (12%). **Conclusions:** These results represent the longest observation to date of patients with aMCC receiving first-line anti-PD-1, and demonstrate durable tumor control, a favorable OS rate, and a manageable safety profile. An additional 7.5 mos of follow-up and correlative studies including tumor PD-L1 expression will be presented. Clinical trial information: NCT02267603.

9507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Two-year efficacy and safety update from JAVELIN Merkel 200 part A: A registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy. *First Author: Paul Nghiem, University of Washington Medical Center at South Lake Union, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer with poor prognosis. Studies of second-line chemotherapy for metastatic MCC (mMCC) have reported median progression-free survival (PFS) of up to 3 months and no benefit to overall survival (OS). Avelumab, a human anti–PD-L1 monoclonal antibody, is approved in several countries for the treatment of mMCC. Here, we report updated efficacy and safety data from part A of the pivotal, single-arm, phase 2, JAVELIN Merkel 200 trial of avelumab in patients (pts) with mMCC and ≥2 y of follow-up. **Methods:** Pts with mMCC and progression on prior chemotherapy received avelumab 10 mg/kg intravenously every 2 weeks until disease progression or intolerable adverse event (AE). Objective response rate (ORR), duration of response (DOR), and PFS were evaluated by independent review per RECIST v1.1; OS and AEs (per NCI CTCAE v4.0) were also evaluated. **Results:** As of Sep 26, 2017, 88 pts were followed for a median of 29.2 mo (range 24.8-38.1). The median duration of treatment was 3.9 mo (range 0.5-36.3); treatment was ongoing in 9 pts (10.2%). The confirmed ORR of 33.0% (95% CI 23.3-43.8; complete response in 11.4%) remained unchanged from previous analyses at 1 y and 18 mo; responses were ongoing in 19 of 29 pts, including 12 pts with > 2 y response duration. Median DOR had not been reached (range 2.8-31.8 mo; 95% CI 18.0-not estimable). Durable responses led to stable rates of PFS (29% at 1 y, 29% at 18 mo, and 26% at 2 y). Median OS was 12.6 mo (95% CI 7.5-17.1) and the 2-y OS rate was 36% (50% at 1 y and 39% at 18 mo). Clinical activity was observed across all pt subgroups, irrespective of tumor PD-L1 and MCPyV status. The AE profile remained consistent with previous analyses: 67 pts (76.1%) had a treatment-related AE (TRAE), 10 pts (11.4%) had a grade ≥3 TRAE, 20 pts (22.7%) had an immune-related AE, and no treatment-related deaths occurred. **Conclusions:** At ≥2 y of follow-up, avelumab shows continued durable responses and meaningful survival outcomes in pts with mMCC, exceeding the outcomes associated with cytotoxic chemotherapy. Efficacy and safety results confirm the lasting clinical benefit of avelumab in pts with mMCC. Clinical trial information: NCT02155647.

9508 Poster Discussion Session; Displayed in Poster Session (Board #335), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Interim analysis of a randomized, open-label phase 2 study of talimogene laherparepvec (T-VEC) neoadjuvant treatment (neotx) plus surgery (surgx) vs surgx for resectable stage IIIB-IVM1a melanoma (MEL). *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: There is no approved neotx for resectable stage IIIB-IVM1a MEL. T-VEC, an HSV-1-based oncolytic virus, may reduce the risk of developing visceral and bone metastases in unresectable Stage IIIB-IVM1a MEL (Andtbacka SSO 2015). We conducted a randomized study to evaluate the effect of neotx T-VEC in high risk resectable MEL (NCT02211131). **Methods:** Patients (pts) with resectable stage IIIB/C/IVM1a MEL, ≥ 1 injectable cutaneous, subcutaneous, or nodal lesions ≥ 10 mm, and no systemic tx 3 mos prior were randomized 1:1 to 6 doses/12 wks of T-VEC followed by surgx (Arm 1) vs upfront surgx (Arm 2). T-VEC was given at standard dosing until surgx, no injectable tumors, or intolerance. This interim analysis was planned for when the 75th pt in Arm 1 completed the safety follow-up visit (30+ days post surgx). **Results:** 150 pts were randomized (76 Arm 1, 74 Arm 2). Of all pts, ≥ 94% had no prior radio/systemic tx, 91% had prior surgx and 84% had no plans for adjuvant tx. 75% in Arm 1 and 93% in Arm 2 had surgx as planned. Of the 19 pts who did not have surgx in Arm 1, 11 had progressive disease. In Arm 2, 17 pts recurred within 14 wks post-surgx. For pts who had surgx in Arm 1, the pathological complete response (pCR) rate was 21%. Negative margin resection (R0) rates were 56.1% for Arm 1 and 40.6% for Arm 2 (80% CI: 3-28% for the difference). For all randomized pts, pCR rate in Arm 1 was 15.8%; R0 rates were 42.1% (Arm 1) vs 37.8% (Arm 2). Overall response (OR) rate (CR+PR) in Arm 1 was 14.7% (80% CI: 9-22%). In the safety set (73 pts in Arm 1, 69 pts in Arm 2), tx-emergent adverse events (TEAE) was 93% in Arm 1 (1 grade 4 pain, no grade 5) and 45% in Arm 2 (all ≤ grade 3). In Arm 1, preop AE was 89.5% (most common: pyrexia 35%) and intra/postop AE was 29.8% (most common: seroma 5.3%). In Arm 2, intra/postop AE rate was 45% (most common: pain 7.2%). 17.8% (Arm 1) vs 2.9% (Arm 2) pts had an SAE; of these, 5.5% (Arm 1) and 2.9% (Arm 2) were deemed surgx-related. **Conclusions:** 12 wks of neo T-VEC produced a pCR rate in stage IIIB-IVM1a MEL higher than observed by ORs and may account for the higher R0 margin in Arm 1. No unexpected toxicities were noted. The primary analysis of RFS is ongoing. Clinical trial information: NCT02211131.

9509 Poster Discussion Session; Displayed in Poster Session (Board #336), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Vismodegib in neoadjuvant treatment of locally advanced basal cell carcinoma: First results of a multicenter, open-label, phase 2 trial (VISMONEO study). *First Author: Laurent Mortier, Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France*

Background: Surgery is the main treatment of basal cell carcinoma. In locally advanced basal cell carcinoma (laBCC), surgery may cause functional or aesthetic damages. Neoadjuvant administration of vismodegib in laBCC may reduce tumor size, facilitate resection and potentially reduce functional and aesthetic consequences of surgery. VISMONEO was conducted to assess efficacy and safety of vismodegib in the neoadjuvant treatment of laBCC. **Methods:** VISMONEO (NCT02667574) is an open-label, non-comparative, multicenter, phase II study. Patients with at least one histologically confirmed BCC of the face, inoperable or operable with functional or major aesthetic sequelae risk were included. Oral vismodegib 150 mg once-daily was administered for a period of 4 to 10 months, before surgery. Surgery was done once the best response under vismodegib was observed. Primary endpoint was the percentage of BCC patients with tumor down-staging following surgical resection after neoadjuvant vismodegib. Downstaging was defined according to a six-stage surgical classification related to the aesthetic and functional risk of the surgery. **Results:** 55 patients with laBCC were included. Median age of the patients was 73.1 years. At inclusion, 4 were inoperable, 15 were operable with a major functional risk and 36 were operable with a minor functional risk or a major aesthetic risk. Mean size of target lesion was 47.3 mm (SD = 27,2mm). 44 patients had a procedure after vismodegib treatment (80.0%, 95%CI [67 to 90]). Of these 44 responders, 27 had a complete response proved by biopsy. Main adverse events were dysgeusia, muscle spasms, alopecia, fatigue and weight loss (20 % of patients with grade ≥ 3) **Conclusions:** Neoadjuvant vismodegib allows a downstaging of surgical procedure for laBCCs in functionally sensitive locations. Final data will assess quality of long-term local control. Clinical trial information: NCT02667574.

9510 Poster Discussion Session; Displayed in Poster Session (Board #337), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Neoadjuvant (neo) immune checkpoint blockade (ICB) in patients (Pts) with high-risk resectable metastatic melanoma (MM). *First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Nivolumab (nivo) and combination ipilimumab (ipi) + nivo are highly active in pts with unresectable and stage IV MM. Nivo is also safe and effective adjuvant treatment for MM pts with resected stage III disease. Preclinical studies demonstrate that neo ICB may be more effective than adjuvant treatment, but the safety and efficacy of neo ICB in pts is unknown. We designed a randomized trial to assess the safety and activity of neo nivo +/- ipi ICB in pts with high-risk, resectable MM. **Methods:** We conducted a non-comparative randomized phase II study for pts with resectable, clinically detectable stage III or oligometastatic stage IV MM. Pts were randomized to receive neo nivo 3mg/kg IV every 2 weeks for up to 4 doses (Arm A) or neo ipi 3mg/kg + nivo 1mg/kg IV every 3 weeks for up to 3 doses (Arm B) prior to surgery, then nivo 3mg/kg IV every 2 weeks for 13 doses (Arms A and B) after surgery (NCT02519322). Planned total accrual was 40 pts (1:1 randomization) with stratification by stage and PD-L1 status. The primary endpoint was pathologic complete response (pCR) rate. **Results:** The trial was closed after 23 pts were enrolled (12 to Arm A, 11 to Arm B). Neo nivo achieved 25% pCR and 25% radiographic response rate (RR), but 17% were unable to undergo surgery due to rapid disease progression during neo therapy. All pts on neo ipi + nivo underwent surgery, and the pCR and RR rates were 45% and 73%, respectively. Grade 3 treatment related adverse events occurred in 8% of pts on Arm A and 73% on Arm B. **Conclusions:** Neo treatment with nivo +/- ipi can produce pCR in high-risk resectable MM. While neo nivo was well tolerated, RRs were lower than observed in stage IV pts and some pts experienced rapid progression that precluded surgery. Neo ipi + nivo achieved higher RRs but with high toxicity. This data provides a foundation for further optimization and testing of neo ICB. Clinical trial information: NCT02519322.

9511 Poster Discussion Session; Displayed in Poster Session (Board #338), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Epacadostat plus nivolumab for advanced melanoma: Updated phase 2 results of the ECHO-204 study. *First Author: Adil Daud, University of California, San Francisco, San Francisco, CA*

Background: Indoleamine 2,3-dioxygenase 1 (IDO1) enzyme-induced immunosuppression in the tumor microenvironment supports tumor cell evasion of immune surveillance. Epacadostat (E) is a potent and selective oral inhibitor of the IDO1 enzyme. ECHO-204 is an open-label, phase (P) 1/2 study of E plus PD-1 inhibitor nivolumab (N) in patients (pts) with advanced cancer. Updated efficacy and safety/tolerability outcomes for the P2, advanced (unresectable or stage IV) melanoma cohort are reported. **Methods:** Pts received E (100 or 300 mg PO BID) plus N (240 mg IV Q2W). Response was assessed every 8 weeks (RECIST v1.1). Safety/tolerability was assessed in pts receiving ≥1 study treatment dose. PD-L1 expression was assessed (Dako 28-8 assay; PD-L1 positive: ≥1% tumor cell staining). **Results:** As of 29 Oct 2017, all of the planned 50 pts were enrolled in the P2 expansion cohort (n = 40 treatment naive for advanced disease). Median (range) duration of follow-up was 417 days (70 to 617 days). Across all pts, overall response rate (ORR) was 62% (31/50; 9 complete response [CR], 22 partial response [PR]) and disease control rate (DCR; CR + PR + stable disease) was 78% (39/50). In treatment-naive pts, ORR was 65% (26/40; 8 CR, 18 PR) and DCR was 80% (32/40); responses were observed in both PD-L1-positive pts (75% ORR [9/12]; 92% DCR [11/12]) and PD-L1-negative pts (56% ORR [9/16]; 69% DCR [11/16]); the majority (88%; 23/26) of responses were ongoing at data cutoff; duration of response ranged 55+ to 565+ days (median not reached); rate of progression-free survival at 6 and 12 months was 77% and 63%, respectively (median not reached); and the rate of overall survival at 12 months was 92% (median not reached). In the overall population (N = 50), the rate of grade ≥3 treatment-related adverse events (TRAEs) was 48% with E 300 mg BID (n = 42; most common grade ≥3 TRAEs: rash [19%], ALT increase [12%]) and 13% with E 100 mg BID (n = 8; pneumonitis [13%] was the only grade ≥3 TRAE). Eight pts discontinued treatment due to TRAEs (all E 300 mg BID). There was no AE-related death. **Conclusions:** E + N continues to show promising antitumor activity in pts with advanced melanoma and is generally well tolerated. E 100 mg BID is the selected dose for P3 studies of E + N in pts with advanced cancer. Clinical trial information: NCT02327078.

9512 Poster Discussion Session; Displayed in Poster Session (Board #339), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase 2 trial of the IDO pathway inhibitor indoximod plus checkpoint inhibition for the treatment of patients with advanced melanoma. *First Author: Yousef Zakharia, University of Iowa Hospitals and Clinics, Holden Comprehensive Cancer Center, Iowa City, IA*

Background: The indoleamine 2,3-dioxygenase (IDO) pathway is a key counter-regulatory mechanism that, in cancer, is exploited by tumors to prevent and evade anti-tumor immunity. Inhibitors of the IDO pathway, such as indoximod, are an increasingly validated class of potential cancer therapeutics. Pre-clinical data and an increasing body of clinical data support evaluating the combination of a checkpoint inhibitor (CI) with an IDO pathway inhibitor as potential treatment for advanced melanoma. **Methods:** Advanced melanoma patients were enrolled in a single arm Phase 2 trial evaluating the addition of indoximod to standard of care CI as approved for melanoma. Prior therapy excluding CI was allowed. Investigators administered their choice of approved CI (pembrolizumab (P), nivolumab (N), ipilimumab (I). Indoximod was administered continuously (1200mg po BID), concurrent CI dosed per approved US label. Study endpoint was best overall response (overall response rate (ORR) = complete response (CR) + partial response (PR)) per site reported RECIST 1.1. **Results:** 102 patients were enrolled in Phase 2. 70 patients with unresectable stage III or IV cutaneous or mucosal melanoma were treated with P and had an on treatment imaging meeting the per protocol, pre-specified definition of evaluable for efficacy (EE). Additionally, 15 patients had uveal melanoma, 4 received I, 4 received N, and 1 was never treated. 8 patients came off study prior to the first on-treatment imaging study. The ORR for the EE population was 55.7% (39/70, 36 confirmed) with CR of 18.6% (13/70, all confirmed). Median PFS was 12.4 months (95% CI 9.0-NA). Archival tissue was available from 41 of 70 EE patients. The PD-L1 staining $\geq$ 1% was 54% (22/41). The combination was well tolerated and most common AEs regardless of attribution were fatigue, nausea, pruritus. An additional 21 patients have been enrolled to a biopsy cohort. **Conclusions:** The combination of indoximod and pembrolizumab demonstrates an ORR of 55.7%, CR 18.6% which compares favorably with reported ORR for P alone (33%). Updated data including biopsy cohort will be presented. Clinical trial information: NCT02073123.

9513 Poster Discussion Session; Displayed in Poster Session (Board #340), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase 1b/2, open label, multicenter, study of the combination of SD-101 and pembrolizumab in patients with advanced melanoma who are naïve to anti-PD-1 therapy. *First Author: Antoni Ribas, UCLA Johnson Comprehensive Cancer Center, Los Angeles, CA*

Background: SD-101 is a CpG-ODN agonist of TLR9. Pembrolizumab is a PD-1 inhibitor. DV3-MEL-01 (NCT02521870) assesses safety and preliminary efficacy of the combination of SD-101 and pembrolizumab in stage IIIC-IV melanoma. **Methods:** Phase 1b evaluated SD-101 at multiple doses injected in a single tumor Q1W x 4 then Q3W x 7 in combination with a fixed dose of pembrolizumab (200 mg IV Q3W); both drugs started on D1. Phase 2 is evaluating SD-101 at 8 mg in 1 lesion and 2 mg/lesion in 2-4 lesions beginning 21 days after the first dose of pembrolizumab. First scan was performed at D64, after 6 weeks of combination therapy. Per-protocol best overall responses (ORR) were assessed per investigator using RECIST v1.1/ irRECIST at $\geq$ D127 after at least 15 weeks of combination therapy. The per-protocol population comprised patients who received $\geq$ 1 dose of each drug and had $\geq$1 post-baseline scan. ITT results are not presented below. **Results:** 9patients enrolled in phase 1b; 54 in phase 2: median age 67 y, male 67%, Stage IVM1a/b 27%, Stage IVM1c 37%, LDH $>$ ULN 22%, treatment naive 70%. SD-101 safety profile consists of transient flu-like symptoms. Frequently observed Grade $\geq$3 treatment-related AEs were myalgia 9%, headache 9%, fatigue 9%, chills 7%, and malaise 5%. Immune-related AEs (irAEs) have been reported in 17%. With protocol specified scans on D64 and D127, half of responses were observed $\geq$ D127 with early discontinuation from PD occurring before D127. The per-protocol ORR was 60% or 15/25 (CR 12%/PR 48%/SD 16%[DCR = 76%]/PD 24%) (median f/u = 223 d).15 pts had CR or PR of 19 with $\geq$ D127 scans; 6 pts with D64 scans discontinued with PD before D127. Non-evaluable pts (n = 5) without post-baseline scans discontinued from study prior to D64: 1 irAE (gr2 pneumonitis), 1 withdrew consent, and 3 clinical PD. **Conclusions:** The combination of SD-101 and pembrolizumab appears to be showing promising response rates compared to those expected with pembrolizumab alone. The combination is well tolerated with no evidence of an increased rate of irAEs. Clinical trial information: NCT02521870.

9514 Poster Discussion Session; Displayed in Poster Session (Board #341), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Phase II trial of pembrolizumab (pembro) plus 1 mg/kg ipilimumab (ipi) immediately following progression on anti-PD-1 Ab in melanoma (mel). *First Author: Daniel Olson, University of Chicago, Chicago, IL*

Background: Immunotherapy with anti-PD-1 + CTLA-4 Abs improves response rates over anti-PD-1 Ab alone; however, the utility of this combination after first line anti-PD-1 is unknown. We report the first prospective data evaluating pembro + low dose ipi immediately following progression on anti-PD-1 (NCT02743819). **Methods:** Patients (pts) with mel and measurable disease, no autoimmunity, and no prior anti-CTLA-4 who had progressed immediately prior on an anti-PD-1 (or non-CTLA4 combination) were eligible. Prior BRAF inhibitor was allowed (none received it). Pts received pembro 200 mg + ipi 1 mg/kg Q3W for 4 doses, then pembro alone. The primary endpoint was response rate (RR) as assessed by irRECIST. An optimal Simon two-stage design was employed to test the null hypothesis of a 10% RR vs 30% alternative (1-sided alpha 0.10, 90% power, $\geq$2/12 RR to continue to total of $\geq$6/35). The data analysis cutoff date was January 2, 2018. **Results:** 22 patients have been accrued with 17 evaluable for the primary endpoint (4 have not yet had their first imaging evaluation and 1 was not enrolled). Prior treatment included 21 on anti-PD-1 alone and 1 on combination with IDO inhibitor. Median length of treatment on prior anti-PD-1 was 5.6 months among all 22 pts. The study met its interim efficacy analysis with 5/12 responses to move to stage 2. Among the 17 response-evaluable pts there were 2 CR, 6 PR (47% RR), and 5 SD for disease control rate (DCR) of 76% and rejection of the null hypothesis. Progression-free survival at 6 months was 75% (CI 47%-90%). All responses are ongoing. At last follow-up, 8 pts have gone off treatment with 14/22 (64%) having any drug-related and 3/22 (14%) $\geq$ grade 3-4 drug-related AE (hyperglycemia, acute kidney injury and skin tissue disorder, diarrhea and rash acneiform). Among 11 response-evaluable pts with staining results currently available, RR and DCR were 67% and 100% in PD-L1+ (n = 3) and 50% and 88% in PD-L1 negative (n = 8) tumors. Further biomarker analysis is underway. **Conclusions:** Pembro + 1 mg/kg ipi is tolerable and has antitumor activity in pts with mel who have progressed immediately prior on an anti-PD-1 Ab. The trial sample size has been expanded to further explore this regimen. Clinical trial information: NCT02743819.

9515 Poster Discussion Session; Displayed in Poster Session (Board #342), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

A phase 2 study to evaluate the safety and efficacy of Intratumoral (IT) injection of the TLR9 agonist IMO-2125 (IMO) in combination with ipilimumab (ipi) in PD-1 inhibitor refractory melanoma. *First Author: Adi Diab, Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PD-1/L1 inhibitors have transformed MM treatment, however many patients (pts) remain refractory. Subsequent treatment options including ipi offer modest benefit (~13% respond) (Long, SMR 2016). IT IMO, a Toll-like receptor 9 agonist, may improve response to ipi by activating innate and adaptive immune responses to overcome immune escape. Tumor biopsies obtained from both injected/local and uninjected/distant lesions during earlier studies show maturation of the mDC1 subset (CD1c+CD303-), upregulation of PD-L1 by tumor cells, and an IFNα response gene signature. On treatment(week 8) biopsies of uninjected/distant tumors show expression of CD56+ and Ki67+ effector CD8+T cells in responding pts, indicative of an abscopal effect. Initial clinical experience with IMO + ipi is promising resulting in the selection of 8mg as the RP2D. Here we report an analysis of the first 15 subjects that received 1+ doses of study drugs. **Methods:** This is a phase 2 study for adults with unresectable or MM refractory to a PD-1 inhibitor pts are eligible if they have an accessible tumor for IT administration of IMO. 8mg IMO is administered to a single tumor during weeks 1,2,3,5,8, and 11 along with ipi per the product label. The primary endpoint is overall response rate (ORR) using a 2-stage design. **Results:** A total of 24 pts have been treated with IMO + ipi including pts that received injections to deep visceral lesions and lymph nodes. Grade 3 /4 Immune-related AE were observed in 6 subjects [hypophysitis (N = 2), hepatitis (1), Gastritis (1), Guillain-Barre syndrome (1), Colitis (1), Neutropenia (1)]. These responded well to standard measures. Of 24 pts treated at the RP2D of 8mg, 15 were assessed for response with 47% ORR of and 67% disease control rate (1 Complete Response, 6 Partial Response(3 confirmed), 3 Stable disease). Phase 2 accrual is ongoing. **Conclusions:** IMO + ipi is a robust strategy to revive the immune response in PD-1/L1resistant tumors and the demonstrated substantial clinical benefit including durable responses in this clinically challenging pt population. This data supports the initiation of a phase 3 study compared to ipi alone. Clinical trial information: NCT02644967.

9516 Poster Discussion Session; Displayed in Poster Session (Board #343), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: Pembro has demonstrated robust antitumor activity and safety in several studies of advanced melanoma, including KEYNOTE-001, -002, and -006. Here, we describe the 5-year outcomes for all pts and for those who were treatment naive in the phase 1b KEYNOTE-001 study (NCT01295827). **Methods:** Pts aged ≥18 y with previously treated or treatment-naive, advanced or metastatic melanoma received pembro 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W until disease progression, intolerable toxicity, or pt/investigator decision to withdraw. The Kaplan-Meier method was used to estimate OS and PFS. ORR and PFS were based on immune-related response criteria by investigator assessment. Data cutoff was Sep 1, 2017. **Results:** KEYNOTE-001 enrolled 655 pts (151 treatment naive; 504 previously treated). After a median follow-up of 55 mo (range, 48-69), 35 pts are on pembro treatment. 63% (n = 412) of all pts died. The estimated 5-year OS rate was 34% in all pts and 41% in treatment-naive pts, similar to the 4-year rates of 38% and 48%, respectively. Median OS was 23.8 mo (95% CI, 20.2-30.4) in all pts and 38.6 mo (95% CI, 27.2-NR) in treatment-naive pts. 5-year PFS rates were 21% in all pts and 29% in treatment-naive pts; median PFS was 8.3 mo (95% CI, 5.8-11.1) and 16.9 mo (95% CI, 9.3-35.5) in all pts and treatment-naive pts, respectively. Median response duration was not reached; 73% of all responses and 82% of treatment-naive responses were ongoing at data cutoff; the longest response observed in all pts was ongoing at 66 mo. Treatment-related AEs (TRAEs) occurred in 86% (n = 562) of pts, including 17% (n = 114) with grade 3/4 TRAEs and 7.8% (n = 51) who discontinued because of a TRAE. **Conclusions:** Pembro provides a 5-year OS rate of 34% in pts with previously treated and treatment-naive advanced melanoma, with a 5-year OS rate of 41% in treatment-naive pts. These data, representing the longest follow-up for pembro to date in any cancer, confirm the durable antitumor activity and tolerability of pembro in advanced melanoma. Clinical trial information: NCT01295827.

9517 Poster Discussion Session; Displayed in Poster Session (Board #344), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Utility of 1-year FDG-PET (PET) to determine outcomes from anti-PD-1 (PD1) based therapy in patients (pts) with metastatic melanoma (MM). *First Author: Aaron C. Tan, Royal North Shore Hospital, St Leonards, Australia*

Background: PD1 based therapy has durable clinical activity for some pts with MM, however there are few predictors of long-term response and the optimal duration of therapy is unknown. Whether PET imaging may assist with this remains unclear. **Methods:** A prospectively assembled cohort of consecutive pts treated at a single center with PD1 based therapy from May 2013 to Sep 2017, who underwent baseline and 1-year PET was examined retrospectively. Demographics, disease features, treatment, response and outcome data were collected. 1-year response was determined using RECIST for CT and EORTC criteria for PET, and was coded as complete response (CR or CMR), partial response (PR or PMR), stable disease (SD or SMD) or progressive disease (PD or PMD) on CT and PET, respectively. **Results:** 118 pts were evaluated with median follow-up 21.0 mo and 98% remain alive. PD1 based therapy included pembrolizumab (50%) or nivolumab (13%) monotherapy, and combination therapy (with iplimumab, TVEC or epacadostat/placebo in 37%). At 1-year, 25% of pts had CR, 60% PR and 15% SD/PD on CT, while 68% had CMR, 17% PMR and 15% SMD/PMD on PET (Table). RECIST progression-free survival (PFS) was improved in pts with CMR vs non-CMR (median not reached [NR] vs 19.8 mo; HR 0.09; $p < 0.01$), and in the pts with CMR, PFS was not statistically different between pts with CMR+CR vs CMR+PR/SD (median NR in both groups; $p = 0.11$). In pts with PR on CT, PFS was improved in pts with PR+CMR vs PR+non-CMR (median NR vs 21.3 mo; HR 0.12; $p < 0.01$). In the 80 pts with CMR, median time on treatment was 14.8 mo, 60% had discontinued treatment with median follow-up post discontinuation 9.9 mo, and 99% had ongoing response. **Conclusions:** Whilst only a small proportion of pts who survive one year with PD1 based therapy have a complete response on CT, most have a complete metabolic response on PET, and 99% have ongoing response. PET may have utility in predicting long-term benefit and guide discontinuation of therapy. Prospective evaluation using PET at earlier intervals is warranted.

	No. of pts (%)			
	CR	PR	SD	PD
CMR	27 (23)	49 (42)	3 (3)	1 (1)
PMR	2 (2)	15 (13)	2 (2)	1 (1)
SMD	0	1 (1)	0	0
PMD	0	6 (5)	2 (2)	9 (8)

Correlation of CT and PET responses at 1 year

9518 Poster Discussion Session; Displayed in Poster Session (Board #345), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Transcriptomic and immunophenotypic profiles of melanoma tissue from patients (pts) treated with anti-PD-1 +/- ipilimumab to define mechanisms of response and resistance. *First Author: Tuba Nur Gide, Melanoma Institute Australia, The University of Sydney, Sydney, Australia*

Background: Immune checkpoint blockade improves the survival of patients with metastatic melanoma, but many patients fail to respond to immunotherapy and the lack of accurate predictors of response or progression remains a major clinical problem. We investigated potential mechanisms of response and resistance to anti-PD1 +/- ipilimumab. **Methods:** 141 melanoma biopsies from advanced melanoma pts treated with anti-PD-1 monotherapy (n= 54), or anti-PD1 + ipilimumab (n= 51) were classified as responders (CR/PR/SD > 6 mo) or non-responders (SD≤6 mo/PD) based on RECIST. The transcriptomic and immunophenotypic profiles of 105 baseline (PRE) and 36 early-during treatment (EDT) tumor biopsies from pts treated with monotherapy (n= 33 responders, n= 21 non-responders) or anti-PD-1 + ipilimumab (n= 38 responders, n= 13 non-responders) were characterized via RNA sequencing and multiplex immunofluorescence. **Results:** Responders to monotherapy displayed increased expression of genes associated with a Type 1 interferon response, tissue-resident T-cells and drug targets (TIGIT, ADAR, ADORA2A, CD137, IDO1 and LAG3) (diff. $p < 0.05$). Genes unique to anti-PD-1 + ipilimumab responders included T-cell and NK-cell genes EOMES, CD48, CD96, and FASLG. Non-responders displayed significantly higher expression of genes associated with WNT signaling along with novel hypoxic and metabolic pathways, including CA9 and NABP1 ($p < 0.05$). Non-responders with high CD8/PD-L1 densities expressed novel immune drug targets (IDO1 expressed by 37% of monotherapy non-responders, ICOS (37%), TNFRSF9 (26%), LAG3 (16%), TIGIT (16%) and ADORA2A (16%)). In contrast, TIL-low tumors displayed a lack of expression of the aforementioned targets (42% of monotherapy and 86% of anti-PD-1 + ipilimumab non-responders). **Conclusions:** These findings demonstrate that combinations of novel drug targets may provide clinical benefits in non-responding and non-CR responding patients with high TILs. TIL-low non-responders may require modulation of WNT, hypoxic and metabolic pathways to overcome resistance, facilitating the development of novel synergistic drug targets.

9519 Poster Discussion Session; Displayed in Poster Session (Board #346), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Primary analysis of phase 2 results for cemiplimab, a human monoclonal anti-PD-1, in patients with metastatic cutaneous squamous cell carcinoma (mCSCC). *First Author: Danny Rischin, Peter MacCallum Cancer Centre, East Melbourne, Australia*

Background: CSCC is rivaled only by basal cell carcinoma as the most common cancer in the US. There is no standard of care for patients with mCSCC; hence there is a significant unmet need in these patients. Cemiplimab (REGN2810) treatment at 3 mg/kg Q2W demonstrated encouraging preliminary activity in CSCC in a phase 1 study (ASCO 2017, #9503). We present the primary analysis of the mCSCC cohort from the pivotal phase 2 study (NCT02760498; data cutoff date Oct 27, 2017). **Methods:** Patients with mCSCC (defined as nodal and/or distant) received cemiplimab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks (Q2W). Tumor measurements were performed every 8 weeks. The primary objective was to evaluate overall response rate (ORR; complete response [CR] + partial response [PR]) according to independent central review (per RECIST 1.1 for scans; modified WHO criteria for photos). Duration of response (DOR) was a key secondary endpoint. Durable disease control rate (DDCR) was defined as stable disease or response for ≥16 weeks. **Results:** 59 patients were enrolled (54 M/ 5 F; median age: 71.0 years [range: 38–93]; ECOG performance status: 0 and 1 in 23 and 36 patients, respectively). 33 patients (55.9%) had received prior systemic therapy and 50 (84.7%) had received prior radiotherapy. Median duration of follow-up was 7.9 months (range: 1.1–15.6). ORR by central review was 47.5% (95% CI: 34.3–60.9; 4 CRs and 24 PRs). Responses were observed irrespective of prior systemic therapy. Median DOR has not been reached. Only 3 responding patients had subsequent disease progression at the time of data cut-off. DDCR was 61% (95% CI: 47.4–73.5). Median time to response was 1.9 months (range: 1.7–6.0). The most common adverse events (AEs) regardless of attribution (all grades, ≥Grade 3) were diarrhea (27.1%, 1.7%), fatigue (23.7%, 1.7%), and nausea (16.9%, 0.0%). Immune-related AEs ≥Grade 3 (per investigator assessment) occurred in 10.2% of patients. **Conclusions:** In the largest prospective study reported in patients with mCSCC, cemiplimab 3 mg/kg Q2W showed substantial activity and durable responses with an acceptable safety profile. Clinical trial information: NCT02760498.

9520 Poster Session (Board #347), Mon, 1:15 PM-4:45 PM

Ipilimumab combined with stereotactic radiosurgery in melanoma patients with brain metastases: A multicenter, open label, phase 2 trial. *First Author: Laurent Mortier, Université Lille, Centre Hospitalier Régional Universitaire de Lille, Lille, France*

Background: Brain metastasis commonly occur in patients with metastatic melanoma (MM) and are managed with surgery or stereotactic radiosurgery (SRS) and/or systemic treatment based on BRAF status and prior treatment. After SRS alone, the median survival is poor (5.6 months). Ipilimumab (Anti CTLA-4) was the first checkpoint inhibitor to demonstrate a survival benefit in patients with metastatic melanoma. The median survival was more recently estimated at 6 months after initiation of ipilimumab alone for brain metastasis. No prospective studies have evaluated the use of ipilimumab in combination with stereotactic radiosurgery for the treatment of brain metastasis from MM. **Methods:** This open-label, multi-center, phase 2 study (NCT02662725) evaluated the efficacy of one administration of ipilimumab (10 mg/kg) followed by SRS and the maintenance ipilimumab in a cohort of patients with MM brain metastases. Inclusion criteria included: patients of 18 years or older, performance status 0-1, fewer than 4 brain metastases on MRI. The primary objective was to show an increase at least 50% of the median overall survival time of patients receiving SRS alone. The secondary endpoints were to determine the safety profile of the combination, the intra- and extra-brain response rate. This study was supported by Bristol-Myers Squibb. **Results:** 57 patients (32 males) were enrolled. Median age was 54 (47-67). The study met his primary endpoint: median survival time was 13.2 m, higher than the median survival time of 5.6 m in the reference population (HR = 0.29; 95%CI = 0.19 to 0.39; $p < 0.0001$). The disease control rate was 49% (28/57). The most serious treatment-related adverse events were colitis (10.5%), hepatitis (10.5%), hypophisitis (8.77%) and headhache (8.77%). One radionecrosis was observed. **Conclusions:** High dose Ipilimumab plus SRS seemed effective with a manageable safety profile in patients with brain MM. Considering that this is the best survival rate ever observed in this setting, these results seem to confirm a synergy in the combination of immunotherapy and radiotherapy and should be confirmed in a randomized trial. Clinical trial information: NCT02662725.

9521 Poster Session (Board #348), Mon, 1:15 PM-4:45 PM

Redirected T cell lysis in patients with metastatic uveal melanoma with gp100-directed TCR IMCgp100: Overall survival findings. *First Author: Takami Sato, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA*

Background: IMCgp100 is a bispecific biologic comprised of a soluble T cell receptor recognizing the gp100 antigen fused to a scFV anti-CD3 and redirects T cell lysis of melanoma cells expressing gp100. Safety and preliminary efficacy of IMCgp100 were assessed in a Ph 1/2 study in metastatic UM (mUM). **Methods:** HLA-A*0201+ pts with mUM were treated with QW dosing of IMCgp100 *iv* at Cycle 1, Day 1 (C1D1, 20 mcg) and C1D8 (30 mcg), followed by the escalated dose administered at C1D15 and beyond. **Results:** Pts with mUM (n = 19), elevated LDH (87%), liver metastases (100%), and median of 4 prior therapies (0 – 8) were treated across 4 doses (54 to 73 mcg) in Ph 1; 23 pts were treated in the Ph 2 RP2D (68 mcg) expansion cohort. Related AE included pruritus (90%), pyrexia and fatigue (84%), and hypotension (74%). Gr 3/4 related AE include AST elevation, erythema and hypotension (all, 16%). Ten of the 19 pts in Ph 1 were treated at or above the RP2D. Objective PR by RECIST in Ph 1 were observed in 2 pts and minor responses in 4 pts (6/19 responses); median duration of response was 30.6 wk. One year PFS rate by irRC was 66% (95% CI [39, 83]). One year OS rate in Ph 1 was 74% (95% CI [48, 88]). Median OS in this cohort has not been reached (median follow up of 15.9 mo). The PKPD relationship of exposure was modeled with extent and duration of lymphocyte trafficking. The EC50 for lymphocyte extravasation to the periphery was estimated at 1.4 ng/mL. At high doses, maximal trafficking of 50% was observed compared to baseline. The extent of lymphocyte trafficking is saturable, however the duration was dose dependent. The EC90 represents the dose of 70 mcg, supporting the RP2D. In the full cohort (n = 42), rash of Gr $\geq$2 within the first 3 weeks of dosing is associated with prolonged OS when compared to pts with mild (G1) or no occurrence of rash (HR 0.122, 95% CI [0.03, 0.45], p = 0.0015). **Conclusions:** IMCgp100 is tolerable with the intra-patient escalation dosing regimen and leads to prolonged OS. A potential association of prolonged OS with rash severity was observed. PKPD modeling demonstrates a relationship between lymphocyte trafficking and exposure to IMCgp100. Pivotal trials in the setting of metastatic UM continue to enroll (NCT03070392, NCT02570308). Clinical trial information: NCT02570308.

9522 Poster Session (Board #349), Mon, 1:15 PM-4:45 PM

Efficacy and safety of cobimetinib (C) combined with vemurafenib (V) in patients (pts) with *BRAF*^{V600} mutation–positive metastatic melanoma: analysis from the 4-year extended follow-up of the phase 3 coBRIM study. *First Author: Brigitte Dreno, Dermatology Departement, CHU Nantes, Nantes, France*

Background: The coBRIM study demonstrated that first-line C+V improved progression-free (PFS) and overall survival (OS) compared with placebo (P)+V in pts with *BRAF*^{V600}-mutated advanced melanoma. We report updated survival outcomes and safety after extended follow-up. **Methods:** coBRIM was a double-blind, multicenter study in which 495 patients were randomized to receive C (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle; n = 247) or P (n = 248) in combination with V (960 mg twice daily). PFS and OS were primary and secondary endpoints, respectively. **Results:** At database closure, median follow-up duration for the overall intent-to-treat population was 18.6 months (range, 0.5–55.1 months); 176 pts (71%) in the C+V arm and 190 pts (77%) in the P+V arm had discontinued the study, with the most common reason being death (C+V = 148 pts [60%]; P+V = 162 pts [65%]). Median PFS among pts receiving C+V was 12.6 months (95% confidence interval [CI], 9.5–14.7 months) vs 7.2 months (95% CI, 5.6–7.5 months) in pts receiving P+V. Median OS among pts receiving C+V was 22.5 months (95% CI, 20.3–28.8 months) vs 17.4 months (95% CI, 15.2–20.5 months) in pts receiving P+V. A greater proportion of pts receiving C+V were alive at 1, 2, 3 and 4 years vs pts receiving P+V (Table). Median duration of treatment in the C+V arm was 9.0 months (range, 0.1–53.1 months) for C and 9.2 months (range, 0.3–53.3 months) for V. Pts in the P+V arm had a shorter median duration of treatment of 5.6 months (range, 0.2–43.9 months) for P and 5.7 months (0.2–53.2 months) for V. Grade 3/4 adverse events (AEs) were reported in 75% and 61% of pts in the C+V and P+V arms, respectively. Grade 5 AEs were reported in 2% of pts in each study arm. A larger proportion of pts discontinued C+V (19%) versus P+V (10%) due to AEs. **Conclusions:** Extended follow-up of the phase 3 coBRIM study confirmed the survival benefit of C+V over P+V. No new safety signals were observed. Clinical trial information: NCT01689519.

	Landmark OS, % (95% CI)	
	C+V	P+V
1-year	74.5 (68.9–80.1)	63.8 (57.6–70.0)
2-year	49.0 (42.5–55.6)	39.0 (32.7–45.4)
3-year	38.5 (32.1–44.9)	31.1 (25.0–37.2)
4-year	34.7 (28.4–41.0)	29.2 (23.1–35.2)

9523 Poster Session (Board #350), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of advanced Merkel cell carcinoma to reveal insights into immunotherapy response. *First Author: Todd Cory Knepper, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Merkel Cell Carcinoma (MCC) is a rare and aggressive neuroendocrine skin malignancy. Recently, high response rates to immune checkpoint inhibitor therapy (ICT) have been demonstrated, but predictive factors for response are lacking. We therefore performed immunogenomic analyses on a cohort of MCC patients (pts) with concurrent review of clinical outcomes. **Methods:** A retrospective chart review was performed to collect demographic, clinical, disease, treatment, and outcomes variables on 57 pts with advanced MCC whose tumors underwent comprehensive genomic profiling by FoundationOne testing. Genomic data were analyzed for recurrent alterations, tumor mutational burden (TMB, calculated as the number of non-driver somatic, coding mutations per megabase of genome sequenced), and mutational signatures. Presence of Merkel Cell Polyomavirus (MCPyV) was evaluated by de novo assembly of non-human sequencing reads. **Results:** MCC TMB demonstrated a striking bimodal distribution between TMB high ($\geq$20 mutations/mb) and TMB low ($<$ 6 muts/mb) with only 4 pts having an intermediate TMB. Overall, 21/57 (36.8%) MCC samples were TMB high (median 63 muts/mb) and all carried mutations in TP53, RB1, or NOTCH1. 21/21 (100%) TMB high pts had a mutational signature consistent with UV damage. 21/32 (65.6%) TMB low (median 1 mut/mb) pts were positive for MCPyV integration as opposed to 0/25 (0%) TMB high or intermediate pts (P = 1.03e-07, Fisher's exact). 34/57 (59.6%) pts were treated with at least one ICT. Within this group, response to ICT dramatically impacted overall survival with 15/15 (100%) responders vs. 3/19 (15.8%) non-responders alive at date of last contact and significantly prolonged survival ($p < 0.0001$, Kaplan-Meier). 7/11 (64%) pts classified as TMB high responded to ICT compared with 8/23 (35%) low/intermediate TMB pts (p = 0.13). Viral status in the TMB low group had no significant impact on response rates, with MCPyV integration detected in 6/8 (75.0%) responders and 9/13 (69.2%) non-responders. **Conclusions:** Response to ICT leads to high rates of durable overall survival in advanced MCC. High TMB and prolonged UV exposure, but not viral status, are associated with higher responsiveness to ICT.

9524 Poster Session (Board #351), Mon, 1:15 PM-4:45 PM

Association between hospital volume and overall survival (OS) of stage 3 and 4 cutaneous malignant melanoma (MMel). *First Author: Anuhya Kommalapati, University of South Carolina, Columbia, SC*

Background: Therapeutic advances altered the course of MMel in the last decade. The therapeutic and survival disparities of MMel were evaluated based on hospital volume using the National Cancer Data Base (NCDB). **Methods:** Patients with MMel diagnosed between 2004 & 2015 were included and classified into tertiles based on hospital volume. Cox regression analysis was performed to adjust for covariates, including patient demographics, tumor characteristics, LDH, insurance & therapy received. Kaplan Meier estimates of OS were compared with log-rank test. **Results:** A total of 50, 254 MMel patients were treated at 1317 facilities. The median age at diagnosis was 62 & 67 y for stages 3 & 4, respectively. The median annual facility volumes were 10 & 6 patients/yr for stages 3 & 4, respectively. Multivariable analysis showed that facility volume was an independent predictor of OS ($p < 0.0001$). Stage 3 (n = 34, 666): Hospitals were classified into (T: mean cases/year) T1: < 4.56; T2:4.57-15.25; T3:≥15.2 cases/year. The unadjusted median OS by facility volume was: T1: 77 months (m), T2: 94 m, and T3: 124 m ($P < .0001$). Compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had significantly higher risk of death [T2 hazard ratio (HR), 1.11 (95% CI, 1.06-1.16); T1 HR, 1.18 (CI, 1.09-1.27)]. Stage 4 (n = 15,588): T1:1-3; T2: 3-8.67; T3: > 8.68. The unadjusted median OS by facility volume for stage 4 MMel was: T1: 6 m, T2: 8 m, and T3: 11 m ($P < .0001$). Compared with patients treated at T3 facilities, patients treated at lower-tertile facilities had significantly higher risk of death [T2 HR, 1.18 (CI, 1.13-1.23); T1 HR, 1.21 (CI, 1.14-1.30)]. Patients at T3 facilities (vs T1) were more likely to receive chemotherapy (36 vs 27%) and immunotherapy (27 vs 12%) ($p < 0.01$). **Conclusions:** Patients who were treated for MMel at high-volume centers (> 15 cases in stage 3; > 8 cases/yr in stage 4) had significantly improved survival and were more likely to receive chemotherapy and immunotherapy for stage 4 disease.

	Therapy received %						Survival %			
	Stage 3			Stage 4			Stage 3		Stage 4	
	Surgery	Chemo	Immuno	Surgery	Chemo	Immuno	3 yr%	5 yr%	3 yr%	5 yr%
T1 (32%)	92	9	26	29	27	12	66	55	19	14
T2 (35%)	94	7	26	30	29	15	70	58	22	17
T3 (33%)	93	7	27	31	36	27	73	63	25	20

9525 Poster Session (Board #352), Mon, 1:15 PM-4:45 PM

Interim analysis of a prospective, randomized, double blind, placebo controlled, phase IIb trial of the TLPLDC vaccine to prevent recurrence in resected stage III or IV melanoma patients. *First Author: John William Myers, San Antonio Military Medical Center, San Antonio, TX*

Background: The autologous tumor lysate, particle loaded, dendritic cell (TLPLDC) vaccine has been shown to be safe and immunogenic while producing objective tumor responses in a variety of metastatic patients (pts). Here, we present the pre-specified interim results of a randomized, double blind phase IIb trial (NCT02301611) assessing the TLPLDC vaccine to prevent recurrences in high risk melanoma pts. **Methods:** Stage III & IV resectable melanoma pts were identified prior to definitive surgery and consented for tumor collection. Pts were re-consented for treatment and randomized 2:1 (vaccine (V): placebo (P)). TLPLDC or placebo vaccines were initiated within 3 mos of completion of standard of care (SoC) therapies. Intradermal inoculations were given at 0, 1, 2, 6, 12, and 18 mos. Pts were followed for recurrence per SoC, and the primary endpoint is 2 yr disease-free survival (DFS). The interim was pre-specified at 6 mos from the 120th randomization. Survival analysis was performed on the intention-to-treat (ITT) and per treatment (PT) populations. The latter excludes early recurrences during the primary vaccine series (PVS) (up to 6 mos). **Results:** The trial randomized 120 patients (V = 83, P = 37). There were no clinicopathologic or treatment-related differences between the groups except for median age (V = 65 yrs, P = 57 yrs, p = 0.02). There were 3:1 stage III:IV in both groups. Study-wide, only 33% of pts experienced treatment-related adverse events (AEs) with 98.6% being grade 1-2. There were no serious AEs or immune-mediated AEs. In the ITT analysis, there was no difference in recurrence (V = 56.6%, P = 54.1%, p = 0.65) at a median f/u of 11.9 mos. In the PT analysis (V = 51, P = 30), there was a trend toward decreased recurrences in the TLPLDC arm (V = 29.4%, P = 43.3%, p = 0.07) at a median f/u of 12.6 mos. **Conclusions:** The TLPLDC vaccine is safe with minimal toxicity. Among pts completing the PVS period (6 mos), there is a strong trend toward fewer recurrences in the TLPLDC arm. This benefit will be confirmed at the primary analysis of 2 yr DFS; however, these early data provide an encouraging signal that a phase III trial for efficacy may be warranted. Clinical trial information: NCT02301611.

9527 Poster Session (Board #354), Mon, 1:15 PM-4:45 PM

Adjuvant ipilimumab compared with observation in completely resected Merkel cell carcinoma (ADMEC): A randomized, multicenter DeCOG/ADO study. *First Author: J?Rgen C. Becker, Translational Skin Cancer Research, Deutsches Konsortium für Translationale Krebsforschung (DKTK), Essen, Germany*

Background: Merkel cell carcinoma (MCC) is a rare, immunogenic, and highly aggressive skin cancer. Almost 40% of patients with completely resected MCC will relapse within the first two years after initial diagnosis. Currently, there is no accepted adjuvant systemic therapy for MCC. This study was conducted to determine if an immune modulating therapy with ipilimumab improves the disease-free survival (DFS) of MCC patients. **Methods:** Within 12 weeks after complete resection of primary or locoregional metastatic MCC, patients were randomly assigned to four doses of 3mg/kg ipilimumab i.v. every 3 weeks or observation. The primary end point of the study was DFS; secondary endpoints included adverse events and overall survival at 12 months. Futility analysis was performed after screening 20% of the planned patient number. **Results:** At the time of futility analysis, 47 patients had been screened and 40 patients enrolled. Four patients had to be excluded after randomization due to protocol violations or withdrawal of informed consent (ipilimumab = 1; observation = 3). Median follow-up was 22.3 months. Groups were well-balanced with regard to demographics, histology, and tumor stage. DFS was not significantly different between ipilimumab and observation (hazard ratio, 1.8; CI, 0.3 to 10; P = 0.48). However, patients in the treatment arm had a significantly increased incidence of adverse events by 4-fold, i.e. in more than 80% of the patients, compared to the observational arm, which was most relevant for adverse events of grade > = 3. **Conclusions:** Given the lack of efficacy of ipilimumab in preventing disease progression of MCC together with the pronounced toxicity, it was decided to stop enrollment of further patients into this study because a significant survival benefit was unlikely to be achieved as predicted by the futility analysis even across the originally planned cohort. Adjuvant ipilimumab should not be considered in MCC patients. Currently adjuvant nivolumab is tested in comparison to observation to improve DFS. Clinical trial information: NCT02196961.

9528 Poster Session (Board #355), Mon, 1:15 PM-4:45 PM

A phase Ib study of JS001, a humanized IgG4 mAb against programmed death-1 (PD-1) combination with axitinib in patients with metastatic mucosal melanoma. *First Author: Jun Guo, Peking University Cancer Hospital and Institute, Beijing, China*

Background: There was no standard treatment for metastatic mucosal melanoma. Preclinical data showed that axitinib increases the infiltration of immune cells and reduces the suppressive capacity of monocytic MDSCs in an intracranial mouse melanoma model. JS001 is a humanized IgG4 mAb against programmed death-1 (PD-1) with clinical activity in metastasis melanoma.This study is a phase Ib dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of JS001 combination with axitinib in patients with metastatic mucosal melanoma. **Methods:** Eligibility criteria include: histologically confirmed metastatic mucosal melanoma, archival or fresh tumor biopsy, ECOG PS 0-1, no prior system treatment. The patients will receive JS001 (1mg/kg or 3 mg/kg IV Q2W) combined axitinib (5 mg BID) in dose-finding and dose-expansion parts and treatment will be given until confirmed disease progression, unacceptable toxicity, withdrawal, or study termination. After the MTD or the optimal biological dose is identified, an expansion cohort of 30 patients were enrolled to further characterize the safety and efficacy. Other objectives include pharmacokinetics, pharmacodynamics, immunogenicity and tumor tissue biomarkers. **Results:** Enrollment began in April 2017. The majority of melanomas is mucosal origin included esophagus, nasopharynx, rectal melanoma and vaginal melanoma. As of February 10, 2018, enrollment has been completed with 33 patients. No dose-limiting toxicities (DLTs) were reported during dose escalation. 30 patients were treated with JS001 (3 mg/kg) combined axitinib (5mg Bid). The most common treatment-related AEs were grade 1/2, including hypertension, hand-foot skin reaction, oral ulcer, hypothyroidism and fever. Among 24 evaluable patients, no patient have complete response, 12 patients have partial response, and 9 pts achieve stable disease, for an ORR of 50% and a DCR of 87.5%. 10 out of 12 PR pts still have ongoing response. **Conclusions:** JS001 combined with axitinib may benefit for patients with metastatic mucosal melanoma.we will report all results during 2018 asco annual meeting. Clinical trial information: NCT03086174.

9529 Poster Session (Board #356), Mon, 1:15 PM-4:45 PM

Prediction of response and toxicity to immune checkpoint inhibitor therapies (ICI) in melanoma using deep neural networks machine learning. *First Author: Zarmeena Dawood, The Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY*

Background: Challenges in treating melanoma patients with ICI include treatment resistance and adverse events, both of which can lead to discontinuation of treatment. Histopathology of metastatic melanoma lymph nodes (LN) reveal varying histological composition(s) of malignant melanocytes and host LN reactions to tumor. Here we tested the hypothesis that deep machine learning on H&E images of metastatic melanoma LN prior to ICI can predict response and/or toxicity. **Methods:** H&E slides of metastatic and normal LN resected from melanoma patients (n = 45) prior to receiving ICI were digitized and annotated for regions of interest. The Inception v3 Convolutional Neural Network (CNN) was first trained to distinguish tumor LN (n = 56) from independent normal LN (n = 57). Images were tiled (299x299 pixels) at 20X magnification and partitioned into training (70%), validation (15%) and testing (15%) sets. CNNs were next trained on two classifications: 1) complete/partial response (n = 15) vs. progression of disease (n = 30) and 2) no (n = 14) vs. severe (n = 12) toxicity. Images from response (n = 45) and toxicity (n = 26) datasets were partitioned into 80% training and 20% testing sets followed by 5-fold cross validation. Predictive accuracy was measured by area under the curve (AUC) of receiver operating characteristics (ROC) plots. Sensitivity (SEN) and specificity (SPEC) were calculated at the optimal cut-off point of ROC curves. **Results:** Melanoma-infiltrated LNs were unambiguously distinguished from normal LNs with AUC = 1.00 per slide. Three-class training (tumor vs. lymphocytes vs. connective tissue) reported an average per-slide AUC of 0.99 [CI, 0.98-1.00], with 0.96 SEN & SPEC. In predicting response to ICI, machine learning algorithm showed AUC of 0.76 with 0.71 SEN & 0.64 SPEC. Severe toxicity was predicted with AUC of 0.70 and with 0.71 SEN & 0.64 SPEC. The AUC standard error of mean (SEM) was 0.09 for both analyses. **Conclusions:** Our data suggest that deep neural networks have the potential to predict patient response and toxicity to ICI with an accuracy of 70%. Independent larger datasets in clinical trial setting are pre-requisite to support validity of this novel approach.

9530 Poster Session (Board #357), Mon, 1:15 PM-4:45 PM

Efficacy and safety of entinostat (ENT) and pembrolizumab (PEMBRO) in patients with melanoma progressing on or after a PD-1/L1 blocking antibody. *First Author: Sanjiv S. Agarwala, St. Luke's Hospital, Easton, PA*

Background: Immune checkpoint inhibitors (ICIs) have improved prognosis for pts with advanced melanoma, but there is an unmet need for pts who progress after ICI. In this group, we reported that ENT, a class I selective histone deacetylase (HDAC) inhibitor, in combination with PEMBRO showed promising activity, through alteration of the immunosuppressive tumor microenvironment. Here we report the first 34 pts with further information on both prior therapies and pre/on treatment tumor samples. **Methods:** ENCORE-601 is a multicohort study evaluating ENT + PEMBRO. Pts enrolled in Cohort 3 had unresectable or metastatic melanoma, were previously treated with a PD-(L)1-blocking antibody, and experienced progression on or after therapy. The enrollment target was 34 pts and revised to 52 to increase statistical power and decrease Type I error. Pts were treated with ENT 5 mg PO weekly and PEMBRO 200 mg IV Q3W. Primary endpoint was ORR as assessed by irRECIST. Tumor biopsies and blood samples for immune correlates were obtained pre- and on-treatment. **Results:** Of the first 34 patients, 14 had refractory disease to prior PD-(L)1 therapy, and only 2 had a documented prior response. Median duration of prior PD-(L)1 therapy was $<$ 6 months and the median time from last dose was 65 days. 22 pts had prior ipilimumab and 6 had progressed on a BRAF inhibitor. With ENT + PEMBRO, 6 of 34 pts achieved a confirmed PR (ORR = 18%, 95% CI: 6.8-34.5), and 10 pts continue on study (3 have been on treatment $>$ 1 year). Frequent ($>$ 15%) related AEs include nausea, fatigue, diarrhea, and pruritus. Preliminary analysis of gene expression in pts with tumor samples pre- and on-treatment (n = 9) indicates increased inflammation in the tumor microenvironment after treatment; a decrease in MDSCs (–35.7%) and an increase in CD8+ T cells (47.4%) was also observed. **Conclusions:** ENT + PEMBRO continues to demonstrate promising anti-tumor activity and acceptable safety in patients with melanoma who have progressed on prior PD-(L)1 blockade. Preliminary biomarker analysis supports the hypothesis that the addition of ENT restores inflammation in the tumor microenvironment necessary for successful re-treatment with an anti–PD-(L)1. Clinical trial information: NCT02437136.

9531 Poster Session (Board #358), Mon, 1:15 PM-4:45 PM

Treatment-free survival (TFS), a novel outcome applied to immuno-oncology (IO) agents in advanced melanoma (AM). *First Author: Meredith M. Regan, Dana-Farber Cancer Institute, Boston, MA*

Background: Conventional measures, such as median progression-free survival, may suboptimally characterize the full impact of IO agents. Patients (pts) discontinuing IO agents may experience periods of disease control without needing subsequent systemic anticancer therapy (Rx). We propose TFS to simultaneously characterize the antitumor activity and adverse events of this period. Here we present the antitumor activity seen in the TF periods following IO therapy in AM. **Methods:** Data were pooled from 1077 pts initiating Rx in CheckMate 067 and 069 trials of ipilimumab (I) and nivolumab (N) as monotherapy and combination for AM (407 N+I, 313 N, 357 I). I was given for 4 doses; N was given until progression/intolerability. We defined TFS as the area between Kaplan-Meier (KM) curves for 2 conventional time to event endpoints: (A) duration of protocol Rx (randomization until Rx cessation) and (B) subsequent Rx-free survival (randomization until initiation of subsequent Rx or death). We estimated overall survival (OS). Area under each KM curve was estimated by the 36 mo restricted mean time to event. Area under the OS curve until 36 mo was partitioned as time on protocol Rx (mean A), TFS (mean B-A), and post-subsequent Rx time (mean OS-B), and summarized as percentage of the 36 mo period. **Results:** At 36 mo, 58% N+I, 52% N, 36% I pts were alive. Few pts remained on protocol Rx (11% N+I, 17% N, 0% I) and many pts were surviving free of subsequent Rx (47% N+I, 37% N, 15% I). 36 mo restricted mean OS was longer for N+I and N than I (Table). Mean TFS was 31% of time for N+I vs 13% for N, as N+I had shorter mean protocol Rx duration and longer time until subsequent Rx, and 24% for I. Clinical trial information: NCT01844505 and NCT01927419. **Conclusions:** Defining TFS by the area between KM curves for time to protocol Rx cessation and time to subsequent Rx or death, showed AM pts receiving N+I spent more time free of any Rx compared to N or I, and will allow integration of toxicity data to also characterize patient well-being while treatment free.

Restricted mean time, mo (% of 36 mo period)	N+I	N	I
OS	25.7 (72%)	24.9 (69%)	21.4 (59%)
Duration of protocol Rx, A	10.3 (29)	13.9 (39)	2.6 (7)
TFS, B-A	11.1 (31)	4.6 (13)	8.7 (24)
Time after subsequent Rx initiation, OS-B	4.3 (12)	6.4 (18)	10.1 (28)

9532 Poster Session (Board #359), Mon, 1:15 PM-4:45 PM

Activity of targeted therapy after failure of first-line immunotherapy in BRAF-mutant metastatic melanoma. *First Author: Cathy Yi Xia, Melanoma Institute Australia, Sydney, Australia*

Background: There are limited data regarding the best sequence of targeted and immunotherapy in patients (pts) with BRAF-mutant melanoma. Some studies suggest lower activity of immunotherapy after BRAF/MEK inhibitors (BRAF/MEKi), but there are no data examining BRAF/MEKi after immunotherapy. **Methods:** Consecutive patients with BRAF-mutant metastatic melanoma from 6 centers treated with 1 or more lines of immunotherapy then subsequent BRAF/MEKi were identified. Disease characteristics, treatment details, RECIST response and survival data were retrospectively examined. If pts ceased BRAF/MEKi for toxicity prior to first response assessment, response was deemed progressive disease (PD). **Results:** 79 pts were included, with V600E (85%), V600K (13%), V600M (1%) and V600R (1%) mutations. 56% pts were treated with first-line ipilimumab, 21% with PD1 antibodies, 15% with combination ipilimumab/nivolumab, and 5% with other PD1 combinations. Median duration of immunotherapy was 10.9 weeks, and best response was partial response (PR) in 11%, stable disease (SD) in 17%, and PD in 72% pts. 20% of pts had 1 or more further lines of systemic treatment prior to BRAF/MEKi. At commencement of BRAF/MEKi, median age was 60 years, 68% were stage M1c, 25% had brain metastases, 57% had elevated LDH, 24% were ECOG 2/3. Median interval from last dose of immunotherapy was 6 weeks. 55 (70%) pts received combination BRAF+MEKi, 22 (28%) BRAFi alone, and 2 (3%) MEKi alone. 10/79 (13%) pts ceased BRAF/MEKi due to toxicity, 2 prior to first response, and median treatment duration was 21 weeks. 59% pts had a RECIST response (5% CR), 11% had SD and 29% had PD. Median PFS was 4.4 months (3.5 - 6.2). 65% pts had subsequent treatment, including PD1 antibodies in 50%. Median OS from BRAF/MEKi commencement was 18.0 months (14.6 - 40.3), and 39% were alive at 3 years. In the 35 (44%) pts that had received prior PD1 antibodies, the response rate was 66%, median PFS 4.1 months (2.4 - 6.8) and median OS 13.6 months (10.2 – NR). **Conclusions:** BRAF/MEKi have efficacy in pts previously treated with immunotherapy. Despite pts having more adverse disease characteristics than seen in first line trials, response rates may be similar, however PFS appears shorter.

9534 Poster Session (Board #361), Mon, 1:15 PM-4:45 PM

Pembrolizumab as first line therapy in patients with unresectable squamous cell carcinoma of the skin: Interim results of the phase 2 CARSKIN trial. *First Author: Eve Maubec, AP-HP Dermatology department, Avicenne hospital, Université Paris 13, Bobigny, France*

Background: Patients (pts) with advanced squamous cell carcinoma of the skin (SCCS) have a poor prognosis. Response rate (RR) of 46% with an anti PD-1 (REGN2810) was recently shown in 25 pre-treated pts. CARSKIN is an open-label, phase II study evaluating pembrolizumab (Pembro) in unresectable SCCS. We report preliminary efficacy and safety findings. **Methods:** Chemotherapy naive pts who had unresectable SCCS, with an ECOG PS of < 2 were eligible. Baseline PD-L1 expression was centrally assessed on tumor. Pembro kindly provided by Merck was administered IV (200 mg Q3W) for a period up to 24 mths. CT evaluation was performed at baseline, 9, 15, 24 wks and thereafter Q12W and was independently reviewed. The primary endpoint was RR at 15 wks (RECIST criteria). Using Simon two-stage design, ≥ 4 responses were required out of 19 pts in stage 1 to continue accrual to 39 pts. Results of stage 1 are reported. **Results:** Nineteen pts (6, 7 and 6 with local, regional and distant metastasis, respectively) were recruited between March and July 2017, of which 15 (79%) were male. Median age was 80 yrs (range, 61-88); 61% of pts were PS 1. Median number of Pembro infusions was 9 (range, 0-13). Median follow-up was 7 mths. Seventeen pts were evaluable for tumor response, and 19 for toxicity. RR at 15 wks in the ITT population was 42 % (95% CI: 23–63%) corresponding to 7 PR (2 unconfirmed) and 1 CR. Disease control rate at 15 wks was 58% (11/19 including 3 SD). Only 1 responder progressed. Median PFS is 7 mths and median OS is not reached. There was no Pembro-related death or SAE. One pt discontinued Pembro due to grade 2 colitis. Pembro-related AE occurred in 63% of pts, the most frequent AEs being rash (32%), pruritus (16%), fatigue (26%), dysthyroidism (10%), and diarrhea (10%). Baseline PD-L1 expression was positive in 11 cases (58%). Median PD-L1 expression (Q1-Q3) was 28% (1-75%) in responders vs 0% (0-3%) in non-responders at 15 wks (P = .15). **Conclusions:** As first line treatment, pembrolizumab monotherapy provided encouraging clinical activity characterized by a high RR and durable response and was well tolerated in these elderly pts. The second stage of CARSKIN is ongoing. Clinical trial information: NCT02883556.

9535 Poster Session (Board #362), Mon, 1:15 PM-4:45 PM

Radioembolization for treatment of uveal melanoma hepatic metastasis: Results of a phase II, single institution, prospective trial. *First Author: Carin F. Gonsalves, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA*

Background: The liver is the first site of metastasis in $>$ 90% of uveal melanoma (UM) patients. Transarterial catheter directed therapies have been used to control growth of liver tumors and prolong overall survival (OS). We report results of the first prospective, phase II trial using radioembolization ([RE] Y-90 resin microspheres) for treatment of UM hepatic metastases. **Methods:** Between November 2011 and January 2017, RE was performed on 24 treatment naïve patients [Group A (13 men; median age 63; range, 29 -77)] and 24 patients who progressed after immunoembolization [Group B (9 men; median age 59, range, 34-77)]. Patients received unilobar or lobar treatments separated by 3-5 weeks. Patients were followed for 1 month for acute toxicity and every 3 months for delayed toxicity (CTCAE v 3.0). MR, CT and PET imaging was obtained every 3 months to evaluate for tumor response (PFS; RECIST) and extrahepatic disease. Results: Group A: Unilobar (n = 7) or bilobar (n = 17) RE was performed (median dose, 32.6 mCi; range, 17.7-56.1). One patient was removed from the trial for incomplete lobar treatment. RE response included PR (n = 7), SD (n = 13) and PD (n = 3). Median PFS was 8.1 months (range, 3.3 - 33.7). Median OS was 18.9 months (range, 6.5 -66.9) with 4 surviving patients (range, 14.0-66.9 months). One year survival was 61%. Extrahepatic disease occurred in 17 patients (median, 6.3 months; range, 3.3 – 11.9). Group B: Unilobar (n = 5) or bilobar (n = 19) RE was performed (median dose, 35.0 mCi; range, 19.2 -50.8). RE response included PR (n = 6), SD (n = 8) and PD (n = 10). One patient withdrew from the trial. Median PFS was 4.3 months (range, 2.5 -18.6). Median OS was 19.1 months (range, 4.8-68.4) with 5 surviving patients (range, 18.6 – 68.4 months). One year survival was 70%. Extrahepatic disease occurred in 15 patients (median, 5.5 months; range 0.8-9.9). No procedure-related complications occurred. Grade 3 treatment-related toxicities included transient leukopenia (n = 2), nausea/vomiting (n = 1) and pain (n = 1). **Conclusions:** RE is a safe and effective treatment for UM hepatic metastases and should be considered as a treatment option for patients with and without prior transarterial catheter directed therapies. Clinical trial information: NCT01473004.

9536 Poster Session (Board #363), Mon, 1:15 PM-4:45 PM

Relapse after cessation of PD-1 based therapy for complete responders in metastatic melanoma. *First Author: Khang Nguyen, Princess Alexandra Hospital, Brisbane, Australia*

Background: Treatment of metastatic melanoma using programmed death (PD-1) inhibitor has revolutionised systemic therapy, with a proportion able to achieve a durable complete response (CR). Little is known about the longterm relapse rate after cessation of therapy and the outcomes on re-induction. **Methods:** A retrospective review of patients (pts) who ceased PD-1 therapy after achieving CR was conducted across five institutions. The primary outcome was rate of relapse and response to therapy after relapse. **Results:** 182 pts that ceased PD-1 therapy following CR were included. Relapse occurred in 19 pts (10.44%), BRAF wildtype (N = 13), BRAF mutant (N = 6). Median follow-up post cessation was 22 (5-34) months. The mean duration on therapy prior to cessation was 16 (3-32) months and the mean interval between cessation of therapy and relapse was 14 (1-33) months. Relapse occurred in a site of new disease (N = 5) and in a site of prior disease (N = 14). On relapse, 12 pts were rechallenged with PD-1 therapy. Currently these pts were in CR (n = 3), partial response (n = 1), stable disease (N = 4) and progressive disease (PD) resulting in death (n = 1) or were waiting restaging (n = 3). Remaining relapses were treated with gamma knife (n = 1, this pt died following PD), gamma knife and PD-1 therapy (n = 1, pt in CR) or surgical resection (n = 3, all in CR). Two pts are waiting restaging following commencement of LAG3 inhibitor (n = 1) or topical imiquimod (n = 1). One pt elected for nil intervention following relapse and is alive with PD. **Conclusions:** Emerging data is suggesting that cessation of PD-1 based therapy for complete response is possible with durable disease control. This to date is the largest cohort of pts who have been followed up post cessation for complete response to describe patterns of relapse and response to subsequent re-challenge. Further long term follow-up of current trials is needed.

9537 Poster Session (Board #364), Mon, 1:15 PM-4:45 PM

Second-line avelumab treatment of patients (pts) with metastatic Merkel cell carcinoma (mMCC): Experience from a global expanded access program (EAP). *First Author: John Walker, University of Alberta, Edmonton, AB, Canada*

Background: Avelumab is a human anti–PD-L1 IgG1 antibody that showed a favorable efficacy and toxicity profile in pts with mMCC and progressive disease (PD) on or after chemotherapy (CT) in the phase 2 JAVELIN Merkel 200 trial (JM 200; NCT02155647), leading to accelerated approval in the US and Europe. We describe real-world experience with avelumab in a global EAP for pts with mMCC. **Methods:** Pts participating in the EAP (NCT03089658) had stage IV mMCC and PD on or after CT or were ineligible for CT. In contrast to JM 200, pts in the EAP could have ECOG performance status of 2, treated brain metastases, or immunosuppressive conditions with sponsor medical approval. Pts received avelumab 10 mg/kg IV Q2W until PD or unacceptable toxicity. A 3-mo supply of avelumab for approved pts was provided to treating physicians; additional re-supply was allowed for pts who had complete response (CR), partial response (PR), stable disease (SD), or clinical benefit per treating physician assessment. No central imaging was obtained. **Results:** Between Jan 2016 and Jan 2018, 460 requests for avelumab were received from 37 countries: 395 were approved, 45 were medically rejected for various reasons (eg, incorrect diagnosis, lack of appropriate prior therapy, incomplete information), and 37 were withdrawn. Most requests were from France (n = 97), Italy (n = 69), and Australia (n = 46). Median age was 74 y (range, 28-95), and 65.7% of pts were male. Among 131 response-evaluable pts, the objective response rate was 51.1%, including CR in 22.1% (n = 29) and PR in 29.0% (n = 38; including 1 pt with HIV); 19.1% (n = 25) had SD and 29.8% (n = 39) had PD. Durable responses were observed in immune-competent and immunosuppressed pts. Updated data will be presented. The safety profile was similar to that of JM 200. The EAP is ongoing but will close in 2018 (US closed in April 2017) with regulatory approval in multiple countries. **Conclusions:** The avelumab EAP rapidly enrolled many pts with mMCC and answered an unmet, urgent medical need for pts ineligible for clinical trials or for whom no approved alternative treatments were available. In a real-world setting, avelumab demonstrated safety and efficacy consistent with JM 200. Clinical trial information: NCT03089658.

9538 Poster Session (Board #365), Mon, 1:15 PM-4:45 PM

Clinical and economic outcomes associated with sequential treatment in *BRAF* mutant advanced melanoma patients. *First Author: Ahmad A. Tarhini, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH*

Background: Patients with *BRAF* mutant advanced melanoma can use immunotherapies (IO) and BRAF+MEK inhibitors. We evaluated the clinical and cost outcomes associated with treatment sequences for *BRAF* mutant advanced melanoma. **Methods:** A discrete event simulation was developed to estimate cost (USD) and life-years (LYs), over patient lifetime. In the absence of head-to-head trial data, a matching adjusted indirect treatment comparison (MAIC) was conducted. Treatment sequences and corresponding efficacy data sources are presented below (table). Safety and cost data were obtained from published literature. **Results:** Treatment sequences starting with IO followed by BRAF+MEK appear to be associated with 3.7–5.2 years of additional survival vs sequences starting with BRAF+MEK followed by IOs. This was primarily due to a longer treatment-free interval (TFI) of 2.5–4.4 years after first-line (1L) IOs and longer time on BRAF+MEK as second-line (2L) post-IO therapy. LYs and TFI were higher with sequences starting with anti-PD-1+anti-CTLA-4 vs anti-PD-1 alone. Sequences starting with anti-PD-1 +anti-CTAL4 ($77,918) or anti-PD-1 monotherapy ($85,813) had lower average cost/LY compared to BRAF+MEK ($107,266). **Conclusions:** Initiating 1L treatment with IO appeared to provide longer survival benefit compared to BRAF+MEK, driven by long TFI and, in many cases, lack of subsequent therapy need, leading to lower average cost/LY. Because these data may be biased by unaccounted for and unknown factors, findings will require validation in prospective randomized clinical trials (EA6134 - NCT02224781).

1L	2L	Total Costs ($)	Total LYs	Cost per LY ($)
BRAF+MEK[1]	**Anti-PD-1**[2]	$345,693	3.22	$107,266
Anti-PD-1+Anti-CTLA-4[3]	**BRAF+MEK**[3]	$656,692	8.43	$77,918
Anti-PD-1[3,a]	**BRAF+MEK**[3]	$595,727	6.94	$85,813

Sources: 1. MAIC, COMBI-v & COMBI-d (23.8 & 23 m) 2. CheckMate 037 (24 m), KEYNOTE-002 (10 m[b]). 3. CheckMate 067 & 069 (25.7 & 16.9 m). Notes: m, mean months; BRAF+MEK, dabrafenib+trametinib; Anti-PD-1+Anti-CTLA-4, nivolumab+ipilimumab; Anti-PD-1: nivolumab/pembrolizumab; [a]Pembrolizumab assumed similar efficacy as nivolumab; [b]Median.

9539 Poster Session (Board #366), Mon, 1:15 PM-4:45 PM

A phase II study of JS001, a humanized PD-1 mAb, in patients with advanced melanoma in China. *First Author: Zhihong Chi, Peking University Cancer Hospital and Institute, Beijing, China*

Background: JS001, a humanized IgG4 antibody specific for human PD-1, has demonstrated favorable safety profile and promising anti-tumor activity in phase I clinical trial. **Methods:** This multi-center, open-label, phase II registration study is designed to evaluate safety and efficacy of JS001 in advanced melanoma patients who have failed systemic treatment. JS001 is given at 3 mg/kg IV Q2W until disease progression or intolerable toxicity. (Clinical Trial ID: NCT03013101). **Results:** Enrollment was completed by 9/15/2017 with 128 melanoma subjects enrolled (51 acral, 21 mucosal, 18 chronically sun-damaged (CSD), and 38 Non-CSD or origin unknown). As of 1/4/2018, among 121 evaluable subjects, all had at least two evaluations per RECIST1.1 by independent radiologic review committee. 1 CR, 24 PR and 48 SD were observed for an ORR at 20.7% and a DCR at 60.3%. ORR was lower in acral (14.3%) and mucosal (0%) subtypes when compared with CSD (35.3%) and non-CSD (33.3%). Nevertheless, significant DCRs were achieved in acral (53.1%) and mucosal (42.1%) melanoma subjects. Additional factors have been analyzed for correlation with clinical responses (Table 1). Median duration of response has not been reached, as most responses (23/25) are ongoing. There is no treatment related death in the study. The most common treatment related AEs were grade 1/2, including proteinuria (25%), ALT increase (25%), rash (22%), hyperglycemia (20%), amylase increase (18%), leukopenia (17%), anemia (16%), vitiligo (16%), AST increase (16%), pruritus (14%) and hypothyroidism (13%). Treatment related grade 3/4 AEs occurred in 18% subjects. **Conclusions:** This is the first reported large scale prospective anti-PD-1 clinical study in advanced melanoma subjects with an emphasis on acral and mucosal subtypes. Anti-PD-1 mAb appears more efficacious for CSD and non-CSD than acral and mucosal subgroups. Patients will be continuously monitored for safety and efficacy readouts (DOR, PFS and OS). Clinical trial information: NCT03013101.

Clinical response analysis in subgroups.

Group	Value	n	ORR %
ECOG	0	70	20.0
	1	51	21.6
Prior lines of systemic therapy	1L	38	29.0
	2L	28	25.0
	3L	26	11.5
	≥4L	29	13.8
PD-L1 (≥1% cutoff with SP142)	Positive	24	45.8
	Negative	80	15.0
LDH (U/L)	≤ 280	104	21.2
	> 280	17	17.7
Total		**121**	**20.7**

9540 Poster Session (Board #367), Mon, 1:15 PM-4:45 PM

Tolerance and efficacy of BRAF plus MEK inhibition in patients with melanoma who have received PD-1 based therapy. *First Author: Karim Saab, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Combined BRAF and MEK inhibition (BRAF-MEK) is a standard therapy for BRAF V600 mutant melanoma, but doses and adverse event (AE) profiles were defined in trials conducted largely before the era of PD-1 based frontline therapy. The tolerance, AE profile, rates of hospitalization, and efficacy are not well defined for BRAF-MEK in the post-PD-1 setting. **Methods:** A sequential cohort of patients (pts) with BRAF V600 mutant melanoma who received combined BRAF+MEK following prior PD-1 based therapy was assembled from 4 tertiary care centers in the US and Australia. Dose modification (mod) was defined as a treatment break, dose reduction, or planned intermittent dosing due to AEs. Rates of hospitalization, emergency room (ER) visits, and discontinuation due to AEs were collected, and OS was calculated using Kaplan-Meier methods from time of BRAF-MEK start. **Results:** 78 pts were identified; 48 (62%) male, median age (range) was 58 (26-88). Most primaries were cutaneous (82%) or unknown (12%). V600 mutations were -E in 71 (91%) and -K in 7 (9%). Most pts had M1c or M1d stage (80%); performance status was 0 (22%), 1 (57%) and 2-3 (21%). LDH was high in 54%. 55 pts (71%) were BRAF-naïve. 81 total BRAF-MEK regimens were utilized; 68 (84%) dabrafenib-trametinib (DT); 12 (15%) vemurafenib-cobimetinib (VC); 1 other. Median (range) interval between last PD-1 dose and BRAF-MEK start was 35 days (1-410). Most common AE for DT was fever (88%) and for VC was rash (83%). Atypical AEs included cytopenias (12%) and central nervous system events (7%). 25 (31%) had an AE-related hospitalization and 18 (22%) an ER visit. 12 pts (15%) stopped BRAF-MEK for AEs. 68 of 81 regimens (84%) had ≥1 dose mod; median time to first dose mod was 14 days, 59 (87%) occurred within 90 days, and 70% involved fever. Among BRAF-naïve pts, after median follow-up of 12.5 months (mo), median time on BRAF-MEK was 6 mo and median OS was 15 mo. **Conclusions:** The majority of patients receiving BRAF-MEK inhibitors after PD-1 therapy require dose interruptions, and a significant minority require hospitalization or ER utilization for AEs. In this higher-risk population, median time on therapy and OS may be inferior to those in published Phase 3 trials.

9541 Poster Session (Board #368), Mon, 1:15 PM-4:45 PM

Efficacy and genetic analysis for a phase II multicenter trial of HF10, a replication-competent HSV-1 oncolytic immunotherapy, and ipilimumab combination treatment in patients with stage IIIb-IV unresectable or metastatic melanoma. *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: HF10, a bioselected replication-competent oncolytic virus derived from HSV-1, has been evaluated in combination with ipilimumab (ipi) in a Phase II trial (NCT02272855) in unresectable/unresected Stage IIIB-IV melanoma pts. Herein we report the recent efficacy and gene expression findings correlating with responders. **Methods:** HF10 injected into single or multiple tumors (1×10^7 $TCID_{50}$/mL/dose, up to 5mL depending on tumor size and numbers); 4 injections q1wk; then up to 15 injections q3wk. Four ipi IV infusions (3 mg/kg; concurrent with HF10) were administered q3wk. AEs assessed per CTCAE 4.0. Tumor responses were assessed per mWHO and irRC at 12, 18, 24, 36 and 48 wks for patients (pts) continuing on HF10 monotherapy. Primary endpoint was Best Overall Response Rate (BORR) at 24 wks. Evaluation of correlative studies (nCounter PanCancer Immune Profiling Panel) including tumor biopsy was performed at baseline and on Days 85 and 169. **Results:** 46 pts were enrolled and treated: 59% men, median age 67 yrs (range 28 to 91); disease stage 20% IIIB, 43% IIIC and 37% IV; 57% were treatment naïve and 43% with ≥ 1 prior cancer therapy for unresectable/metastatic melanoma. HF10+ipi combination was well tolerated. HF10 adverse event (AE) profile was similar in combination with ipi as in HF10 monotherapy. 28.3% pts had treatment-related ≥G3 AEs, and the majority of ≥G3 AEs were due to ipi. Of the 44 efficacy evaluable pts, irRC BORR at 24 weeks was 41% (18% irCR and 23% irPR); disease stability rate was 68% (27% irSD). As of Feb 07, 2018, median PFS was 19 months and median overall survival was 26 months. Responding tumors exhibited an activation of the adaptive immune response with increased total tumor infiltrating lymphocytes and CD8+ T-cells, and decreased CD4+ T-cells. **Conclusions:** The combination HF10 and ipilimumab treatment demonstrated a favorable benefit/risk profile and encouraging antitumor activity in advanced melanoma pts by inducing immune-cell infiltration in the tumor microenvironment. Clinical trial information: NCT02272855.

9542 Poster Session (Board #369), Mon, 1:15 PM-4:45 PM

BRAF/MEK inhibition in melanoma patients with rare BRAF mutations. *First Author: Jessica Cecile Hassel, Section of DermatoOncology, Department of Dermatology and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany*

Background: BRAF/MEK inhibition is standard of care in patients (pts) with a BRAF V600E/K mutated melanoma. Efficacy data for pts with less frequent BRAF mutations are limited so far. **Methods:** 71 metastatic melanoma pts with rare activating BRAF mutations (excluding BRAF V600E/K) treated at 13 melanoma centers with either a BRAF inhibitor (i) or MEKi monotherapy or the combination were included. BRAF mutation, patient and disease characteristics, response and survival data were examined. **Results:** 41 (58%) pts harbored a rare BRAF V600 mutation and 30 (42%) a non V600 mutation (Table). The most frequent mutations were V600R (30 pts, 42%) and K601E (10 pts, 14%). The median age was 61 years, 75% were male. Most melanomas were of cutaneous origin (84%) and a nodular subtype (40%). At treatment start, most pts had stage IV M1c (44%) or M1d melanoma (28%) (AJCC 2017), and 40% had an elevated LDH. Most pts received combined BRAFi/MEKi (48%) or BRAFi monotherapy (45%). In the 41 pts with V600 mutations (30 = V600R, 4 = V600D) the response rate (RR) to single agent BRAFi and combination BRAFi/MEKi was 33 and 61%, respectively. Median PFS was 3.7 months and 8.2 months. In the 30 pts with non-V600 mutations (10 = K601E, 6 = L597Q/S) the RR to BRAFi was 7%, to MEKi 40% and to combination treatment 36%. Median PFS was 1.6 vs 4.8 vs 3.8 months. **Conclusions:** Patients with rare BRAF mutations can respond to targeted therapy. Pts with non-V600 mutations are less likely to respond to BRAFi monotherapy, but activity with MEKi alone or in combination with BRAFi appears more promising.

BRAF genotype	Treatment	N	ORR (CR + PR)	Median PFS (in months)	Median OS (in months)
V600	Total	41	20 (49%)	7.3	16.1
	BRAFi	18	6 (33%)	3.7	10.5
	MEKi	0	-	-	-
	BRAFi/MEKi	23	14 (61%)	8.2	31.1
V600R	Total	30	14 (50%)	6.5	14.8
	BRAFi	12	3 (25%)	3.7	8.9
	MEKi	0	-	-	-
	BRAFi/MEKi	18	11 (61%)	8.2	31.1
Non-V600	Total	30	7 (23%)	2.5	7.8
	BRAFi	14	1 (7%)	1.6	7.6
	MEKi	5	2 (40%)	4.8	6.9
	BRAFi+MEKi	11	4 (36%)	3.8	8.0
K601E	Total	10	1 (10%)	2.2	7.2
	BRAFi	5	0	1.4	7.2
	MEKi	1	0	0.4	5.2
	BRAFi/MEKi	4	1 (25%)	3.8	NA*

*Median not reached

9543 Poster Session (Board #370), Mon, 1:15 PM-4:45 PM

Phase II trial of pembrolizumab (MK-3475) in metastatic cutaneous squamous cell carcinoma (cSCC). *First Author: Ragini Reiney Kudchadkar, Winship Cancer Institute, Atlanta, GA*

Background: cSCC is the second most common skin cancer in the U.S. with over 700,000 new cases and 2000 deaths per year. Though most cSCCs are curable with surgery or radiation, 5% metastasize and are treated typically with platinum-based chemotherapy and EGFR inhibitors as standard of care. These agent have overall response rates (ORR) of only10-20%. No current treatments have been shown to improve overall survival. **Methods:** Clinical activity of pembrolizumab in metastatic cSCC patients not curable by surgery or radiation was evaluated. Primary objective was to establish the ORR of pembrolizumab in metastatic cSCC per RECIST 1.1 Secondary objectives were 6-month progression-free survival (PFS) and 1 year overall survival. The study was conducted with Simon's optimal two-stage design, with goal of 12 patients in the first stage with 3 or more responses would lead to stage two that would include an additional 13 patients. Patients were treated with pembrolizumab 200mg IV every 3 weeks for up to 2 years. Normal skin, blood, and tumor tissue were obtained for biomarker studies including PD-L1, expression of co-stimulatory and co-inhibitory molecules on and functionality of T cell populations. **Results:** Ten subjects (2 females) with a median age of 68.7 years are reported. All subjects were Caucasian. ORR was 40%, with 10% (1) complete response (CR),30% (3) partial responses (PR), 10% (1) stable disease (SD) 10% (n = 1), progressive disease (PD) 20% (n = 2), and 3 subjects are not yet evaluable. Three subjects had prior chemotherapy, 2 of the 3 had PD, 1 subject not yet evaluable. All patients with CR, PR, and SD are yet to progress at current follow up. No subject deaths have occurred on study. Two grade 3 related-adverse events were noted, hepatitis and pneumonitis. No unexpected adverse events related to treatment have occurred. Median PFS and OS has not been reached as of February 2018. Further follow up as well as biomarker correlates will be presented. **Conclusions:** Pembrolizumab has significant clinical activity in cSCC. Expansion into the second stage of the trial is indicated. Further follow up is needed in order to establish survival benefit for these patients. Clinical trial information: NCT02964559.

9545 Poster Session (Board #372), Mon, 1:15 PM-4:45 PM

Hyperacute toxicity with combination ipilimumab (ipi) and anti-PD1 immunotherapy. *First Author: Helen Clare Dearden, Melanoma Institute Australia, Sydney, Australia*

Background: Combination ipi and nivolumab is approved for advanced melanoma and is in trials across oncology. Toxicity (tox) most often occurs 6-10 wks into treatment. Whether early tox is harder to manage or influences treatment efficacy is unknown. **Methods:** Consecutive metastatic melanoma patients (pts) who developed hyperacute (HA) tox, defined as grade (G) 2 or higher (2+) tox within 21 d of receiving combination immunotherapy (ipi + PD1), were retrospectively identified from 9 centres. Demographics, disease characteristics, tox and outcome data were examined. **Results:** 80 pts developed HA tox, at a median (med) 10 d (range 1-21). Pts had med age 55y, 66% were stage IV M1c/d, 49% had elevated LDH, 14% were ECOG 2. 61 (76%) pts were treatment naïve, 9 had received prior BRAF inhibitors, 4 ipi, 2 PD1 antibodies. Most frequent HA tox was colitis (n = 23), rash (n = 17), hepatitis (n = 9), endocrine (n = 9), pneumonitis (n = 6), and neurotoxicity (n = 4). 39% were G2, 54% G3, 8% G4. 48% required treatment beyond oral steroids, including IV steroids (21%), infliximab (18%), and other immunosuppression (9%) including mycophenolate and IVIG. Pts required a med 45 days on $>$ 10mg prednisone equivalent. 83% of HA colitis pts required treatment beyond oral steroids (22% IV steroids, 61% infliximab), with a med 75 d on $>$ 10mg prednisone. 20% pts received further combination therapy, 48% permanently discontinued all immunotherapy. 48% pts developed additional tox (10% had 3+ further tox), and 31% with G3-4 HA tox developed another G3-4 tox without further therapy. The overall response rate (ORR) was 54%, and after a med 11.6 mo follow-up, med PFS was 8.74 mo. Patients with G2 tox had a similar ORR but greater PFS than those with G3-4 tox (65% vs 47%, p = 0.19; 10.2 vs 2.8 mo, p = 0.01). There was no difference in ORR and PFS by type or duration of immunosuppression. **Conclusions:** Hyperacute toxicities from combination immunotherapy are varied. Many pts require treatment beyond oral steroids and for a prolonged duration, and pts are at risk of further severe tox. Efficacy in such pts appears similar to trial populations, although severe tox may correlate with worse outcomes. The degree and duration of immunosuppression does not appear to influence the efficacy of immunotherapy.

9546 Poster Session (Board #373), Mon, 1:15 PM-4:45 PM

Ipilimumab and radiation in patients with unresectable melanoma brain metastases: A multicenter, open label, phase-2, Spanish Melanoma Group (GEM) study (NCT-2013-001132-22). *First Author: Jose A. Lopez-Martin, Medical Oncology Department, Hospital 12 de Octubre, Madrid, Spain*

Background: Laboratory and clinical experiences suggest that radiotherapy may be synergistic with anti-CTLA-4 strategies. This hypothesis is explored in melanoma patients (pts) with brain metastases (BM) not candidate to surgery/radiosurgery. **Methods:** Single arm phase-2 trial evaluating Ipilimumab (IPI) and whole brain RT (WBRT), in pts with melanoma and unresectable BM. Endpoints: Primary: 1-year overall survival (OS@1y). Secondaries: progression free survival (PFS), objective response rate (ORR) and safety. Main eligibility criteria: first-BM episode, non-suitable for radical therapy; Barthel Index $>$ 10; RTOG-RPA class-2; measurable disease; Karnofsky $>$ 70%; LDH $<$ 2 xULN; no rapid clinical deterioration; dexamethasone $<$ 16 mg/d. Treatment: IPI 3mg/Kg q3weeks (4 cycles); WBRT 30Gy in 10 fractions (or equivalent). Evaluable pts: Safety $>$ 1 IPI dose. Efficacy: complete WBRT and $>$ 1 IPI dose. Trial required 56 evaluable pts to detect an 35% OS@1y, assuming the historical 20% OS in this population (α:0.05, β:0.8; 1-stage Fleming design). **Results:** From April/2014 to January/2017, 58 pts were included; 51 completed WBRT and $>$ 1 IPI dose. Demographic characteristics: Age (median/range) 63 (37/85). Male/Female 36/22. Karnofsky (100/90; 80/70) 42. 16. BM (1, $>$ 1, nonspecified) 14; 43; 1. Barthel Index ($>$ 15; 10-15) 56; 2. Steroids at baseline 31 (53,4%). Prior treatments (1, $>$ 1) 20 (34,5%), 9 (15,5%). Previous BRAF/MEKinhibitors 18 (31%). Liver metastases 16 (27,6%). Treatment intensity: WBRT: completed in 55 pts (3 early termination). IPI 4/3/2/1 doses: 31/10/10/7 pts. Efficacy: OS@1y: 31.8% (95%CI 18.8-44.8%). 15 pts are alive $>$ 1 year. Median PFS: 4.8mo (95%CI 2.2-3.4). Median OS 5.8mo (95%CI 3.6-5.9). Safety: Serious AEs: 40 pts (69%). Treatment-related SAEs: 11 pts (19%). IPI-related: ALT/AST (4), diarrhea (4), intestinal perforation (1), headache (1). RT-related: headache and vomiting (1). **Conclusions:** Concomitant IPI+WBRT is feasible and there were no unexpected safety issues. Steroids at baseline do not impair the effect of IPI in this population. OS@1y in this trial is higher than the historical results. Clinical trial information: 2013-001132- 22.

9547 Poster Session (Board #374), Mon, 1:15 PM-4:45 PM

Sex differences in tolerability to Anti-PD1 therapy: Are we all equal? *First Author: Narjust Duma, Mayo Clinic, Rochester, MN*

Background: Immune related adverse events (IRAEs) have emerged as a serious clinical problem in the use of immune checkpoint inhibitors. The etiology and risk factors for these potentially life-threatening adverse events remain unknown. Therefore, we assessed sex differences in tolerability to anti-PD1 therapy. **Methods:** All patients (pts) with metastatic melanoma treated with anti-PD1 therapy at Mayo Clinic Rochester from 2014 to 2017 were reviewed. Ocular melanoma cases were excluded. Kaplan-Meier method was used for time-to-event analysis. **Results:** 245 pts were identified, 148 (60%) were men, 30 (12%) were premenopausal (Pre-M) (≤52 years) and 67 (27%) were postmenopausal (Post-M) women. Baseline characteristics were similar among groups (Table 1). Pre-M women were more likely to experience IRAEs compared to Post-M women and men (67% vs. 60% vs. 46%, $p < 0.04$). In 23% of Pre-M women anti-PD1 therapy was discontinued due to irAE (men 12%). Pre-M women were more likely to experience endocrinopathies (35% vs. 10%, $p < 0.02$) and cutaneous reactions (25% vs. 15%, $p < 0.02$) compared to men. All cases of diabetic ketoacidosis were observed in Pre-M women (n = 6). No differences in grade ≥3 toxicities were seen across groups. Pts with IRAEs were more likely to have a radiographic response to anti-PD1 therapy regardless of sex (68% vs. 44%, $p < 0.002$). There was a trend towards better PFS in men with IRAEs compared to men without IRAEs (16.5 months vs. 9.7 months, $p < 0.05$). **Conclusions:** Pre-M Women were more likely to experience IRAEs compared to Post-M women and men. An association between IRAEs and response to therapy was also observed. Larger studies are needed to confirm these results and investigate etiologic mechanisms underlying these associations.

Characteristics	Pre-M % (n)	Post-M % (n)	Men % (n)	p value
Liver metastasis	33 (10)	33 (22)	30 (45)	0.91
Lung metastasis	47 (14)	30 (20)	42 (62)	0.16
Prior GM-CSF	43 (13)	27 (18)	18 (27)	0.01
Prior radiation	37 (11)	54 (36)	59 (87)	0.08
Prior chemotherapy	13 (4)	16 (11)	18 (27)	0.79
IRAEs	67 (20)	60 (40)	46 (68)	0.04
≥3 grade IRAEs	50 (10)	43 (17)	31 (21)	0.12
Discontinuation of anti-PD1 due to toxicity	23 (7)	15 (10)	12 (18)	0.37

9548 Poster Session (Board #375), Mon, 1:15 PM-4:45 PM

A randomized phase Ib/II study of the selective small molecule axl inhibitor bemcentinib (BGB324) in combination with either dabrafenib/trametinib or pembrolizumab in patients with metastatic melanoma. *First Author: Oddbjorn Straume, Department of Oncology, Haukeland University Hospital, Bergen, Norway*

Background: Upregulation of the receptor tyrosine kinase Axl has been linked with both a reduced response to PD-1 blockade and the development of therapy resistance to BRAF directed therapies in melanoma. Bemcentinib (BGB324) is a first-in-class orally bioavailable selective inhibitor of Axl which is currently explored in several ph II clinical trials. BGBIL006 (NCT02872259) is an open label phase Ib/II trial designed to explore whether combination with bemcentinib improves ORRs to standard of care therapies in pts with metastatic melanoma (MM). **Methods:** Dose escalation of bemcentinib in combination with 150mg twice daily / 2mg daily D/T in newly diagnosed, BRAF pos. MM with high tumour load followed a 3+3 design (part 1). In part 2, pts were randomized 2:1 to receive D/T or pembro +/- bemcentinib at RP2D, respectively, based on mutation status and tumour load. Pts were allowed to switch D/T with pembro and *vice versa* upon progression (part 3). Tumor responses were assessed per investigator using RECIST v1.1. Plasma protein biomarker levels were measured using the DiscoveryMap v3.3 panel (Myriad RBM) in a selection of pts pre-dose and at C2D1. **Results:** In part 1, 6 newly diagnosed pts were enrolled (age 34-71, male 66%, LDH > 1 x ULN 50%). There was1 dose limiting toxicity (G3 rash). As of Feb 7 2018, a further 13 pts have been enrolled into part 2 of the study. The most common treatment-related AEs (TRAEs) were diarrhea (42%), pyrexia (37%), fatigue (31%) and rash (31%). Grade 3 TRAEs were observed in 3 (16%) pts. No G4 AEs or treatment related deaths occurred. The bemcentinib RP2D (200 mg daily) is well tolerated in combination with both D/T and pembro with AE profiles consistent with those reported for either therapeutic approach alone. Protein biomarkers candidates predictive of pt benefit following bemcentinib treatment were identified. **Conclusions:** Bemcentinib can be administered in combination with established first line therapies in patients with melanoma. Safety and efficacy as well as biomarker candidates will continue to be explored. Clinical trial information: NCT02872259.

9549 Poster Session (Board #376), Mon, 1:15 PM-4:45 PM

Outcomes of metastatic melanoma (MM) patients (pts) after discontinuation of anti-Programmed-Death 1 (PD1) therapy without disease progression. *First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The optimal duration of PD1 therapy for MM pts that do not progress remains unknown. There is limited information available about long-term outcomes of patients that discontinue treatment due to toxicity. **Methods:** Our institutional database was queried to identify stage IV or unresectable stage III MM pts that received single-agent anti-PD1 from January 1, 2012, to July 31, 2016, with at least 6 months of clinical follow-up. Pts that discontinued PD1 therapy for reasons other than progression were identified, including maximal clinical benefit (MCB) and toxicity. MCB was defined as either completion of two years or discontinuation per physician's discretion. Data on demographics, tumor characteristics, treatment variables and outcomes were collected. **Results:** From 580 MM pts treated with PD1, 41 pts discontinued treatment for MCB and 34 for intolerable toxicity (75 total). 56% of pts achieved a complete response (CR), 35% partial response (PR), and 9% stable disease (SD). Response rate was similar among patients discontinuing therapy due to MCB (93%) and toxicity (88%), but CR rates were higher in the MCB group (76% vs 32%, $p < 0.001$). Median time on PD1 was 19.5 months in the MCB group and 6.5 months in the toxicity group; median time to response was 2.9 months, and median time to CR was 7.3 months. With median follow-up of 16 months after discontinuation, 89% were disease-free and 93% were alive; 6 patients died; no deaths were due to disease progression, and 3 were due to PD1 treatment complications. 8 pts progressed (3 in the MCB group, 5 in the toxicity group). 2 out of 3 in the MCB group were successfully rechallenged with PD1 (1 CR, 1 PR) and one had surgery and is still off therapy. One pt in the toxicity group was rechallenged, 2 are receiving ipilimumab, one had a single brain lesion resected (still off therapy) and one died of cardiac arrest while on T-VEC. No baseline factors were associated with relapse. **Conclusions:** Anti-PD1 was safely discontinued in the majority of MM pts, and no deaths due to disease progression were seen. Further prospective validation of early discontinuation for MM pts achieving MCB is warranted to prevent unnecessary toxicity and financial costs.

9550 Poster Session (Board #377), Mon, 1:15 PM-4:45 PM

Phase 1 study to evaluate safety and efficacy of nivolumab (nivo) + ipilimumab (ipi) + external beam radiotherapy (RT) in patients with metastatic melanoma. *First Author: Michael A. Postow, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: RT causes immunologic effects that enhance the efficacy of immune checkpoint blockade in preclinical models. No prospective clinical trial data exist for the safety and efficacy of combining RT with the nivo + ipi combination. **Methods:** We conducted a prospective study (NCT02659540) where patients with metastatic melanoma were treated with nivo (1 mg/kg) + ipi (3 mg/kg) every 3 weeks (Q3W) for up to 4 doses, with optional nivo maintenance Q2W per standard of care. Following the first nivo + ipi dose, patients were treated with conventionally fractionated RT (30 Gy in 10 fractions) to one melanoma metastasis. Treatment-related (TRAE) and treatment-emergent (TEAE, all causality) adverse events within the first 24 weeks of immunotherapy initiation were summarized overall and by CTCAE grade. Objective response rate (ORR) was assessed by RECIST 1.1 outside and within the irradiated fields. ORR rates were provided with binomial 95% confidence intervals (CI). **Results:** Ten patients (median age: 65 [range: 28-86] years; 6 female) received at least 1 dose of study therapy and were included in the safety analyses. One patient withdrew consent prior to efficacy assessment and was excluded from efficacy analyses. All patients had ≥1 any grade (G) TEAE. G3/4 TRAE occurred in 4 patients (40%), and G3/4 TEAE occurred in 7 patients (70%). G3/4 TRAE were anemia, thrombocytopenia, increased lipase, and pruritus. ORR outside of the irradiated field was 44% (4/9, 95% CI: 14-79%). Responses were also seen within the irradiated fields. Two patients died due to disease progression. **Conclusions:** This first prospective study in a small group of patients suggests it is safe to combine conventionally fractionated RT with nivo + ipi. Based on acceptable G3/4 TRAE in this fully accrued cohort testing conventionally fractionated RT, accrual is ongoing to a second cohort where patients receive higher dose per fraction RT with nivo + ipi. Clinical trial information: NCT02659540.

9551 Poster Session (Board #378), Mon, 1:15 PM-4:45 PM

42-month follow-up of sonidegib efficacy and safety in advanced basal cell carcinoma: Final analysis from BOLT. *First Author: Michael Robert Migden, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Sonidegib is a hedgehog pathway inhibitor (HPI) approved in the United States for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiotherapy; and in Switzerland and Australia also for metastatic basal cell carcinoma (mBCC). Here we report the final analysis at 42 months from the phase 2 BOLT study, the longest follow-up data available from a clinical trial of an HPI. **Methods:** BOLT was a randomized, double-blind, multicenter, phase 2 study. HPI treatment–naïve patients (N = 230) with advanced BCC (laBCC, n = 194; mBCC, n = 36) not amenable to curative surgery/radiotherapy were randomized 1:2 to sonidegib 200 mg, or to 800 mg QD, respectively. Data analyses were performed at 6, 12, 18, 30, and 42 months. The primary endpoint was objective response rate (ORR) per central review. Secondary endpoints included rate of complete response, duration of response (DOR), time to tumor response (TTR), progression free survival (PFS), and safety. **Results:** Primary and secondary endpoint results were very similar to the 30-month data (Table). Tumor responses were durable in patients with either subtype of advanced BCC (≥23 months). The safety profile of sonidegib was manageable and consistent with prior analyses. **Conclusions:** Efficacy was maintained at the 42-month analysis, with no new safety signals identified. These data continue to support sonidegib's durability of response in patients with advanced BCC. Proactive management of adverse effects may prolong treatment duration and improve outcomes.Clinical trial information: NCT01327053.

Sonidegib efficacy at 6, 30 and 42 months in advanced bcc by central review.

	6 months				30 months				42 months			
	laBCC		mBCC		laBCC		mBCC		laBCC		mBCC	
	200mg n = 66	800mg n = 128	200mg n = 13	800mg n = 23	200mg n = 66	800mg n = 128	200mg n = 13	800mg n = 23	200mg n = 66	800mg n = 128	200mg n = 13	800mg n = 23
ORR, %	47.0	35.2	15.4	17.4	56.1	45.3	7.7	17.4	56.1	46.1	7.7	17.4
DCR, %	90.8	78.2	92.3	82.6	90.8	82.1	92.3	91.3	90.9	82.0	92.3	91.3
DOR, mo	NR	NR	NR	8.3	26.1	23.7	24.0	NR	26.1	23.3	24.0	NE
PFS, mo	NR	NR	13.1	7.6	22.1	22.0	13.1	11.1	22.1	24.9	13.1	11.1

DCR: disease control rate; NE: not estimable; NR: not reached

9552 Poster Session (Board #379), Mon, 1:15 PM-4:45 PM

Characterization of complete responders to combination nivolumab (nivo) and ipilimumab (ipi) in patients (pts) with advanced, unresectable melanoma. *First Author: Allison Betof Warner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Among pts who discontinue treatment with nivo + ipi due to toxicity with a partial response or complete response (CR), ~30% ultimately progress. Less is known about whether pts who achieve CR to nivo + ipi maintain the CR after discontinuing treatment and how progression occurs. **Methods:** We conducted a single-institution (Memorial Sloan Kettering Cancer Center), retrospective analysis of checkpoint inhibitor naïve pts with advanced, unresectable melanoma treated with at least one dose of nivo + ipi and ≥6 months of follow-up from time of first treatment (n = 201). Pts with acral, uveal and mucosal melanoma were excluded. CR was defined by absence of radiographically apparent disease or after a biopsy showed no viable melanoma in radiographically apparent residual tissue. Overall survival (OS) was calculated by the Kaplan-Meier method. **Results:** Of the 201 pt cohort with a median follow-up of 27 months (mos) among survivors, the median OS has not been reached. Estimated 24-month OS is 74.5%. 56 pts (28%) achieved CR. Estimated 24-month OS among the pts in CR is 93.5%. Of the 56 pts with CR, only 2 (4%) remain on anti-PD-1 maintenance. 34 (61%) discontinued immunotherapy for toxicity, and 20 (36%) discontinued for reasons other than toxicity (i.e. protocol completion, CR, pt preference). Among the CR pts who discontinued therapy, 50 remain in CR (longest duration of CR = 71 mos) with a median follow-up of 20.5 mos from time of CR. 4 of the 56 pts ultimately had disease progression (PD); none of these pts was on treatment at time of PD (range of treatment duration: 1-16 mos). Two patients had PD within 3 months of CR, one in the bladder/pelvis and the other in bone. One patient had PD in the brain 18 months after CR, and one had PD in a regional lymph node after 41 months. **Conclusions:** Patients with advanced, unresectable melanoma can have durable CR, even after discontinuing therapy. OS and CR rates in our large dataset are similar to published trials yet follow-up time for some pts exceeds that reported in clinical trials. The incidence of disease progression after CR to nivo + ipi is low after 3 months. The need for ongoing systemic and intracranial surveillance requires further study

9553 Poster Session (Board #380), Mon, 1:15 PM-4:45 PM

Distinct patterns of response and toxicity (tox) by sites of metastases (mets) in patients (pts) treated with ipilimumab combined with PD-1 antibodies (ipi +PD1). *First Author: Ines Esteves Domingues Pires Da Silva, Melanoma Institute Australia, Sydney, Australia*

Background: Combined ipilimumab and nivolumab has the highest response rate (RR), progression-free survival (PFS) and overall survival (OS) for any immunotherapy in metastatic melanoma (MM), but the pattern of response and tox is variable. We sought to examine the association between site and size of mets with the pattern of response and tox in pts treated with ipi+PD1. **Methods:** MM pts treated with first line ipi+PD1 (nivolumab or pembrolizumab) had all mets > 5 mm (brain > 1 mm, lymph nodes > 15 mm in short axis) on CT/MRI measured. Lesional response was determined by RECIST. Demographics, disease characteristics, tox and outcomes were examined. **Results:** 140 pts were studied with 819 mets (median 5/pt); median (med) follow-up 12.9 months (mo). Mets with complete response (CR) were significantly smaller than non-CR mets (med 13 vs 17 mm, $p < 0.0001$) and the rate of patient CR decreased as number of mets increased within a pt, with no CR if > 8 mets ($p < 0.0001$). Med tumour regression was -64%, higher in subcutis (-90%, $p < 0.01$), soft tissue [ST] (-87%, $p < 0.01$), gastrointestinal [GI] (-82%, $p = 0.04$) and lung (-71%, $p = 0.03$), and lower in liver (-7%, $p = 0.06$) and spleen (0%, $p = 0.03$). The highest RR was in lung, GI and ST mets (69%), while splenic mets had the lowest RR (33%). GI mets had the fastest time to response (2.7mo) and liver the slowest (8.2mo). In multivariate analysis, pts with lung mets had superior RR (OR 2.75, $p = 0.02$) and PFS (HR 0.47, $p = 0.03$) and pts with liver mets had inferior RR (OR 0.33, $p = 0.02$) and PFS (HR 3.08, $p < 0.01$), while OS was poorer in pts with liver (HR 4.38, $p = 0.01$) or brain mets (HR 2.82, $p = 0.06$). Pts with lung mets had more rash (31% vs 9%, $p = 0.05$), while pts with liver and GI mets had less rash (6% vs 33%, $p = 0.02$) or thyroiditis (0 vs 14%, $p = 0.02$) compared with pts without these mets. Disease burden and number of metastases did not associate with tox. **Conclusions:** Metastases in different anatomical locations display distinct response patterns with combination immunotherapy, with inferior responses in liver mets and shorter survival in patients with liver mets, similar to that seen with PD1 monotherapy. Patterns of metastasis may influence toxicity.

9554 Poster Session (Board #381), Mon, 1:15 PM-4:45 PM

Off treatment survival (OTS) in patients (pts) with advanced melanoma after anti-PD1 therapy. *First Author: Shelly Ann Christiansen, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Anti-PD1 alone and combined with anti-CTLA4 therapy has improved survival in pts with advanced melanoma. Optimal treatment duration has not been defined and it is unclear if survival is compromised when pts discontinue (DC) therapy. **Methods:** A single institution review of pts with advanced melanoma treated with nivolumab or pembrolizumab monotherapy (anti-PD1) or nivolumab plus ipilimumab (nivo-ipi) was performed. Response rate (RR; provider assessed), reason for treatment DC and survival were analyzed. Outcomes in pts after treatment DC with CT scan response, PET/CT and/or biopsy of residual disease was assessed. OTS in pts with disease control was defined from time of last anti-PD1 dose to time of subsequent systemic therapy or death. **Results:** Of 96 pts, 44 received anti-PD1 and 52 received nivo-ipi. Median age 64 yrs, 62% male, 95% ECOG 0-1, 73% stage M1c, 37% BRAF mutant, 39% elevated LDH, and 28% brain metastasis. Overall RR was 34% for anti-PD1 and 63% for nivo-ipi. Another 25% and 6% of pts had stable disease, respectively. Median overall survival (OS) was not reached, although survival was significantly greater with nivo-ipi ($P = 0.007$). At 24 months, 80% of nivo-ipi pts were alive vs 51% anti-PD1 pts. 41 pts with disease control DC treatment for toxicity (n = 21) or pt/provider choice (n = 20). Of the latter, 17 pts DC treatment after one year for partial/complete response on CT scan (n = 4), negative PET/CT scan (n = 9), and positive PET/CT with negative biopsy (n = 4). 3 pts DC treatment after 2 years for positive PET/CT and negative biopsy. Median OTS was not reached for either group (91% and 77% were event free at 18 months); median follow up was 13.5 and 27.5 months, respectively. In the pt/provider choice group, 1 pt had progressive disease (PD) managed surgically and 1 pt died from non-melanoma causes; none received further systemic treatment. In the toxicity group, 4 pts had PD requiring further systemic therapy. **Conclusions:** In our experience, superior OS was seen with nivo-ipi over anti-PD-1 alone. OTS appears durable in pts with disease control if treatment DC due to toxicity or pt/provider decision. PET/CT and biopsy may be an effective strategy for safe DC of therapy after 1 year. Further prospective study is warranted.

9555 Poster Session (Board #382), Mon, 1:15 PM-4:45 PM

Impact of simultaneous radiotherapy in melanoma patients treated with pembrolizumab in the French early access program. *First Author: Philippe Saiag, General & Oncology Dermatology, CHU Ambroise Paré APHP & University of Versailles, Boulogne-Billancourt, France*

Background: Information on the use of radiotherapy in anti-PD-1 monoclonal antibody-treated melanoma pts is limited although some data support a synergistic effect. **Methods:** We investigated the influence of simultaneous radiotherapy in a multicenter ambispective cohort of advanced melanoma patients initiating pembrolizumab between May 2014-sept 2015 (CCTIRS, #15.640). Palliative or curative intent of radiotherapy was recorded. Overall (OS) and progression-free (PFS) survivals were analyzed using Kaplan-Meier survival analysis and Log rank tests were used to compare curves. **Results:** 663 pts (151 pts with brain metastases) were included in 40 French centers, with 125 pts (19%) receiving simultaneous radiotherapy (43 pts with $\geq$1 brain metastasis, 82 without). No significant difference in baseline LDH level, ECOG performance status, N of metastatic sites, previous treatment lines or post-progression therapies was observed between pts who did or did not receive radiation. As compared to pts without brain metastases, radiotherapy was performed in brain metastases pts closer to initiation of pembrolizumab (median 1.1 m vs 3.7 m, p = 0.009) and more frequently with a curative intent (72% vs 37%, $p < 0.001$). Globally, OS was longer in radiated vs non-radiated pts (median 18.9 m vs 12.5 m, HR:0.78, 95%CI: 0.57-0.96). This benefit was mainly driven by the pts with brain metastases (OS: median 26.0 m vs 6.0 m, HR:0.35, 95%CI:0.22-0.56, $p < 0.001$)(PFS: 6.4 m vs 2.5 m, HR:0.54, 95%CI:0.36-0.81, $p < 0.002$). No significant difference was seen for OS in radiated pts without brain metastasis, who were mainly radiated later and for palliative reasons and had shorter PFS (2.8 vs 3.4 m, HR 1.32, $P < 0.03$). **Conclusions:** Simultaneous radiotherapy may enhance efficacy of anti-PD1 therapy, particularly when initiated early and in brain metastases pts. Controlled studies are needed. Clinical trial information: 15.640.

9556 Poster Session (Board #383), Mon, 1:15 PM-4:45 PM

Survivorship experience for patients (pts) with metastatic melanoma (MM) on long-term targeted therapy (TT). *First Author: Chloe Chia Hoey Khoo, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: TT has improved survival for pts with MM. The lived experience for long-term responders remains under-studied. We characterised pt issues using a cross-sectional survey. **Methods:** Eligible pts had MM, aged > 18, $\geq$ 6 months post initiation of TT, and had a complete response. A 72-item survey including items from validated measures and custom questions covering physical and psychological effects, impact on lifestyle, access to information, satisfaction with care, and availability of support was administered. Impact of treatment duration ($\leq 12 / > 12$ months) on pt experience was assessed. **Results:** 36/42 (86%) pts responded from Aug-Dec 2017: median age 59 (range 30-84); 18 (50%) male; 21 (58%) had M1c disease; 34 (94%) were receiving TT as 1st line therapy. The majority (31, 86%) were still on treatment; most (22, 74%) had been on treatment for > 12 months. Long-term toxicities including fatigue (33, 92%), dry/itchy skin (25, 69%) and arthralgias (23, 64%) were common. Typical acute toxicities, such as fevers, rashes and gastrointestinal toxicities, were minimal. Psychological morbidity was high, including fear of cancer recurrence (31, 86%), concern regarding long-term toxicities (30, 83%), anxiety awaiting results (29, 81%), concern regarding ongoing sun exposure (28, 78%) and fear of death (26, 72%). The prevalence of both physical and psychological issues was higher among pts on treatment > 12 months, and persisted in 5 (14%) who ceased treatment. Patients reported difficulties with finances (19, 53%), undertaking recreational activities (23, 64%), and performing domestic tasks (14, 39%). Most would value screening for skin cancers (35, 97%), for other cancers (34, 94%), and a survivorship care plan (SCP) to guide management (34, 94%). **Conclusions:** Physical, psychological and functional issues exist in long-term responders to TT. These issues may increase with increasing duration on treatment. Pts may benefit from ongoing toxicity management, tailored psychological support and an SCP.

9557 Poster Session (Board #384), Mon, 1:15 PM-4:45 PM

Phase 1 study of cemiplimab, a human monoclonal anti-PD-1, in patients with unresectable locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC): Final efficacy and safety data. *First Author: Taofeek Kunle Owonikoko, Emory University, Atlanta, GA*

Background: Initial analysis of expansion cohorts (ECs) patients in a phase 1 study showed that cemiplimab (REGN2810) demonstrated a positive risk/benefit profile and produced antitumor activity in patients (pts) with advanced CSCC. We now report mature final data from the CSCC ECs of the phase 1 study (NCT02383212). **Methods:** Pts with distantly metastatic and locally advanced CSCC were enrolled in EC 7 and 8, respectively. All pts received cemiplimab 3 mg/kg by intravenous infusion over 30 minutes every 2 weeks for up to 48 weeks. Tumor measurements were performed every 8 weeks according to RECIST 1.1 to determine overall response rate (ORR; complete response [CR] + partial response [PR]). The data cutoff date was Oct 02, 2017. Tumor response was assessed by an independent central review committee. **Results:** A total of 26 pts were enrolled (21 M/ 5 F; 10 in EC 7, 16 in EC 8; median age: 72.5 years [range, 55–88]; ECOG performance status 1 in 16 pts and 0 in 10 pts). Median duration of cemiplimab exposure was 36.0 weeks. The most common treatment-related adverse event (TRAE) of any grade was fatigue (26.9%). The following $\geq$Grade 3 TRAEs occurred once: asthenia, maculopapular rash, increased alanine aminotransferase, increased aspartate aminotransferase, adrenal insufficiency, and myalgia. ORR was 50.0% (95% CI: 29.9–70.1); 0 CR and 13 PRs. Disease control rate (DCR; ORR + stable disease [SD] + non-CR + non-progressive disease [PD]) was 76.9% (95% CI: 56.4–91.0); 6 SD and 1 non-CR/non-PD. Durable DCR (SD/non-CR/non-PD or response for $\geq$105 days) was 65.4% (95% CI: 44.3–82.8). 3 pts were not evaluable for response. The median duration of response has not been reached; however, for pts with PR, the duration of response exceeded 6 months in 7 pts and 12 months in 2 pts. Median time to response was 2.3 months (range, 1.7–7.3). Median duration of follow-up was 11.0 months (range: 1.1–17.0). **Conclusions:** In this study, cemiplimab demonstrated a positive risk/benefit profile and produced substantial antitumor activity as well as durable responses in pts with advanced CSCC. Clinical trial information: NCT02383212.

9558 Poster Session (Board #385), Mon, 1:15 PM-4:45 PM

Chemoimmunotherapy combination after PD-1 inhibitor failure to improve clinical outcomes in metastatic melanoma patients. *First Author: Jesus Vera Aguilera, Mayo Clinic, Rochester, MN*

Background: Clinical management of metastatic melanoma (MM) after PD-1 blockade failure remains a challenge and lacks a standard of care. Chemo-immunotherapy (CIT) combinations have demonstrated favorable efficacy and safety profiles in lung cancer patients (pts). Our pre-clinical study has shown that in MM pts who have failed PD-1 blockade, the addition of chemotherapy can reshape a subset of tumor-reactive CD8+ T cells, resulting in enhanced anti-tumor immune responses. We conducted a retrospective study comparing the clinical outcomes of CIT with immunotherapy or chemotherapy alone after PD-1 blockade failure. **Methods:** We retrospectively reviewed MM pts seen at Mayo Clinic, Rochester between Jan, 2012 and Jun, 2017 who had failed anti-PD1 therapy. We identified 48 pts who received subsequent CIT (carboplatin/paclitaxel n = 22; temazolomide n = 1, nab-paclitaxel n = 1), or immune checkpoint inhibitors (ICI) or chemotherapy alone. The overall survival (OS), objective response rate (ORR), time-to-next therapy (TTNT), and toxicities were assessed between these groups. **Results:** Among the 48 pts, 24 received CIT after disease progression on PD-1 blockade. At median follow up of 3.9 years, pts who received CIT had a median OS of 5 years (95% CI: 2-NR) versus 1.8 years (95% CI: 0.9-2; p = 0.002) for those who received either ICI (n = 9) or chemotherapy alone (n = 15), with ORR of 61% versus 17% (p = 0.001), respectively. The median TTNT was 8 months (95% CI: 6-15) for CIT cohort versus 3.4 months (95% CI: 2.8-4; p = 0.004) for those who received ICI or chemotherapy alone. **Conclusions:** In MM pts who have failed anti-PD-1 therapy, the chemo-immunotherapy combination showed favorable clinical outcomes and acceptable toxicity profile. This regimen should be considered for MM pts in this setting who have limited treatment options.

	CIT (n = 24)	ICI or Chemotherapy Alone (n = 24)	p value
Age, median (range)	54 (30-77)	57 (21-77)	0.73
Male sex, n (%)	15 (62)	14 (58)	0.76
BRAF mutation, n (%)	10 (41)	9 (37)	0.76
Brain metastasis, n (%)	9 (37)	8 (33)	0.76
ORR, n (%)	14 (61)	4 (17)	**0.001**
Response, n (%)			
- CR	5 (22)	3 (12)	
- PR	9 (39)	1 (4)	
- SD	1 (4)	2 (8)	
- PD	8 (35)	18 (75)	
Grade ≥ 3 AE, n (%)	5 (20)	5 (20)	0.71

9559 Poster Session (Board #386), Mon, 1:15 PM-4:45 PM

Analysis of the kinetics and effects of vemurafenib (V) + cobimetinib (C) on intratumoral and host immunity in patients (pts) with BRAFV600 mutant melanoma (BRAFmM): Implications for combination with immunotherapy. *First Author: Suthee Rapisuwon, Georgetown University, Lombardi Comprehensive Cancer Center, Washington, DC*

Background: Prior studies in pts with BRAFmM have shown increased density of tumor infiltrating lymphocytes (TIL) at 2 weeks (wks) with BRAF +/- MEK inhibition(i), but did not fully characterize kinetics or functional state of the TIL. To better assess the impact of BRAFi +/- MEKi on the tumor microenvironment, we conducted a study to evaluate serial tumor biopsies (Bx) and blood through the first 4 wks of V+/-C therapy (Tx). **Methods:** Subjects with Bx-accessible BRAFmM received either V alone or V+C Tx. Staging CT scans were performed at baseline, wks 6, 12 and q12 weeks until PD or study withdrawal. Tumor Bx and heparinized blood samples were obtained at baseline, day (d) 8, 15, and 29. Bx samples were formalin-fixed paraffin-embedded (FFPE), frozen in OCT, and processed for TIL. PBMC and plasma were isolated from blood. FFPE slides were analyzed by quantitative immunofluorescence (QIF), NanoString 770 Immune Panel and TCRseq (Adaptive). Frozen tumors were analyzed for single cell (sc)RNAseq. TIL and PBMC were analyzed by flow cytometry. **Results:** 5 pts (4M/1F) with BRAFmM were enrolled (3 received V and 2 V+C). All had initial tumor response (2 CR, 3 PR) and subsequent PD. No unusual or G4-5 toxicities were observed. In 4 of 5 tumors, $CD8^+$ and $CD4^+$ TIL increased by d8 or d15 by QIF and NanoString, waning thereafter. %$CD4^+$ cells expressing $CD45RO^+$ decreased over time suggesting a dominance of naïve T cells in new infiltrates. No specific change in %$CD8^+$ TIL expression of $CD45RO^+$ was seen. NanoString showed no significant change in FoxP3, arginase or TGFB1 expression and no change in IFNG, granzyme B or Caspase 3. Other analyses are in process. **Conclusions:** BRAFi +/- MEKi leads to tumor T cell infiltration by d8 that peaks at d15. $CD4^+$ cells are increasingly antigen-inexperienced, while CD8 cells do not change. CD8 infiltrates are not accompanied by inflammatory or apoptotic response. Immune cell influx is not required for tumor response. The data suggest that T cell influx is not related to the generation of new anti-tumor immunity and that BRAF/MEKi Rx may, at best, augment an existing immune response rather than priming a new one. Clinical trial information: NCT01813214.

9560 Poster Session (Board #387), Mon, 1:15 PM-4:45 PM

Safety and preliminary activity data from a single center phase II study of triplet combination of nivolumab (N) with dabrafenib (D) and trametinib (T) [trident] in patients (Pts) with BRAF-mutated metastatic melanoma (MM). *First Author: Hussein Abdul-Hassan Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Targeted therapies and immunotherapies (IMTs) have each improved survival for pts with BRAF V600 mutated MM, however many still progress and ultimately die from this disease. New combinatorial approaches targeting known mechanisms of resistance are needed. Preclinical data demonstrates that BRAF inhibition (BRAFi) in BRAF-mutated tumors is associated with increased T cell tumor infiltration and enhanced responses with combined BRAFi and PD-1 blockade in murine models, supporting the rationale for a clinical combinatorial approach. We hypothesize that N + DT is safe and will demonstrate clinical activity in BRAF-mutated pts with MM. **Methods:** We are conducting a phase II study (NCT02910700) of NDT in pts with BRAF-mutated unresectable stage III or IV MM. Prior PD-1 therapy is allowed but prior BRAFi/MEKi treatment is excluded. Pts with brain metastases are allowed if untreated and asymptomatic or mildly symptomatic/requiring stable or decreasing steroids (up to 4 mg PO dexamethasone). Pts receive 3mg/kg Q2wks of N, 150mg BID of D and 2mg QD of T, all starting on Day 1 q28 days. This study is continuously monitored for safety and futility. The primary endpoint of the study is objective response rate (ORR). **Results:** 6 pts were enrolled onto the safety run-in phase of the study and no DLTs were experienced. The study continues to accrue; 14 pts have been treated with NDT to date. 3 pts discontinued therapy due to toxicity (gr 3 immune-mediated hepatitis at 12 wks, and immune-mediated nephritis after 8 and 10 mos of therapy, respectively). 11 pts have been assessed for response 10 have achieved a PR (ORR 91%), and 1 experienced PD. 6 of the 10 pts achieving PR received prior IMT, as did the pt experiencing PD. This study is currently being amended to allow a formalized evaluation of a separate cohort of pts with untreated brain metastases (n = 24). **Conclusions:** Treatment with NDT is well-tolerated at full doses and shows preliminary clinical activity. The combination warrants further evaluation in pts who have received prior immunotherapy and in patients with brain metastases. Clinical trial information: NCT02910700.

9561 Poster Session (Board #388), Mon, 1:15 PM-4:45 PM

Tumor mutational burden, clinical features, and outcomes to PD-1 mono- and combination therapy in patients with cutaneous and unknown primary melanoma. *First Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor mutational burden (TMB) in cutaneous and unknown primary (CUP) melanomas is associated with benefit to PD-1 monotherapy (mono), but the impact of TMB on nivolumab plus ipilimumab (combo) is not well established. Few TMB analyses have included standard clinical features in a multivariate analysis (MVA). **Methods:** All patients (pts) with CUP melanoma who underwent 340+ gene sequencing at Memorial Sloan Kettering Cancer Center and received PD-1 mono or combo as initial checkpoint inhibitor were analyzed. Somatic TMB/megabase (Mb), AJCC 8 stage, ECOG performance status (PS), sites of metastases (mets), lactate dehydrogenase (LDH) elevation, and neutrophil:lymphocyte ratio (NLR) > 4.73 were included in a Cox proportional hazards model and MVA built using backward selection. Overall survival (OS) and time to treatment failure (TTF), the interval until next therapy, clinical progression, or death, were calculated from PD-1 start. **Results:** 154 pts received PD-1 mono; median follow up was 11 months. 125 pts received combo; median follow up was 19 months. Pts receiving combo vs PD-1 mono were younger (median age 62 vs 71, $p < 0.001$) and had higher rate of elevated LDH (34% vs 18%, $p = 0.04$) and stage M1c/d (66% vs 41%). TMB did not vary by combo vs PD-1 mono (median 15.1 vs 18.4 mut/Mb, $p = 0.21$). Stage was associated with TTF and OS for PD-1 mono and combo (all $p < 0.03$). On MVA for PD-1 mono, TMB (hazard ratio [HR] 0.98; $p = 0.005$) and NLR > 4.73 (HR 2.16; $p = 0.002$) were associated with TTF; PS (ECOG 2+ vs 0, HR 9.86, $p < 0.001$; 1 vs 0, HR 2.59, $p = 0.03$) and LDH (HR 3.16, $p = 0.005$) were associated with poorer OS. TMB was not associated with TTF or OS for combo. On MVA for combo, brain (HR 2.64, $p = 0.004$) and bone mets (HR 2.28, $p = 0.008$) were associated with TTF; PS (ECOG 2+ vs 0, HR 5.37, $p = 0.009$), NLR > 4.73 (HR 2.27, $p = 0.037$), and bone mets (HR 2.86; $p = 0.014$) were associated with OS. **Conclusions:** For patients with cutaneous and unknown primary melanomas, TMB is associated with improved TTF in PD-1 mono but not combo. Performance status, NLR, and bone mets, but not TMB, are associated with OS in PD-1 combo. Models assessing clinical utility of TMB should also include established prognostic features.

9562 Poster Session (Board #389), Mon, 1:15 PM-4:45 PM

Association of body mass index (BMI) with overall survival (OS) in metastatic melanoma (MM) patients (pts) treated with combined anti-CTLA4 + anti-PD1. *First Author: Jennifer Leigh McQuade, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Obesity has recently been associated with improved outcomes in male, but not female, MM pts treated with single-agent anti-CTLA4 and with single-agent anti-PD1 immunotherapy. However, the association between BMI, sex, and outcomes in MM pts treated with combined anti-CTLA4 + anti-PD1 is unknown. **Methods:** We examined the association of WHO BMI category at treatment initiation with outcomes in an international, multi-institutional cohort of MM pts treated with anti-CTLA4 + anti-PD1. Kaplan-Meier analysis was used to estimate progression free survival (PFS) and OS. Associations between BMI, PFS, and OS were assessed in Cox proportional hazard models adjusted for age, sex, AJCC 8 stage, LDH, and performance status. **Results:** The cohort included 413 pts from 4 institutions. Median age was 57; 67% were male, 56% had ECOG PS > 0, 31% had elevated LDH, 46% had $BRAF^{V600}$ mutation. Clinical stage was 9% III, 12% M1a, 20% M1b, 40% M1c, 19% M1d. 75% of pts were overweight/obese (BMI$\geq$25), including 83% of males and 58% of females. In multivariable (MV) models, BMI was not associated with PFS (BMI$\geq$25 vs. BMI $<$ 25 HR 1.0, 95% CI 0.7-1.4) or OS (HR 1.0, 95% CI 0.6-1.7) in the full cohort. On sex-stratified MV analysis, BMI$\geq$25 was associated with shorter OS in females (HR 2.6, 95% CI 1.1-5.8); no significant association was detected in males (BMI$\geq$25 vs. BMI $<$ 25 HR 0.7, 95% CI 0.4-1.3; $p_{interaction} = 0.03$). BMI was not associated with PFS in either sex. Pts with higher BMI were more likely to have immune related adverse events (irAEs) leading to treatment discontinuation ($p = 0.03$); this association did not differ by sex. **Conclusions:** Higher BMI is associated with shorter OS in female MM pts treated with combined anti-CTLA4 + anti-PD1 immunotherapy. There was a significant interaction between BMI and sex, consistent with analyses of other cohorts. However, unlike observations in cohorts of MM pts treated with anti-PD1 or anti-CTLA alone, higher BMI was not associated with improved PFS or OS in males with combined anti-PD1 + anti-CTLA4. Rates of irAEs were higher in patients with higher BMI. Further studies should examine the basis for the observed associations.

9563 Poster Session (Board #390), Mon, 1:15 PM-4:45 PM

HORIZON: A French descriptive cohort of 663 patients treated for melanoma with pembrolizumab with a focus on the mucosal subgroup (n=59). *First Author: Caroline Dutriaux, Hôpital Saint-André,CHU Bordeaux, Bordeaux, France*

Background: Advanced mucosal melanoma is a rare subgroup of tumors for which few data on immune therapeutic approaches is available as they are rarely or not included in pivotal trials. Pembrolizumab, a monoclonal anti-PD1 antibody, has been approved in France as a first-line treatment of patients with advanced melanoma since October 2015. Although it has been shown to significantly improve OS and PFS of cutaneous melanoma, we have few data on its efficacy in mucosal melanoma. **Methods:** Horizon is a real-life setting descriptive cohort analysis of patients treated with pembrolizumab from June 2014 to September 2015 in the context of the French national early access program, at the dose of 2 mg/kg/3 weeks. Here are presented the results of the second interim analysis (data cut-off January 7th, 2017) in the mucosal melanoma subpopulation. **Results:** A total of 663 patients were included with a median follow-up of 12.95 months (95%CI: [11.15-16.16]). Among those patients, 59 (8,9%) had a primary mucosal melanoma. Twenty-two (37,3%) had no prior therapy. The median OS was 7.54 months (95%CI: [5.25-10.52]) versus 16.75 months (95%CI: [13.15-18.89]) in the non-mucosal melanoma population ($p < .0001$). The median PFS was 2.69 months (95%CI: [2.26-3.05]) versus 3.41 months (95%CI: [3.02-4.03]) in the non-mucosal group ($p < .0001$). The ORR was 11.9% (31.5% in the no- mucosal group), the DCR was 18.6% (44.2% in the non-mucosal group), and the median DR was 7.64 months (not reached in the non-mucosal group). Withdrawal of pembrolizumab was necessary for 47 patients (79,7%); the main reason for discontinuation was disease progression (68,1%), far ahead toxicity (14,9%) or complete remission (6,38%). Immune related adverse events were consistent with previous reports on pembrolizumab. **Conclusions:** Pembrolizumab provides objective activity in some mucosal melanoma patients, although less than that observed in the non-mucosal population. Anti-PD1 should be considered as a relevant treatment option for these patients. Nevertheless, further studies are warranted to describe underlying resistance mechanisms involved in order to improve management of this rare subgroup.

9564 Poster Session (Board #391), Mon, 1:15 PM-4:45 PM

Immune checkpoint inhibition (ICI) in advanced cutaneous squamous cell carcinoma (cSCC): Clinical response and correlative biomarker analysis. *First Author: Jong Chul Park, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: ICI has shown major benefit in cutaneous malignancies including melanoma and Merkel cell carcinoma. Efficacy data in cSCC is, however, limited. Here we report our institutional experience of anti-PD-1 therapy in patients (pts) with advanced cSCC, and biomarker analysis. **Methods:** We conducted a retrospective analysis of cSCC pts treated with nivolumab or pembrolizumab at Massachusetts General Hospital. NGS and IHC for PD-L1 expression and immune cell composition were performed, and correlation with response was analyzed. **Results:** 13 cSCC pts treated with ICI were identified, 7 of whom had predisposing conditions: CLL or other lymphoma (n = 3), xeroderma pigmentosum (n = 2), and Marjolin's ulcer (n = 2). 8 pts were treated with pembrolizumab and 5 with nivolumab. 9 pts (69%) had prior cytotoxic chemotherapy or cetuximab. At median follow-up of 16.5 months, 7 pts (62%) achieved objective responses with 2 complete responses. 4 pts had stable disease over 6 months and 2 had primary resistance. 12-month progression-free survival (PFS) and overall survival (OS) was 68.4 % and 83.3%, respectively. Median PFS and OS were not reached. Grade ≥ 3 adverse events were observed in 3 pts (23%), including 1 treatment-related death (myocarditis). Pre-treatment tissues were available for 11 pts. CD4, CD8 T cells and Tregs were present in variable frequencies and showed no association with response. PD-L1 expression in either tumor (TC) or immune cells (IC) was observed in most pts (78%). Mean TC and IC PD-L1 expression in responders vs nonresponders was 11.5 vs 0% and 5 vs 5%, respectively. TC but not IC PD-L1 expression correlated with response (cut-off 1%, $p = 0.04$). TP53, PIK3CA, DKN2A, and TERT promoter alterations were common. Tumor mutation burden analysis is underway, and its correlation to response will be analyzed. **Conclusions:** Our single institution "real-world" experience with anti-PD-1 therapy in advanced cSCC shows promising activity, including in pts who would not be eligible for clinical trial enrollment. PD-L1 expression was common and TC expression correlated with response. Further molecular analysis to identify potential predictive biomarkers is ongoing.

9566 Poster Session (Board #393), Mon, 1:15 PM-4:45 PM

Treatment of metastatic uveal melanoma (mUM) directed by a comprehensive molecular tumour analysis program (CMTA). *First Author: Serge Leyvraz, Charité Comprehensive Cancer Center, Berlin, Germany*

Background: There is a lack of active treatment against mUM. Such "hard-to-treat" tumour might benefit from treatment decisions driven by a complete genomic and transcriptomic analysis program. **Methods:** From 1.3.2016 to 1.12.2017, mUM were included in the prospective TREAT20Plus study and were subjected to a CMTA including WGS, WES, RNAseq, cell culture and systems biological/pharmacodynamic modelling. Treatment recommendations were made by a molecular tumour board. **Results:** Twenty six patients (12 F, 14M). Age: 61 (32-80). PS: 0 (0-2). Metastases: 4 (1-10). Abnormal LDH: 19. Pre-treatment: 1 (0-5) and type: iv chemotherapy: 11, checkpoint-inhibitors (-i): 7, intra-hepatic: 13, vaccine: 1. Insufficient material in 3 patients. The mutation burden was low: 32 (15-449). The treatment recommendations (TRec) were based on the different mutations or activation profiles: A) MEK-i. for mutations of *GNAQ*: 11, *GNA11*: 13. B) a MET-i. for MET overexpression: 17. ALK-i. for the oncogenic ALK^{ATI} isoform: 3. C) CDK4/6-i. for CDKN2A loss: 1. D) checkpoint-i. for mutation burden > 100: 3. E) For the other alterations no off-label treatment was available: mutation of *BAP1:* 8 or *SF3B1: 10,* overexpression of *MYC*: 14, *BCL2*: 24, *CCND2*: 16, *ERBB3*: 5 , biallelic loss of TNFAIP3: 1. Among novel non-recurring gene-fusions: inactivating gene fusion affecting MITF: 1. In 1 patient repeated biopsies at time of recurrence after MEK-i disclosed biallelic loss of *CDKN2A*. The pharmacodynamic modeling confirmed TREc in 10 and helped with the decision in 8 patients. A treatment was initiated in 15 patients: Trametinib: 6, Cabozantinib: 3, Crizotinib: 6, Palbociclib: 1. A treatment was not initiated for 8 patients: 4 too early, 4 rapid progression. Among the 12 evaluable patients the antitumor response was: minor response: 2, stable disease: 4, progressive disease: 5, too early: 1. Median PFS of the treated patients: 5,5 months. **Conclusions:** Precision medicine in mUM is clinically feasible. It leads to a better understanding of the biology of the tumour and of the potential therapeutic targets. Its clinical efficacy is limited by the non-availability of drugs as single agent or in combination. Clinical trial information: EA4/063/13.

9567 Poster Session (Board #394), Mon, 1:15 PM-4:45 PM

Adverse events of special interest in the phase 3 COLUMBUS study. *First Author: Helen Gogas, First Department of Medicine, Laiko General Hospital, National and Kapodistrian University of Athens School of Medicine, Athens, Greece*

Background: Combination BRAF/MEK inhibitor (BRAFi/MEKi) therapy is standard of care for *BRAF*V600-mutant metastatic melanoma. In COLUMBUS Part 1, encorafenib 450 mg once daily (QD) + binimetinib (BINI) 45 mg twice daily (BID) (COMBO450) reduced risk of progression or death vs encorafenib 300 mg QD (ENCO300) or vemurafenib 960 mg BID (VEM) in patients (pts) with advanced *BRAFV600*-mutant melanoma. Adverse events of special interest (AESIs) including pyrexia, serous retinopathy, photosensitivity, and rash are reported here. **Methods:** Pts were randomized 1:1:1 to receive COMBO450, ENCO300, or VEM. Pts had standard physical and laboratory assessments, and regular dermatologic, cardiac, and ophthalmologic evaluations. AESIs comprised known effects of available BRAFi and/or MEKi. **Results:** Safety was evaluated in 192, 192, and 186 pts in the COMBO450, ENCO300 and VEM arms, respectively. Median duration of exposure to treatment was 51 weeks for each component in the COMBO450 arm, 31 weeks in the ENCO300 arm, and 27 weeks in the VEM arm. Pyrexia incidence with COMBO450 was low (grade 1/2: 14%; grade 3: 4%) and led to treatment discontinuation in 1% of pts and to dose modification in 4%. Photosensitivity was infrequent with COMBO450 (grade 1/2: 4%; grade 3: 1%), required dose modification in 1% of cases, and did not lead to treatment discontinuation. Rash occurred in 22% of pts with COMBO450 (grade 1/2: 21%, grade 3: 1%, grade 4: 1%), led to discontinuation in 0.5%, and to dose modification in 2%. Serous retinopathy (grade 1/2: 17%; grade 3: 3%) and left ventricular dysfunction (grade 1/2: 6%; grade 3: 2%) with COMBO450 did not lead to discontinuation and were generally reversible (in 89% and 93% of pts, respectively). **Conclusions:** Common BRAFi/MEKi toxicities were generally manageable and reversible and were infrequently associated with treatment discontinuation. Pyrexia and photosensitivity were uncommon with COMBO450. The observed safety profile suggests COMBO450 may provide a meaningfully differentiated treatment option for patients with *BRAF*V600-mutant melanoma. SPONSOR: Array BioPharma Inc. Clinical trial information: NCT01909453.

9568 Poster Session (Board #395), Mon, 1:15 PM-4:45 PM

Multi-spatial whole-lesion molecular heterogeneity of an immunotherapy-resistant metastatic melanoma. *First Author: Akash Mitra, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Genomic and immune intratumor heterogeneity (ITH) can be a major reason for therapy failure in patients undergoing checkpoint blockade immunotherapy. Here, we report comprehensive molecular and immune analysis of a sequential anti-CTLA-4- and anti-PD-1-resistant metastatic lesion, sampled and reconstructed in 3D, combined with a longitudinal view of a pre-immunotherapy lesion. **Methods:** We performed 3D reconstruction of a metastasis obtained at palliative surgery from a patient progressing on sequential anti-CTLA-4 and anti-PD-1 therapy utilizing genomic (gene expression, methylation, whole exome sequencing and neoantigen prediction) and immune (immunohistochemistry, RNA- and DNA-based T cell receptor sequencing) profiling of 67 spatially distinct regions. **Results:** Limited point-mutation heterogeneity was found in melanoma driver genes however, copy number alteration analysis revealed changes over time and space with gain of chromosome 7 and 13, and loss of chromosome 10 in spatially-distinct regions. Differences in immune signatures were observed across regions of the tumor with pockets of immune activation and suppression. TCR profiling revealed dominance of three T cell clonotypes distributed across the tumor, highlighting spatial patterns in tumor immunogenicity and T cell response. Neoantigen prediction and expression indicated the persistence of a neoantigen detectable prior to anti-CTLA-4 therapy enriched in different regions of the post-anti-PD-1 tumor. Gene expression correlated with the distribution and dominance of a specific T cell subclone. **Conclusions:** 3D-reconstruction of a sequential immune checkpoint blockade treated progressing tumor shows marked spatially-distinct genomic and immune ITH in the setting of a relatively homogenous somatic gene mutation landscape. As immune markers move into the mainstream for use as biomarkers, the use of single biopsies to inform treatment choice may be confounding. These data further impress the need for comprehensive, integrated molecular phenotyping approaches to unravel immunotherapy response and resistance in metastatic melanoma.

9569 Poster Session (Board #396), Mon, 1:15 PM-4:45 PM

Immune checkpoint inhibitor (ICI) treatment in advanced melanoma (aMel) patients (pts) with renal or hepatic dysfunction (dysf): Real-world patient characteristics and outcomes. *First Author: Susan Spillane, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD*

Background: ICIs were approved for first line (1L) therapy in aMel. However, pts with renal or hepatic dysf are often excluded from clinical trials; little is known about usage or outcomes for these pts. **Methods:** We retrospectively analyzed de-identified real-world data aggregated by Flatiron Health from US community oncology practices. Pts had confirmed aMel, a documented order/administration of an ICI as 1L therapy from 1/1/11 to 12/1/17 and ≥1 hepatic or renal lab value up to 30 days before 1L start. Renal [serum creatinine (cr)] and hepatic [total bilirubin (Tbili), aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] function labs were graded by Common Terminology Criteria for Adverse Events v4.03. Dysf was defined as grade 2+. Categorical variables were assessed using Chi-square test; continuous variables with Kruskal-Wallis test; therapy duration and OS with log-rank test. **Results:** 1475 pts with relevant data were identified (Table). **Conclusions:** In this real-world aMel cohort, <3% of ICI-treated pts had baseline hepatic or renal dysf. Relative to pts with normal organ function, pts with baseline renal dysf were more often male and were more likely to be older. Although only hepatic dysf was significantly associated with shorter ICI duration, both renal and hepatic dysf pts had significantly shorter median OS. The OS findings may reflect competing risk from underlying comorbidities, practice patterns, tolerance (renal dysf), toxicity and/or ICI efficacy in the setting of organ dysf. Additional research is needed to better understand ICI treatment for real-world pts with baseline renal or hepatic dysf.

	Baseline					
	Renal			Hepatic		
	Normal N=1396	Dysf N=37 (2.6%)	*p-value*	Normal N=1272	Dysf N=31 (2.4%)	*p-value*
Demographics						
Male, %	67.5	87.0	.023	68.5	67.7	.999
Age, median years (IQR)	68 (58.0, 77.0)	78 (73.0, 81.0)	<.001	68 (58.0, 77.0)	64 (62.5, 75.0)	.940
ICI duration						
Median, days (IQR)	68 (43, 238)	64 (43, 107)	.178	69 (44, 231)	22 (1, 64)	<.001
OS						
Median, months (IQR)	20.8 (6.2, *)	7.9 (2.6, 18.2)	<.001	19.9 (6.0, *)	2.7 (1.1, *)	<.001

Normal = Grade 0-1; dysf = Grade 2-3, * = not observed

9570 Poster Session (Board #397), Mon, 1:15 PM-4:45 PM

Characterization and spatial localization of the tumor immune microenvironment in metastatic uveal melanoma. *First Author: Kimberly Mayumi Komatsubara, Columbia University Medical Center, New York, NY*

Background: Uveal melanoma (UM) is a rare subset of melanoma that is resistant to immune checkpoint blockade. High density of macrophages (Mϕ) and TILs is associated with poor prognosis in primary UM but little is known about the tumor microenvironment (TME) in metastatic UM (MUM). Here we performed quantitative spatial analysis using multiplex immunohistochemistry (mIHC) to characterize the TME in MUM, compare the TME of MUM to metastatic cutaneous melanoma (MCM), and identify potential mechanisms of MUM resistance to immunotherapy. **Methods:** We identified pts with untreated metastatic melanoma with clinical follow-up and available pre-treatment tissue who consented to an IRB-approved protocol. 5μm slides were stained using Opal mIHC for DAPI, CD3, CD8, CD68, HLA-DR, Ki67, and SOX10. Tumor areas were pre-selected by a dermatopathologist, visualized using Vectra and analyzed for density and spatial localization using inForm software. **Results:** 6 MUM and 8 MCM cases were evaluable at the time of this analysis. CD3+ and CD8+ T-cell density is similar between MUM and MCM, however, there is a trend towards a higher density of proliferating cytotoxic T lymphocytes (CTL) (CD8+Ki67+) in MCM ($p = 0.05$). Interestingly, CD68+ Mϕ density is lower in MUM compared to MCM ($p = 0.03$). Both CD68+HLA-DR+ Mϕ (activated) and CD68+HLA-DR- Mϕ (inactivated) density is lower in MUM. Using nearest neighbor spatial analysis, CD8+ CTLs are significantly farther from activated Mϕ (CD68+HLA-DR+) ($p = 0.01$), but not from inactivated Mϕ (CD68+HLA-DR-) in MUM compared to MCM. **Conclusions:** Unlike primary UM, our sample of untreated MUM is not characterized by a high Mϕ density. Fewer Mϕ are present in untreated MUM compared to MCM and activated Mϕ are located farther from CTLs in UM. Density of CTLs is similar in MUM and MCM, although proliferating CTL are more numerous in MCM. These preliminary results suggest that Mϕ may play a less prominent role in innate resistance to immunotherapy in MUM. Gene expression analysis and further classification of Mϕ type is ongoing. Additional cases are ongoing analysis and will be reported.

9571 Poster Session (Board #398), Mon, 1:15 PM-4:45 PM

Factors predicting the use of immunotherapy for patients with advanced melanoma. *First Author: Richard Wayne Joseph, Mayo Clinic, Jacksonville, FL*

Background: Both pembrolizumab (PEMBRO) and the combination of ipilimumab and nivolumab (IPI+NIVO) are approved by the US FDA for treatment of advanced (unresectable or metastatic) melanoma. Clinical trials have demonstrated different benefit-risk profiles associated with each that may impact selection in the real-world. We performed a retrospective chart review of patients with advanced melanoma to understand patient characteristics associated with PEMBRO vs IPI+NIVO treatment selection. **Methods:** A retrospective, chart-review study was conducted in the US; 12 oncologists from 12 US academic centers and affiliated satellite clinics were recruited to contribute patients ≥18 years of age with advanced melanoma receiving PEMBRO or IPI+NIVO in any line between Jan 1, 2016 – Dec 30, 2017. Demographics and baseline disease characteristics were compared between cohorts in univariate analysis. A mixed-effects logistic regression model with site of treatment specified as a random effect was created to predict PEMBRO vs IPI+NIVO selection using parameters identified in univariate analysis. **Results:** 400 patients were included, 200 each PEMBRO and IPI+NIVO. There were no significant differences in mean age, race, gender, family income, education level, insurance status, comorbidity index, site of metastasis, and line of therapy between the cohorts. However, the PEMBRO cohort had poorer Eastern Cooperative Group (ECOG) status at treatment start 70.5% ECOG 0 or 1 vs 88.0% ($p < 0.001$), were more likely to be PD-L1 positive (76.9% vs 63.1%, $p = 0.011$), and less likely to harbor a BRAF mutation (34.8% vs 49.7%, $p = 0.003$). In regression, PEMBRO was favored over IPI-NIVO in ECOG 2-3 patients vs 0-1 (OR 6.6, 95%CI 3.0, 14.7), and PD-L1 expression positive (OR 4.5, 95%CI 1.9, 10.4). Those with BRAF wild-type were more likely to receive PEMBRO (OR 2.2, 95%CI 1.4, 3.6) than IPI+NIVO. **Conclusions:** In the real-world, patient factors are significantly associated with treatment selection in advanced melanoma. PEMBRO appears to be selected more often than IPI+NIVO in patients with poorer ECOG performance status, PD-L1 positive tumors, BRAF wild-type tumors. Any real-world comparison of outcomes between treatments should take this into consideration.

9572 Poster Session (Board #399), Mon, 1:15 PM-4:45 PM

Perilesional edema and blood vessel characteristics in brain metastases and implications for treatment with immune therapy. *First Author: Thuy Tran, Yale-New Haven Smilow Hospital, New Haven, CT*

Background: Little is known about tumor-associated vasogenic edema in brain metastasis, yet it is the cause of significant morbidity and mortality. Our purpose was to better characterize edema and vessel leakage in humans treated with anti-PD1 and in pre-clinical models. We hypothesized that the etiology of tumor edema is multifactorial and not dependent on tumor volume mass effect alone. **Methods:** We analyzed tumor and edema volume in 18 non-small cell lung (NSCLC) and 18 melanoma patients with untreated brain metastasis treated with pembrolizumab. Cerebral melanoma tumors were stained with anti-CD34 to determine vessel density and the association with vascular leak. We employed an *in vitro* model of the blood-brain barrier using short term cultures from melanoma brain and extracranial metastases to determine tight junction resistance. **Results:** While larger tumors tended to have more edema, the correlation was weak (R^2= 0.30). Edema:tumor volume ratios are similar in NSCLC and melanoma brain metastasis and were not associated with response (P> 0.50), progression-free (P= 0.22), or overall survival (P= 0.17). Patients responding to pembrolizumab had concurrent shrinkage of edema volume (R^2= 0.81). Vessel density by CD34+ cell staining on brain metastasis samples was not correlated with perilesional edema on imaging. Melanoma brain metastasis cells in culture were able to cause decreases in tight junction resistance in an *in vitro* system, whereas cell cultures from extracerebral samples did not. **Conclusions:** Additional factors aside from tumor mass effect cause perilesional edema. Edema itself should not deter physicians from using PD-1 inhibitors; pembrolizumab-sensitive tumors tend to have decreases in both tumor volume and edema on treatment. Factors other than vessel density result in endovascular leak, and should be further studied. Moreover, melanoma cells themselves can cause vessel leakiness in an experimental system void of immune cells, suggesting they secrete properties that affect tight junctions, which might be harnessed for pharmacologic targeting.

9573 Poster Session (Board #400), Mon, 1:15 PM-4:45 PM

Effects of sonidegib dose reduction or delay in locally advanced basal cell carcinoma: 42-month data from BOLT. *First Author: Karl D. Lewis, University of Colorado Comprehensive Cancer Center, Aurora, CO*

Background: Sonidegib is a hedgehog pathway inhibitor (HPI) approved for the treatment of locally advanced basal cell carcinoma (laBCC) not amenable to curative surgery or radiotherapy. Patients treated with sonidegib may require dose reductions and/or interruptions to manage adverse events, and the impact of these adjustments on the long-term efficacy is unknown. **Methods:** BOLT was a randomized, double-blind, multicenter phase 2 study (NCT01327053). Patients with advanced BCC not amenable to curative surgery/radiotherapy and naive to HPI treatment were randomized 1:2 to sonidegib 200 mg or 800 mg QD, respectively. Data were analyzed at 6, 12, 18, 30, and 42 months. Patients receiving 800 mg were allowed two dose reductions (to 400 mg and 200 mg QD, respectively) for an adverse event (AE) related to sonidegib; among patients in the 200-mg arm, a delay was instituted until the AE resolved to ≤ grade 1. The primary endpoint was objective response rate (ORR) per central review; ORR by investigator review was analyzed as a secondary endpoint. We compared ORR in laBCC patients with (≥1) and without dose reduction/delay at the 42-month follow-up. **Results:** ORRs remained consistent with prior follow-up analyses. The frequency of dose reduction/delay was lower in the 200 mg (18%) vs. 800 mg (38%) arm (Table). Importantly, dose reduction/delay did not compromise efficacy. ORRs by investigator assessment were consistently higher than by central review. **Conclusions:** These data support long-term efficacy of sonidegib at the approved dose of 200 mg daily, and also suggest that dose reductions and/or treatment delays are possible without negatively impacting efficacy. Clinical trial information: NCT01327053.

ORR in sonidegib-treated patients by dose reduction/delay (central and investigator review).

	200 mg QD		800 mg QD	
ORR, % (95% CI)	**Central**	**Investigator**	**Central**	**Investigator**
All patients	n = 66		n = 128	
	56 (43, 68)	71 (59, 82)	46 (37, 55)	59 (50, 67)
No dose reduction or delay	n = 54		n = 80	
	57 (43, 71)	67 (53, 79)	34 (24, 45)	53 (41, 64)
≥1 dose reduction or delay	n = 12		n = 48	
	50 (21, 79)	92 (62, 100)	67 (52, 80)	69 (54, 81)

9574 Poster Session (Board #401), Mon, 1:15 PM-4:45 PM

Mutational and immune gene expression profiling at relapse in patients (pts) treated with adjuvant dabrafenib plus trametinib (D + T) or placebo (pbo) in the COMBI-AD trial. *First Author: Reinhard Dummer, University Hospital Zürich Skin Cancer Center, Zürich, Switzerland*

Background: In the COMBI-AD trial, adjuvant D + T resulted in a significant relapse-free survival benefit (HR, 0.47 [95% CI, 0.39-0.58]; $P < .001$) vs pbo in pts with resected stage III *BRAF* V600E/K–mutant melanoma. At a median follow-up of 2.8 y, 37% of pts in the D + T arm and 57% in the pbo arm had relapsed. Resistance mechanisms are largely unknown in the adjuvant setting. We report mutational and immune gene expression profiling at relapse in COMBI-AD. **Methods:** COMBI-AD (NCT01682083) randomized pts with resected stage III *BRAF* V600E/K–mutant melanoma to receive D + T or pbo. DNA and RNA were extracted from the same relapse sample. Mutational landscape and immune gene expression signature were examined by sequencing 570 genes (mean depth ≈ 500×) and gene expression profiling using a customized NanoString panel. Plasma samples were subjected to ctDNA profiling (73 genes). **Results:** At relapse, 66 tissue samples (D + T, n = 24 [n = 4 relapsed on treatment]; pbo, n = 42) were collected (20 distant, 43 local/regional, 3 secondary primary melanoma). Paired baseline samples were available in most cases (n = 57). A *BRAF* V600E/K mutation was detected in all relapse samples except in 1 secondary primary melanoma. The genomic landscape was as expected for melanoma: the most common non–*BRAF* V600 genetic aberrations were *CDKN2A* (38%), *CDKN2B* (24%), *PTEN* (23%), *TP53* (18%), and *ARID2* (14%), and median tumor mutation burden (TMB) was ≈ 10 SNVs/Mb. No substantial differences in mutation frequency, TMB, or *BRAF* copy number were noted in relapse vs baseline samples or between treatment arms. Putative genetic resistance mechanisms in the MAPK (eg, *MAP2K1*, *NRAS* mutations) and non-MAPK (eg, PI3K pathway mutations) pathways were found in a small subset of relapse samples from pts treated with D + T. No significant differences in T-cell–specific/immune gene expression signatures were observed between arms. **Conclusions:** Although mutations in MAPK and non-MAPK pathways were found in a few relapse samples, no uniform adaptations were observed, suggesting that resistance to adjuvant D + T is caused by various genetic/epigenetic mechanisms. Clinical trial information: NCT01682083.

9575 Poster Session (Board #402), Mon, 1:15 PM-4:45 PM

Gut microbiome and immunotherapy response in melanoma patients. *First Author: Brandilyn Peters, NYU School of Medicine, New York, NY*

Background: Treatment of melanoma with checkpoint blockade immunotherapy brings potential for long-term freedom from progression. However, responses to immunotherapy are heterogeneous, and improving outcomes remains a critical need. We explored whether gut microbiota may modulate response to immunotherapy. **Methods:** Stool was collected from 26 stage 3-4 melanoma patients at NYU Langone Health, prior to immunotherapy (Ipi, Nivo, Ipi+Nivo, or Pembro). We conducted 16S rRNA gene sequencing on Illumina MiSeq, followed by the QIIME2 Deblur workflow to characterize taxonomic composition. We examined bacterial community α- and β-diversity, and taxon abundance, in relation to time to disease progression, using survival methods and adjusting for age and sex. **Results:** During follow-up (range: 3-18 months), 12 patients progressed. Higher community diversity was marginally associated with lower risk of progression (Shannon index HR = 0.40; 95% CI = 0.14-1.17; p = 0.09). Overall community composition was also marginally associated with time to progression, according to the non-phylogenetic Jensen-Shannon Divergence (MiRKAT-S p = 0.07 with 1000 permutations), but not according to the phylogenetic weighted UniFrac distance (p = 0.26). Centered log ratio-transformed abundance of several bacterial taxa was related to risk of progression ($p < 0.05$), though small sample size limited detection of associations after false discovery rate adjustment (all $q > 0.44$). An operational taxonomic unit (OTU) within *Faecalibacterium prausnitzii* was associated with significant risk reduction (HR = 0.71; 95% CI = 0.57-0.88; p = 0.002), resulting in significance at higher taxonomic levels (*Faecalibacterium* genus and *F. prausnitzii* species, p = 0.02). Additionally, genus *Desulfovibrio* (HR = 1.24; 95% CI = 1.04-1.49; p = 0.02) and an OTU in *Ruminococcus gnavus* (HR = 1.49; 95% CI = 1.12-2.00; p = 0.007) were associated with increased progression risk. **Conclusions:** We observed that gut microbiome is associated with response to immunotherapy, suggestive that microbiome manipulation may improve immunotherapy outcomes. Forthcoming shotgun metagenome and metatranscriptome sequencing of these samples will further elucidate species and functions related to response.

9576 Poster Session (Board #403), Mon, 1:15 PM-4:45 PM

Validation of a prognostic 53-immune-gene panel in stage II/III melanoma. *First Author: Margaret Borgardus, Columbia University College of Physicians and Surgeons, New York, NY*

Background: Patients with resected stage II/III melanoma are at high risk of systemic metastasis and prognostic indices to stratify these patients for adjuvant immunotherapy. We previously defined and validated a 53-immune-gene panel predictive of non-progression (AUC = 0.787), recurrence free survival (RFS, $p < 0.001$) and disease specific survival ($p = 0.024$). Here, we present a second validation of the prognostic ability of this immune-gene panel in an independent cohort of 81 patients with stage II/III primary melanoma. **Methods:** Dermatopathology reports for 1349 melanoma patients seen at Columbia University Medical Center between 2001 and 2014 were queried to identify 81 patients with stage II-III primary melanoma with FFPE tissue and at least 24 months of clinical follow-up available. Presence of tumor was confirmed by a dermatopathologist, RNA was extracted from tissue, and expression of the 53-immune-gene panel was assessed using NanoString. Data was processed using nSolver software and prediction score calculated. **Results:** 81 patients with stage II-III primary melanoma were analyzed, of whom 61 were alive or had no evidence of disease at death and 20 died from melanoma. Of the 81 patients, 69 had progression data available, 22 patients had progression of disease, while 47 had non-progression. Prediction scores correlated with non-progression (AUC = 0.722). In the complete 81 patient cohort, the signature correlated with disease specific survival ($p = 0.008$) and overall survival ($p = 0.0007$). Over the course of follow up 36 patients died. Using median score as a cutoff, hazard ratio for death in the high risk group was 2.8 (95% CI 1.3-6.0). **Conclusions:** We validate in a second retrospective population the prognostic ability of our previously-identified 53-immune-gene panel in patients with stage II/III primary melanoma. The 53-gene panel may constitute a powerful clinical tool to aid in predicting disease course in melanoma and may allow for stratification of patients for adjuvant immunotherapy, facilitating rapid acquisition of significant survival statistics in clinical trials. Prospective retrospective (PRA) validation of the signature in samples collected as part of the E1697 trial of adjuvant interferon is planned.

9577 Poster Session (Board #404), Mon, 1:15 PM-4:45 PM

A multi-gene risk signature for improved identification of cutaneous squamous cell carcinoma (cSCC) patients with a high risk of recurrence. *First Author: Chrysalyne Schmults, Brigham & Women's Hospital, Boston, MA*

Background: cSCC is rivaled only by basal cell carcinoma as the most common cancer in the U.S. Though most cases are cured by excision, a subset recur and become incurable with number of deaths approximating melanoma (Karia et al., *JAAD*, 2012). Identifying the subset at risk of recurrence is critical for development of clinical trials in cSCC which has no FDA-approved treatments and very few phase II trials. Therefore, we set out to develop a gene expression-based biomarker associated with disease recurrence/metastasis in cSCC. **Methods:** According to an IRB approved multicenter protocol, 230 primary cSCC tumors were analyzed for mRNA expression of 73 candidate genes reported to be associated with cSCC metastasis. After quality filtering, 63 genes and 212 samples were included in the predictive model construction. Multiple machine learning algorithm approaches were applied with 75% of the specimens used for training and the remaining 25% used for validation. **Results:** Six genes demonstrated consistent expression across all samples tested and were used as controls to normalize expression values of the remaining genes. Eighteen genes were differentially expressed between recurrent and non-recurrent cases. Evaluation of the genes with multiple predictive modeling methods identified an optimal model that was 71% sensitive, 90% specific, had a 50% positive predictive value (PPV), and a 96% negative predictive value (NPV) for recurrence. **Conclusions:** This study developed a predictive model for risk of recurrence with a much higher PPV than staging criteria developed by Brigham and Women's Hospital and the American Joint Committee on Cancer (50% vs. approximately 24% and 18% respectively) while maintaining a high NPV (Karia et al., *JCO* 2014; Karia et al., *JAMA Dermatology*, 2017). Clinical application of such a prognostic test with a robust PPV (50% risk of recurrence) will enable identification of cSCC patients who may be appropriate for therapeutic intervention beyond surgical clearance (e.g. nodal staging and/or adjuvant radiation) and enrollment in clinical trials evaluating contemporary therapies.

9578 Poster Session (Board #405), Mon, 1:15 PM-4:45 PM

Time to treatment failure (TTF) as a potential clinical endpoint in real-world evidence (RWE) studies of melanoma. *First Author: Rajeshwari Sridhara, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Time to treatment failure (TTF) has been suggested as a practical clinical endpoint for studies of oncologic agents using real-world evidence (RWE). However, TTF is rarely studied as an endpoint in the clinical trial setting; thus, little is known about its association with commonly used endpoints such as progression-free survival (PFS) or overall survival (OS). **Methods:** All studies submitted to CDER as part of a marketing application between 2010 and 2016 for treatment of patients with advanced melanoma were considered. 11 phase 3, randomized, and active-controlled trials were included in this analysis; 3 studies had 3 arms, resulting in a total of 25 randomized arms. Therapeutic agents were categorized as chemotherapy (CT), single agent PD-1 inhibitors (PD1), all immunotherapy (IT), and targeted therapy (TT). Patient-level association between TTF and PFS or OS was determined using correlation coefficients (corr) for each trial and for each therapeutic category. Additionally, to determine associations of trial-level comparative efficacy measures, pair-wise analyses were performed of hazard ratios (HR) for TTF, PFS, and OS using a weighted linear regression model. **Results:** 6021 patients from 11 clinical trials were included in the analysis. Patient-level corr for each trial ranged from 0.62 to 0.93 for TTF and PFS and from 0.53 to 0.82 for TTF and OS. Corr between TTF and PFS, and TTF and OS by therapeutic category are listed in the Table below. Trial-level associations between TTF HR & PFS HR and TTF HR & OS HR in all patients were poor. However, in TT these associations were much stronger (TTF & PFS: $R^2 = 0.56$ and TTF & OS: $R^2 = 0.80$). **Conclusions:** Though these analyses indicate a clear association of TTF & PFS for all categories, the association of TTF & OS may only exist for a few therapeutic categories. Extension of this work to other disease types and therapeutic categories would benefit the discussion of clinical endpoints for RWE.

Therapeutic Category	N	mTTF	mPFS	mOS	Corr of TTF & PFS	Corr of TTF & OS
All patients	6021	5.1	5.1	18.7	0.80	0.60
CT	786	2.3	2.1	11.2	0.65	0.35
PD1	1354	8.4	6.2	28.2	0.86	0.67
IT	2937	3.2	3.5	18.7	0.79	0.58
TT	2298	7.5	7.4	19.8	0.79	0.72

9579 Poster Session (Board #406), Mon, 1:15 PM-4:45 PM

Blood-based multiplex kinase activity profiling as a predictive marker for clinical response to checkpoint blockade in advanced melanoma. *First Author: Daan Hurkmans, Erasmus Medical Center, Rotterdam, Netherlands*

Background: Prediction of clinical responses to checkpoint inhibitor therapies is urgently needed. Notably, a significant proportion of patients does not benefit from the treatment, agents are costly and may cause serious toxicity. The kinase activity of peripheral blood cells (PBMCs) may reflect biological mechanisms underlying response to immunotherapy. We hypothesized that kinase activity profiles from PBMCs may constitute a predictive marker for clinical response to CTLA4 and/or PD1 blockade immunotherapy in patients with advanced melanoma. **Methods:** In a multicenter effort, data were prospectively collected from 6 cohorts of anti-CTLA4- or anti-PD1-treated advanced melanoma patients (n = 138). Kinase activity profiles were generated by analyzing phosphorylation signatures of PBMC lysates on a peptide micro-array. The PamChip (PamGene, Netherlands) microarray comprises 144 different peptides derived from protein phosphorylation sites that are substrates for protein tyrosine kinases. Performance of the predictive model (PLS-DA) was estimated using cross-validation and described by correct classification rate (CCR). Analyses were based on binary grouping of best overall response (RECIST v1.1; CR/PR/SD vs PD) and early/late progression using PFS data (cut-off 140 days). **Results:** Predictive signatures were discovered for anti-CTLA4 in cohort 1 (anti-CTLA4; n = 10; CCR = 100%; 95%CI 69-100%) and confirmed in cohort 2 (anti-CTLA4; n = 28; CCR = 82%; 95%CI 63-94%), as well as for anti-PD1 in cohort 3 (anti-PD1; n = 17; CCR = 76%; 95%CI 50-93%), which was confirmed in cohort 4 (anti-PD1; n = 29; CCR = 72%; 95%CI 53-87%), cohort 5 (anti-PD1; n = 38; CCR = 75%; 95%CI 57-87%), and cohort 6 (anti-PD1; n = 16; non-evaluable due to the low number of responders). **Conclusions:** In advanced melanoma patients, kinase activity profiles of baseline PBMCs samples can predict the likelihood of response to anti-PD1 or anti-CTLA4 therapy. This assay may serve as a rapid and fast predictive liquid biomarker to stratify patients prior to treatment. Involvement of receptor tyrosine kinases underlying the mechanism are being further elucidated and a larger validation study is underway.

9580 Poster Session (Board #407), Mon, 1:15 PM-4:45 PM

Quantitative multiplex immunofluorescence (qmIF) and genomic evaluation of tumor microenvironment (TME) to identify candidate biomarkers in stage II/III melanoma. *First Author: Robyn Denise Gartrell, Columbia University Medical Center, New York, NY*

Background: Biomarkers are needed to risk stratify for adjuvant trials in early stage melanoma. Features of the immune infiltrate within the TME are hypothesized to be prognostic, but quantification methods are not standardized for clinical practice. Expression profiling of stage II/III melanoma shows that Th1 genes have prognostic value. Combination of genomic and qmIF analyses of the TME may identify prognostic immune biomarkers. **Methods:** We performed qmIF analysis on 104 primary melanoma tumors (stage II-III) diagnosed at Columbia University Medical Center from 2000-2012. Tissue was stained for DAPI (nuclei), CD3 (T cell), CD8 (cytotoxic T cell (CTL)), CD68 (Mj), SOX10 (tumor), HLA-DR (activation) and Ki67 (proliferation). Phenotyping was performed with inForm software. High/low density cut-offs were defined by Classification and Regression Tree Analysis (CART) and Receiver Operating Characteristic (ROC) curves. For 64 patients (pts), with known of cause of death, KM curves were calculated. mRNA expression analysis for 63 immune genes (NanoString) was performed on 44 of 64 pts for whom sufficient tissue was available. **Results:** On qmIF, we find that high CTL and low Mj infiltration, particularly when located in the stroma, correlates with disease specific survival (DSS) ($p = 0.004$ and $p < 0.001$, respectively). Of greatest significance, when combined, low stromal CTL/Mj ratio correlates with death from melanoma using ROC (AUC = 0.724, $p = 0.026$). By AUC cutoff, low CTL/Mj ratio predicts poor DSS ($p = 0.003$) and overall survival (OS) ($p = 0.008$). On multivariable cox analysis, low CTL/Mj was independently associated with DSS ($p = 0.002$) and OS ($p = 0.020$). Genomic analysis identified increased expression of CXCL9, CXCR3, CCL5 and CD37 in non-recurrent pts ($p < 0.050$ after bonferoni correction) which did not correlate with CTL/Mj ratio. **Conclusions:** Multiparameter phenotyping of stage II/III melanoma pts shows that stromal CTL/Mj ratio strongly correlates with survival. mRNA analysis shows that high Th1 gene expression correlates with non-recurrence. Combination of qmIF and mRNA analysis may be useful in stratifying pts to receive immunotherapy.

9581 Poster Session (Board #408), Mon, 1:15 PM-4:45 PM

Phylogenetic analysis of longitudinal melanoma samples to reveal convergent evolution and markers of immunotherapy resistance. *First Author: David Liu, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune checkpoint inhibitors (ICI) have revolutionized treatment in metastatic melanoma (MM), but progression occurs in the majority of patients (pts), and the evolution of resistance to immunotherapy in individual pts is not well characterized. **Methods:** Matched longitudinal tumor and germline samples from MM pts treated with ICI underwent whole exome sequencing (WES), bulk RNAseq, bisulfite sequencing, and multiplex immunofluorescence (IF) staining. Single nucleotide variants, small insertions and deletions, copy number alterations, tumor purity and ploidy, and tumor heterogeneity were inferred using standardized analytical pipelines. Phylogenetic analysis was conducted and validated using independent Bayesian clustering approaches. **Results:** 23 longitudinal tumor samples from a pt with delayed complete response to sequential ipilimumab and nivolumab were sequenced and analyzed. Samples spanned a three year time frame, from pre-treatment primary (n = 1), palliatively resected on-treatment lesions (n = 20), and escape lesions (n = 2, small bowel and brain) which appeared after a 2 year disease-free interval. Mutational load was similar (~500 somatic mutations per tumor) with 400 shared mutations, including driver mutations in *IDH1*, *MAP2K1*, *CTNNB1,* and *ARID2*. Phylogenetic analysis identified 5 melanoma lineages arising out of a common ancestor, with multiple spatially separated lineages co-existing in time. The escape lesions arose out of a lineage characterized by 15q arm loss (including *B2M*), with further acquisition of a genome doubling event as well as biallelic *CDKN2A* loss compared to earlier tumors within the lineage. Interestingly, biallelic *PTEN* loss was found across lineages and in 12/13 tumors after day 39 of therapy compared to 4/10 tumors prior ($p = 0.02$, Fisher's Exact), suggesting convergent evolution. Further analysis of tumor epigenetics, transcriptomics, functional proteomics, and IF is ongoing. **Conclusions:** Our results suggest that multiple mechanisms of immunotherapy resistance develop within the same pt. More broadly, phylogenetic analyses of longitudinal tumor samples may shed light on the clinical evolution of resistance.

9582 Poster Session (Board #409), Mon, 1:15 PM-4:45 PM

Impact of a gene expression profiling risk score and web-based melanoma outcome calculator on the precision of AJCC-based prognostic assessment. *First Author: Georg Brunner, NeraCare GmbH, Cologne, Germany*

Background: AJCC staging of primary cutaneous melanoma (CM), based on clinico-pathological criteria, is limited in its ability to provide a precise prognosis for all patients. To improve risk assessment, a prognostic eight-gene expression profiling (GEP) risk score was identified in CMs and adjacent stroma, predicting clinical outcome, independently of and synergistically with AJCC staging. For the same purpose, a web-based melanoma outcome calculator (MOC) was developed (www.CancerMath.net). This study evaluated single and combined prognostic performance of both tools in complementing AJCC-based prediction of melanoma-specific survival (MSS). **Methods:** Five-yr MSS probabilities were prognosticated by multivariate Cox models, including GEP score + AJCC parameters or MOC parameters. To assess prognostic improvement, the models were compared to each other and to a reference model based on AJCC parameters only (Breslow, ulceration, node status). Data analyses (n=529 CMs, AJCC stages IA-IIIC, median follow-up 65 months) had been pre-specified. **Results:** *GEP score and MOC both improved precision of 5-yr MSS prediction by AJCC* (sensitivity + specificity increased by GEP: 14%, $p<0.001$; by MOC: 11%, $p<0.001$, by GEP + MOC: 15%, $p<0.001$). Combining GEP score and MOC improved precision of 5-yr MSS prognosis by MOC alone (sensitivity + specificity increased by 3%, $p=0.006$). Kaplan-Meier estimates clearly indicated that precision of AJCC-based MSS prediction can be corrected by both tools ($p<0.001$ by logrank test), independently and synergistically (Table 1). **Conclusions:** GEP score (based on 125 CMs) and MOC (based on > 92.000 CMs) are independent and equivalent prognostic tools, which improve the precision of AJCC-based MSS prediction. Correction was highest when the tools were combined. GEP score is a prognostic parameter that complements AJCC staging as well as MOC.

Correction of AJCC-based 5-yr MSS prediction by the prognostic tools (kaplan-meier estimates).

Entire sample cohort		75%
Increase in MSS	GEP low risk	+6%
	MOC low risk	+6%
	GEP low risk + MOC low risk	**+10%**
Decrease in MSS	GEP high risk	-10%
	MOC high risk	-6%
	GEP high risk + MOC high risk	**-15%**

9583 Poster Session (Board #410), Mon, 1:15 PM-4:45 PM

Performance of a 31-gene expression profile melanoma test in clinically relevant clinicopathologic subgroups. *First Author: Brian Gastman, Cleveland Clinic, Cleveland, OH*

Background: Accurate assessment of risk for recurrence and metastasis and early identification of low-burden metastatic disease is of utmost importance for cutaneous melanoma (CM) patient care. Although CM staging has improved with the development of new inflection points to define risk, additional information for risk assessment is critical, particularly considering advances in effective adjuvant therapy. A 31-gene expression profile (GEP) test accurately predicts risk of recurrence and metastasis, classifying CM as Class 1 (1A lowest risk) or Class 2 (2B highest risk). Herein, we analyze its utility for risk stratification beyond traditional staging factors in clinically-relevant subgroups of CM patients. **Methods:** Using an IRB-approved protocol, CM specimens and clinical data were collected from 16 centers. 690 samples met the inclusion criteria of stage I-III disease with at least 5 years follow up or an event. Low-risk patients (stage I-IIA) by national guidelines and the subpopulation of patients with microscopic nodal disease (stage IIIA), were selected to test the association of clinical factors and GEP with patient outcomes. **Results:** GEP Class was a significant predictor of recurrence, distant metastasis, and melanoma-specific survival independent of thickness, ulceration, node-status, and mitotic rate using multivariate Cox regression ($p < 0.05$ all endpoints), and the only significant factor for stage I-IIA cases. Stage I-IIA patients with a GEP Class 2B test result had 5-year recurrence free survival (RFS), distant metastasis free survival (DMFS), and melanoma-specific survival (MSS) rates of 61, 76, and 86% compared with 96, 97, and 100% for Class 1A patients ($n = 393$ $p < 0.0001$). Stage IIIA patients also exhibit statistically significant RFS, DMFS, and MSS when comparing GEP-test class results ($n = 75$ $p < 0.05$ all endpoints). **Conclusions:** GEP class is a robust and independent predictor of metastasis risk that adds prognostic information to clinically-relevant subpopulations. Accordingly, GEP results add benefit to traditional staging factors and thus can be incorporated in clinical decision-making regarding follow-up, surveillance, and may inform adjuvant therapy decisions.

9584 Poster Session (Board #411), Mon, 1:15 PM-4:45 PM

Mutation burden in conjunction with MAPK-pathway mutation status as a prognostic biomarker of overall melanoma survival. *First Author: John Cadley, New York University Langone Health, New York, NY*

Background: The high tumor mutation burden (TMB) in melanoma triggers the increased presentation of neoantigens, which are required to elicit an immune response. As a result, TMB has been proposed as a potential biomarker of immunotherapy treatment (IT). It is highly plausible that immunogenicity is also likely to play a role in melanoma progression. Thus, we explored whether the TMB and neoantigen burden (NB) impact melanoma overall survival (OS), independent of IT treatment. **Methods:** Excluding all patients treated with IT, we used 356 metastatic melanomas from The Cancer Genome Atlas (TCGA), and designed discovery (N = 240 patients) and validation sets (N = 116 patients) by random sampling. For all samples, we calculated total TMB as the number of non-synonymous mutations detected in each sample. We have also calculated NB as a function of specific mutations and HLA-type. Using total TMB and NB separately, we assessed their impact on OS using Kaplan-Meier survival analysis. Finally, we repeated this analysis restricted to a subset of patients with MAPK-pathway mutations (N = 260). **Results:** We found that total TMB predicts better OS in both the discovery and validation sets (p = 2e-04, p = 5e-04, respectively). Patients with fewer than 125 mutations showed significantly worse survival, and this result was replicated by repeated sampling. Restricting the analysis to the patients with a mutation in the MAPK-pathway (BRAF or NRAS), using the same mutation cutoff, we demonstrated a significantly stronger association between total TMB and OS (p = 4e-07). As our final analysis, we determined that NB and total TMB are highly correlated (r^2 = 0.977), and a NB of fewer than 50 neoantigens associated with worse OS (p = 9e-07). **Conclusions:** We have shown that lower total TMB and NB is strongly associated with worse OS in melanoma patients. When restricted to tumors containing MAPK-pathway mutations, we found even greater significance, demonstrating the interdependence of specific mutation status (BRAF- or NRAS-positive), total TMB, and OS. Importantly, this result indicates the potential utility of TMB as a biomarker of melanoma prognosis, outside of the context of IT.

9585 Poster Session (Board #412), Mon, 1:15 PM-4:45 PM

Immune gene profiling of pretreatment tumor samples in "real-world" advanced melanoma patients treated with anti-PD-1 and/or anti-CTLA-4. *First Author: Elisa A. Rozeman, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The immune checkpoint inhibitors (CI) anti-CTLA-4 (ipilimumab [IPI]) and anti-PD-1 (pembrolizumab [PEM] and nivolumab [NIVO]) have improved survival in advanced melanoma patients (pts). Because of the range of upcoming new CI combinations, there is a need for biomarkers identifying pts who benefit from anti-PD-1 monotherapy. The NanoString T cell Inflammation Signature (TIS) is an 18-gene signature including IFN-γ responsive genes related to antigen presentation, chemokine expression, cytotoxic activity and adaptive immune resistance that are reflective of a pre-existing, but suppressed, adaptive immune response in the tumor. TIS was associated with positive treatment outcomes to PEM in advanced stage melanoma and other solid tumors (Ayers, JCI 2017). Here, we evaluate the TIS and other immune-related signatures in pre-treatment tumor samples obtained from "real world" pts treated with anti-PD-1 and/or IPI. **Methods:** RNA isolated from formalin fixed, paraffin embedded pre-treatment tumor samples from pts receiving either IPI, NIVO or PEM outside clinical trials at the Netherlands Cancer Institute were profiled with NanoString PanCancer gene expression panels. RNA samples from 97 pts treated with anti-PD-1 and 55 pts treated with IPI were profiled. Response to therapy was defined as an immune related CR or PR. **Results:** RNA profiling was of sufficient quality in 93 pts treated with anti-PD-1 (NIVO n = 17, PEM n = 76) and 51 pts treated with IPI. There was no significant difference in TIS between the different origins of the tumor samples. The TIS was associated with response in pts treated with IPI (p = 0.002) and first-line anti-PD-1 (p = 0.012). Pretreatment with IPI and/or targeted therapy abolished this significant association of the TIS and response to anti-PD-1 (p = 0.52), which also holds true for other signatures analyzed. **Conclusions:** Immune gene profiling by TIS is a valuable tool for response prediction in "real world" advanced melanoma pts treated with IPI and first-line anti-PD-1. Interestingly, this association was lost in pts treated with anti-PD-1 after targeted therapy or IPI. Validation of our observations in an independent cohort is required.

9586 Poster Session (Board #413), Mon, 1:15 PM-4:45 PM

Surveillance for melanoma (MEL): Results of a database study of stage I-III MEL. *First Author: Corey Rearick, University of Pittsburgh School of Medicine, Pittsburgh, PA*

Background: Optimal surveillance for MEL recurrence is elusive. While consensus guidelines agree on surveillance imaging for high-risk MEL, there is no consensus regarding optimal modality for surveillance and routine imaging surveillance is not recommended for stage IA-IIA MEL. We examined the utility of surveillance in stage I-III MEL. **Methods:** Patients (pts) at the University of Pittsburgh's Melanoma Program 1991-2011 were queried using a clinical database. Eligible pts had stage I-III MEL and underwent routine surveillance with clinical examination, chest x-rays (CXR). Minimum follow-up was 9 months (mos). CXR positivity was determined by primary review of attending radiologist report. Pt documentation was queried for information pertaining to relapse, details of advanced imaging, pathology and treatment. Primary endpoints were the incidence of pulmonary (pulm) and extra-pulm metastases. **Results:** 324 pts with 2,700 CXRs were identified, of whom 114 (35%) had stage I, 63 (20%) stage II, and 147 (45%) stage III MEL. Median duration of screening was 46 mos. During this period, pulm mets were identified in 11%, 25% and 26% of stage I, II and III MEL respectively. Of these, CXR was initially diagnostic in 85%, 81%, and 92% respectively. Incidence of extra-pulm mets was 8%, 24% and 29% for stage I-III MEL, in whom diagnosis was made on advanced imaging ordered to evaluate examination findings and/or pt symptoms. **Conclusions:** Incidence of pulm and extra-pulm mets in MEL increases by stage, and CXR reliably detects pulm mets, although a higher incidence of non-pulm mets in stage II-III pts diminishes the value of CXR for relapses overall. Our data suggests that routine CXR surveillance detects few relapses in high-risk stage II-III pts.

Melanoma mets by site/stage.

		Pulm (N/%)				
	Skin/LN (N/%)	Isolated	Total	Extra-pulm (N/%)	Any site (N/%)	Multiple sites (N/%)
Stage I	3 (3%)	2 (2%)	13 (11%)	9 (8%)	16 (14%)	4 (4%)
Stage II	7 (11%)	5 (8%)	16 (25%)	15 (24%)	23 (37%)	10 (16%)
Stage III	19 (13%)	19 (13%)	38 (26%)	42 (29%)	58 (39%)	25 (17%)
All Pts	29 (9%)	26 (8%)	67 (21%)	66 (20%)	97 (30%)	39 (12%)

9587 Poster Session (Board #414), Mon, 1:15 PM-4:45 PM

Comprehensive genomic profiling of metastatic cutaneous adnexal carcinomas to reveal multiple routes to targeted and immunotherapies. *First Author: Nicolas Girard, Institut Curie, Paris, France*

Background: Carcinomas that arise from the skin adnexae (Cutaneous Adnexal Carcinomas, CAC) may progress to refractory, metastatic disease. We queried whether comprehensive genomic profiling (CGP) of CAC could reveal genomic alterations (GA) that could guide the use of targeted and immune checkpoint inhibitor (ICPI) therapies. **Methods:** A total of 103 relapsed/refractory and metastatic CAC underwent CGP using 50 ng of DNA and a hybrid-capture, adaptor ligation-based next-generation sequencing assay to a median coverage depth of > 600X. Results were analyzed for all classes of GA and tumor mutational burden (TMB) was determined on up to 1.2 Mb of sequenced DNA; microsatellite instability (MSI) determined by principal components analysis of optimal homopolymer loci. **Results:** The 103 CAC included 56 (54%) sweat duct (SWCAC), 21 (20%) sebaceous (SBCAC), 5 (4%) hair shaft/follicle (HRCAC) and 20 (19%) not otherwise specified (NOS) samples (Table). The CAC subtypes had similar median age and male preponderance, except for HRCAC (Table). The CAC had a mean GA/tumor of 5.47 (range 4.33 to 6.90). In CAC overall, potentially targetable GA were in *PTEN*, *ERBB2*, *BRCA2*, *PTCH1*, *NF1* and *BRAF*. More than 20% of CAC had TMB of > 20 mut/Mb, indicating high potential for immunotherapies. Potential ICPI resistance-associated GA included *STK11* inactivating GA (4%) and *MDM2* amplification (2%). MSI-High status was found in 2% of CAC overall, and limited to the SBCAC cohort. **Conclusions:** CAC are a rare and heterogeneous group of epithelial malignancies for which CGP can uncover multiple routes to targeted therapies. The prevalence of high TMB predicts that ICPI could play a role in relapsed and refractory disease.

	All CAC (n = 103)	Sweat Duct (n = 56)	Sebaceous Gland (n = 21)	Hair Shaft (n = 6)	NOS (n = 20)
Median Age	67	71	64	31	64
Gender	35% F 65% M	36% F 64% M	29% F 71% M	82% F 18% M	25% F 75% M
Mean GA/tumor	5.47	4.95	6.90	4.33	5.60
GA in Targetable Genes	*PTEN* 10% *ERBB2* 9% *BRCA2* 8% *PTCH1* 8% *NF1* 7% *BRAF* 4%	*ERBB2* 8% *BRAF* 6% *BRCA2* 6% *PTCH1* 6%	*PTCH1* 14% *ERBB2* 5% *ROS1* 5% *MET* 5% *KIT* 5%		*ERBB2* 10% *EGFR* 10% *NF1* 10%
ICPI Relevant Genes	*STK11* 4% *PRMB1* 1% *MDM2* 2%	*STK11* 2%			*STK11* 10%
Median TMB	3.6	3.5	6.1	5.2	5.2
TMB ≥ 20 mut/MB	21%	20%	29%	18%	15%
MSI-High	2%	0%	11%	0%	0%

9588 Poster Session (Board #415), Mon, 1:15 PM-4:45 PM

Genetic aberrations in the CDK4 pathway and association with innate resistance to PD-1 blockade in acral melanoma. *First Author: Jiayi Yu, Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Collaborative Innovation Center for Cancer Medicine, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Beijing, China*

Background: PD-1 checkpoint blockade immunotherapy induces long durable responses in patients with advanced melanoma. However, only a minor subset of acral melanoma patients could gain benefit from it. In this study, we aim to explore factors that may influence innate sensitivity or resistance to anti-PD-1 therapy and screen drugable targets with potential to be combined with anti-PD-1 antibody monotherapy in acral melanoma. **Methods:** Whole exome sequencing (WES) and RNAseq analyses were performed in 13 biopsies from baseline lesions of advanced melanoma patients who were treated with anti-PD-1 antibody (JS001, Shanghai Junshi Biosciences, China). The copy number variations (CNV) of candidate genes were identified by TaqMan Copy Number Assay in an independent cohort. The effect of CDK4/6 inhibitors combined with anti-PD-1 antibody monotherapy was evaluated by PD-1 humanized mouse (C57BL/6-hPD-1) and patient-derived xenograft (PDX) models. **Results:** WES revealed parallel CNV amplifications in both the CR+PR and PD cohorts, such as 4q22.1, 10q23.32, 15q26.3, 22q13.1. However, several significant CNV amplifications notably only occurred in the PD cohort, such as 1q23.1, 5p15.33, 7p22.3, 11q13.3, 12q14.1, which harbor *Cdk4, Ccnd1, CARD11* and *mTOR* genes. The association between *Cdk4* or/and *Ccnd1* amplification with innate resistance to anti-PD-1 therapy was validated in 46 acral melanoma patients ($P < 0.01$). The CDK4/6 inhibitor treatment increased PD-L1 protein levels in primary acral melanoma cell line and PDX model. Moreover, CDK4/6 inhibitor augments the response to PD-1 blockade in PD-1 humanized mouse (C57BL/6-hPD-1) and PDX models. Tumor growth curves for each treatment group demonstrate the improved efficacy of combining PD-1 blockade with the CDK4/6 inhibitor ($P < 0.05$). **Conclusions:** In summary, we discovered the genetic aberrations in the CDK4 pathways were associated with innate resistance to anti-PD-1 therapy in patients with advanced acral melanoma. Moreover, our study provides evidence for the testing of CDK4/6 inhibitors combined with anti-PD-1 antibody monotherapy in acral melanoma.

9589 Poster Session (Board #416), Mon, 1:15 PM-4:45 PM

Phase III randomized, multicenter trial comparing high-dose IFN-a2b with temozolomide plus cisplatin as adjuvant therapy for resected mucosal melanoma. *First Author: Bin Lian, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Mucosal melanoma is rare and associated with extremely poor prognosis. Standard adjuvant therapy for mucosal melanoma has not been established. Based on the result of phase 2 trial which compared temozolomide-based chemotherapy, high-dose IFN-a2b (HDI) and observation, we compared HDI with temozolomide plus cisplatin as adjuvant therapy for resected mucosal melanoma in this phase 3 trial. **Methods:** In this multicenter, randomized, controlled, phase 3 trial, 204 patients of mucosal melanoma with stageI-III after completely resected were randomized 1:1 into two groups from Feb 2014 to Jun 2016: HDI group (101 patients, treated with i.v. 15×10^6U/m^2/d IFN-a2b on days 1 to 5 each week for 4 weeks, followed by s.c. 9×10^6U IFN-a2b three times per week for 48 weeks), and chemotherapy group (103 patients, per os 200 mg/m^2/d temozolomide on days 1 to 5 plus i.v. 75 mg/m^2 cisplatin divided into 3 days, which was repeated every 3 weeks for six cycles). The primary end point was relapse-free survival (RFS), Secondary end points included distant metastasis-free survival (DMFS), overall survival (OS), and safety. **Results:** At a median follow-up of 23.7 months, the median RFS was 15.53 months (95% CI, 11.37-19.69m) in the chemotherapy group, as compared with 9.47 months (95% CI, 8.49-10.45m) in the HDI group (HR for relapse, 0.56; 95% CI, 0.40 to 0.77; $P < 0.001$). The median DMFS was 16.80 months (95% CI, 9.35-24.25m) in the chemotherapy group, as compared with 9.57 months (95% CI, 7.46-11.67m) in the HDI group (HR for metastasis, 0.53; 95% CI, 0.38 to 0.74; $P < 0.001$). Estimated median OS for chemotherapy group and HDI group was 41.20, 35.73 months ($P = 0.083$). Toxicities were generally mild to moderate in two groups. **Conclusions:** Adjuvant chemotherapy with temozolomide plus cisplatin resulted in a significantly lower risk of relapse and metastasis in resected mucosal melanoma than high-dose IFN-a2b and was not associated with seriously toxic effects. Clinical trial information: BCHMMAT001.

9590 Poster Session (Board #417), Mon, 1:15 PM-4:45 PM

Effect on health-related quality of life (HRQOL) of adjuvant treatment (tx) with dabrafenib plus trametinib (D + T) in patients (pts) with resected stage III *BRAF*-mutant melanoma. *First Author: Dirk Schadendorf, University Hospital Essen, Essen, Germany*

Background: Adjuvant tx of resected stage III *BRAF*-mutant melanoma with D + T significantly reduced risk of recurrence vs placebo (pbo). In the COMBI-AD study, 1-y tx with D + T resulted in improvements in relapse-free survival, distant metastasis–free survival, freedom from relapse, and overall survival. The effect of D + T on HRQOL in the adjuvant setting is reported here. **Methods:** COMBI-AD (NCT01682083) was a randomized, double-blind, phase 3 study evaluating pts with resected stage III *BRAF* V600E/K–mutant melanoma. Pts were randomized 1:1 to receive D 150 mg twice daily plus T 2 mg once daily or matching pbo for 12 mo. HRQOL assessment using the EuroQol-5D (EQ-5D-3L) questionnaire and visual analogue scale (VAS) was an exploratory endpoint. A mixed-model, repeated-measures analysis was used to assess differences in mean scores. **Results:** A total of 870 pts were randomized (D + T, n = 438; pbo, n = 432). Although pts available for assessment declined during study primarily due to consent withdrawal, missed scheduled visits, and deaths, completion rates among available pts were high (98% at baseline [BL], ≥ 90% throughout the 12-mo tx period, and ≥ 75% at assessments after 12 mo). Pts in both arms had similar BL VAS values (D + T, 79.0; Pbo, 80.4 [0-100 scale]). During tx (3- to 12-mo assessments), VAS scores remained similar to BL, with no clinically meaningful differences observed between arms (adjusted mean change from BL at 12 mo: D + T, 0.14; pbo, −0.02). In the D + T arm, no clinically meaningful or statistically significant difference in VAS was reported between pts who did and did not experience pyrexia ($P > .1$). During follow-up (15-48 mo), VAS scores were similar between arms, with no significant or clinically meaningful differences reported. At relapse, a statistically significant reduction in VAS score was observed in both arms (mean difference [pre- vs postrecurrence], D + T, −6.02, $P = .003$; pbo, −6.84, $P < .001$). **Conclusions:** In the absence of disease-related symptoms in the adjuvant setting, these results demonstrate that D + T do not negatively impact HRQOL during tx or in long-term follow-up and further emphasize the importance to pt HRQOL of preventing relapse. Clinical trial information: NCT01682083.

9591 Poster Session (Board #418), Mon, 1:15 PM-4:45 PM

Dabrafenib plus trametinib (D + T) as adjuvant treatment of resected *BRAF*-mutant stage III melanoma: Findings from the COMBI-AD trial analyzed based on AJCC 8 classification. *First Author: James M. G. Larkin, Royal Marsden NHS Foundation Trust, London, United Kingdom*

Background: The COMBI-AD trial demonstrated that adjuvant treatment with D + T in patients (pts) with resected stage III *BRAF*-mutant melanoma significantly reduced the risk of melanoma recurrence vs placebo (pbo). Pts were stratified based on the AJCC 7 disease stage classification. We present efficacy results from COMBI-AD based on the updated AJCC 8 staging classification. **Methods:** COMBI-AD (NCT01682083) is a randomized, double-blind, pbo-controlled, phase 3 study evaluating pts with stage III *BRAF* V600E/K–mutant melanoma without prior anticancer therapy. Pts were randomized 1:1 within 12 weeks of complete resection to receive D 150 mg twice daily plus T 2 mg once daily or matching pbos for 12 months. The primary endpoint was relapse-free survival (RFS). Pts were stratified by disease stage (stages IIIA, IIIB, and IIIC) based on AJCC 7 criteria. This post hoc subgroup analysis evaluated RFS in pts by disease stage based on AJCC 8 (stages IIIA, IIIB, IIIC, and IIID). **Results:** 870 pts were randomized (D + T, n = 438; pbo, n = 432). Pts were recategorized per AJCC 8 into stages IIIA (D + T, n = 50; pbo, n = 39), IIIB (D + T, n = 145; pbo, n = 154), IIIC (D + T, n = 217; pbo, n = 214), and IIID (D + T, n = 22; pbo, n = 17). RFS benefit with D + T over pbo was observed regardless of disease stage (stage IIIA: HR, 0.46 [95% CI, 0.17-1.21]; stage IIIB: HR, 0.46 [95% CI, 0.33-0.65]; stage IIIC: HR, 0.49 [95% CI, 0.38-0.64]), with the largest benefit observed in higher-risk stage IIID pts (HR, 0.34 [95% CI, 0.15-0.80]). When stage IIIB and IIIC subgroups were combined, the HR for RFS (D + T vs pbo) was the same (0.48) regardless of the AJCC classification used. Three-year RFS rates favored pts in the D + T vs pbo arm across all disease stages: IIIA, 83% vs 70%; IIIB, 63% vs 43%; IIIC, 52% vs 33%; and IIID, 40% vs 18%. RFS rates were similar in D + T and pbo arms in pts with stages IIIA, IIIB, and IIIC disease whether classified by AJCC 7 or 8. **Conclusions:** The RFS benefit observed with D + T vs pbo in pts with resected *BRAF* V600E/K–mutant melanoma was similar across all stages and was maintained when reclassified by AJCC 8 compared with the original AJCC 7 classification. Clinical trial information: NCT01682083.

9592 Poster Session (Board #419), Mon, 1:15 PM-4:45 PM

Liver-directed treatment for patients with uveal melanoma hepatic metastasis: A retrospective analysis of overall survival. *First Author: Rino S Seedor, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA*

Background: Despite successful treatment of primary uveal melanomas, up to 50% of patients subsequently develop systemic metastasis, with the liver involved in up to 90% of patients. At our institution, recognition of the poor prognosis associated with liver metastasis has led to the use of various liver-directed treatment modalities including transarterial chemoembolization (TACE) with BCNU, drug-eluting beads with doxorubicin (DEBDOX), immunoembolization (IE) with GM-CSF, and radioembolization with Yttrium 90 radioactive microspheres. The purpose of this study is to compare overall survival between uveal melanoma patients with hepatic metastasis before and after the shift of initial treatment from systemic to liver-directed approaches. **Methods:** A retrospective single-institution chart review was performed on consecutive series of uveal melanoma patients with hepatic metastasis who were treated at Thomas Jefferson University between 1971–1993 (Cohort 1, n = 98) and 2000–2017 (Cohort 2, n = 634). The following data was collected from medical records: primary tumor stage and genetic abnormalities, primary eye treatment, date to hepatic and extra-hepatic metastasis, types of liver-directed and systemic treatments utilized, and date of death. Time from development of hepatic metastasis to death (OS-Liver) and time from initial treatment of primary uveal melanoma to death (OS-Eye) in individual cohorts were measured and analyzed. **Results:** 81% of cohort 1 patients received systemic chemotherapy as their initial treatment for liver metastasis, while 91% of cohort 2 patients (n = 574) initially received liver-directed treatments including IE (n = 296), BCNU TACE (n = 147), DEBDOX (n = 45), radioembolization (n = 37), and other liver-directed treatments (n = 49). OS-Liver in cohort 1 and cohort 2 was 4.8 months and 16.4 months, respectively ($P < 0.001$). More importantly, OS-Eye in cohort 2 (5.1 years) is much longer than that of cohort 1 (3.3 years) ($P < 0.001$). **Conclusions:** Liver-directed treatments provided significant survival benefit for uveal melanoma patients with hepatic metastasis.

9593 Poster Session (Board #420), Mon, 1:15 PM-4:45 PM

Indirect treatment comparison of nivolumab versus placebo as an adjuvant therapy for resected melanoma. *First Author: Alexander Noor Shoushtari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There are no randomized trials of nivolumab and placebo as adjuvant therapy in patients with resected melanoma. This study uses pooled data from CheckMate 238 and EORTC 18071 to evaluate the number of patients needed to treat (NNT) based on recurrence-free survival (RFS) for nivolumab vs. placebo and nivolumab vs. ipilimumab over 12 and 18 months. **Methods:** Patients with stage IIIB or IIIC cutaneous melanoma from the two trials were pooled using propensity score weighting. The following characteristics were adjusted for: age, gender, race, ECOG, time from resection, disease stage, presence of tumor ulceration, lymph node involvement (microscopic vs. macroscopic), baseline LDH, and pretreatment events. The NNTs to achieve one additional recurrence-free survivor for nivolumab compared to placebo and ipilimumab were calculated as the reciprocal of the difference of the weighted RFS rates between treatments at month 12 and month 18. **Results:** After adjustment, baseline characteristics were balanced between the two trials. 1,286 patients with stage IIIB and IIIC cutaneous melanoma treated with nivolumab (N = 277), ipilimumab (N = 644), and placebo (N = 365) were included in the study. After weighting, the RFS rates of nivolumab, ipilimumab, and placebo were 74.2%, 61.9%, and 48.7% at 12 months and 70.7%, 54.1%, and 41.8% at 18 months, respectively. At month 12, NNT to achieve one additional recurrence-free survivor of nivolumab vs. placebo was 3.9 (95% CI: 3.0, 5.6) and nivolumab vs. ipilimumab was 8.1 (95% CI: 5.2, 18.7). At month 18, NNT to achieve one additional recurrence-free survivor decreased for both nivolumab vs. placebo (3.5; 2.7, 4.7) and nivolumab vs. ipilimumab (6.0; 4.2, 10.8). **Conclusions:** In patients with resected stage IIIB and IIIC cutaneous melanoma, adjuvant nivolumab was associated with the highest RFS rates compared to placebo and ipilimumab. To prevent one recurrence/death at 12 months, 4 patients would need to be treated with nivolumab instead of observation. With longer follow-up, the number needed to be treated to prevent one recurrence/death decreased, suggesting the magnitude of the clinical benefit may become more prominent over time. Clinical trial information: NCT02388906 and NCT00636168.

9594 Poster Session (Board #421), Mon, 1:15 PM-4:45 PM

Assessing the value of nivolumab (NIVO) versus placebo (PBO) and ipilimumab (IPI) as adjuvant therapy for resected melanoma. *First Author: Morganna Louise Freeman, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: Healthcare value frameworks consider the clinical benefits in the context of cost when assessing the value of cancer therapies. Here, we assess the cost per recurrence-free life month (RFLM) and associated drug and medical services costs using pooled data from CheckMate 238 and EORTC 18071 for NIVO compared to PBO and IPI as adjuvant therapies in patients with resected melanoma. **Methods:** Patients with stage IIIB or IIIC cutaneous melanoma were pooled using propensity score weighting, adjusting for baseline characteristics. For each treatment, RFLMs within 12 and 18 months were calculated as the area under the weighted Kaplan-Meier curve of RFS. Drug acquisition costs and medical service costs were calculated. No drug costs were considered for PBO. Cost per RFLM was calculated by dividing costs per patient by mean duration of RFLMs. **Results:** 1,286 patients were included in the analysis. After adjustment, baseline characteristics were balanced between the two trials. Overall, the mean duration of RFLM was highest for NIVO vs. both IPI and PBO. NIVO had lower mean drug cost vs. IPI, and lower mean medical cost vs. both PBO and IPI, attributed to lower hospitalizations. **Conclusions:** In patients with resected stage IIIB and IIIC cutaneous melanoma, adjuvant NIVO provides lower medical cost per RFLM due to longer recurrence-free periods and savings in medical costs compared to PBO and IPI over 1 year. The value of RFLM with NIVO continues to evolve over time compared to IPI and PBO, with improvement in drug costs per RFLM over 18 months compared to IPI. Longer term follow-up and consideration of subsequent therapies will further characterize the cost-effectiveness of adjuvant NIVO.

Outcome measures	NIVO 3 mg/kg n = 277	IPI 10 mg/kg n = 644	PBO n = 365
Mean duration of RFLMs			
Within 12 mo	10.2	9.3	8.1
Within 18 mo	14.5	12.8	10.8
Mean drug cost			
Within 12 mo	$133,213	$488,048	$0
Within 18 mo	$133,229	$538,193	$0
Mean medical costs (within 12 mo)	$4,494	$12,585	$5,411
Hospitalization	$3,960	$11,738	$4,986
Emergency room	$14	$25	$3
Outpatient	$514	$813	$420
Home health care	$6	$9	$2
Mean drug cost per RFLM			
Within 12 mo	$13,091	$52,577	$0
Within 18 mo	$9,192	$40,371	$0
Mean medical cost RFLM (within 12 mo)	$442	$1,356	$664

TPS9595 Poster Session (Board #422a), Mon, 1:15 PM-4:45 PM

A phase 2, multicenter study to assess the efficacy and safety of autologous tumor-infiltrating lymphocytes (LN-144) for the treatment of patients with metastatic melanoma. *First Author: Amod Sarnaik, Moffitt Cancer Center, Tampa, FL*

Background: Adoptive cell therapy utilizing tumor-infiltrating lymphocytes (TIL) is recognized as an effective treatment in metastatic melanoma and other solid tumors elliciting durable and complete responses, even in heavily pretreated patients. Despite recent approvals of multiple checkpoint-directed therapies there remains an unmet need to improve therapeutic outcomes in patients with metastatic melanoma post checkpoint therapy. The C-144-01 study is evaluating TIL therapy with LN-144 in metastatic melanoma patients who have progressed on prior checkpoint-targeted therapy. C-144-01 is a phase 2 multicenter, open-label study enrolling patients in the US and Europe. LN-144 is manufactured at centralized GMP facilities providing either a non-cryopreserved (Gen 1), or a second generation cryopreserved (Gen 2) TIL infusion product. The Gen 2 process reduces manufacturing time for LN-144 to 22 days, allowing for dramatic efficiencies in scheduling, distribution and delivery needed for commercial use. **Methods:** Three treatment cohorts are being evaluated: Cohort 1 (N = 30) patients receive a single dose of Gen 1 LN-144; Cohort 2 (N = 30) patients receive a single dose of Gen 2 LN-144; and up to 10 eligible patients from either Cohort 1 or Cohort 2 may enroll in Cohort 3 for re-treatment with a second dose of LN-144. For patients in all cohorts, TIL for LN-144 manufacturing are extracted from surgically-resected tumors. LN-144 infusion is preceded by a non-myeloablative lymphodepletion regimen of Cy/Flu, and followed by up to 6 infusions of IV IL-2. Patients $\geq$ 18 years of age must have confirmed stage IIIc/IV met. melanoma and have progressed following $\geq$1 line of prior systemic therapy including an immune checkpoint inhibitor and BRAF-targeted therapy (if BRAF mutation-positive). Other major eligibility criteria include: minimum of 2 tumor lesions; adequate organ function; ECOG PS of 0 or 1. The primary endpoint is the evaluation of efficacy of LN-144 using ORR per RECIST 1.1; secondary endpoints are CR rate, DOR, DCR, PFS, OS, and safety. Key exploratory objectives include tumor response per irRECIST, immune correlates of response, and HRQoL. Clinical trial information: NCT02360579.

TPS9596 Poster Session (Board #422b), Mon, 1:15 PM-4:45 PM

Phase I/II study of the PI3Kβ inhibitor GSK2636771 in combination with pembrolizumab (P) in patients (pts) with PD-1 refractory metastatic melanoma (MM) and PTEN loss. *First Author: Hussein Abdul-Hassan Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint blockade (ICB) improves overall survival and provides long-term disease control in 35-40% of pts with MM. However, more than a third of pts experience no clinical benefit (de novo resistance) and many progress even after achieving an initial response (acquired resistance). Our group has demonstrated that increased activation of phosphatidylinositol 3-kinase (PI3K) pathway, most commonly through loss of the tumor suppressor gene PTEN, plays a critical role in resistance to ICB. PTEN loss occurs in up to 30% of MM pts and correlates with decreased T cell infiltration and inferior outcomes to ICB. In preclinical models, we showed that loss of PTEN inhibits T cell mediated tumor killing and decreases T cell trafficking into tumors, and that selective inhibition of the PI3Kβ-subunit with GSK2636771 was superior to pan-PI3K inhibitors and significantly increased the activity of ICB, and the number of infiltrating CD4+ and CD8+ T cells. We therefore hypothesized that PI3Kβi will reverse resistance to ICB in MM with PTEN-loss. To test this hypothesis, we are conducting a Phase I/II study of the PI3Kβ inhibitor GSK2636771 in combination with P in pts with PD-1 refractory MM and PTEN loss. **Methods:** The primary objective of the Phase I portion is to determine the safety and Maximum-Tolerated Dose (MTD) and/or the Recommended Phase II Dose (RP2D) of GSK2636771 in combination with P in pts with PD-1 refractory disease and PTEN loss. Pts will be treated with P given at 200 mg IV q 3-wk cycle. GSK2636771 will be given orally starting at a dose level of 300 mg PO qd for 21 days and escalated to a maximum dose of 400 mg PO qd using a "3+3" design. The Phase II portion will enroll a total of 35 pts at the MTD/RP2D. Continuous monitoring for both toxicity and futility will be assessed. The primary objective of the Phase II portion is to determine the safety, tolerability, and efficacy of the combination as defined by Objective Response Rate (ORR) by RECIST 1.1 in MM with PTEN loss. Secondary Objectives include the PKs of GSK2636771 and correlation with ORR and pharmacodynamic effects in tumor tissue as measured by pathway inhibition and T cell trafficking into tumors. Clinical trial information: NCT03131908.

TPS9597 Poster Session (Board #423a), Mon, 1:15 PM-4:45 PM

Combining ipilimumab (ipi) and nivolumab (nivo) in advanced melanoma following progression on a PD-1 inhibitor (SWOG S1616). *First Author: Ari M. Vanderwalde, Division of Hematology/Oncology, The University of Tennessee Health Science Center, West Cancer Center, Germantown, TN*

Background: We hypothesize that patients with advanced melanoma who progress on anti-PD-1 therapy upfront may respond to the addition of the CTLA-4 inhibitor ipi to continue PD-1 inhibition (with nivo), and that responses would occur at a rate higher than would be expected from switching to ipi alone. We surmise that this would occur because melanomas primarily refractory to PD-1 antibodies may not have a sufficient pre-existing T cell infiltrate, which can be corrected by adding treatment with ipi, as CTLA-4 blockade increases new intratumoral T cell infiltration. **Methods:** This is a Phase 2, prospective open-label study of ipi +/- nivo in patients with advanced melanoma refractory to a PD-1 inhibitor. The primary endpoint of the study is progression free survival. Secondary objectives include the difference in T-cell infiltrate in biopsies of patients with response and no-response to therapy; objective response rate; overall survival; and toxicity. Key eligibility criteria include unresectable melanoma; disease progression while on prior PD-1 agents or after stopping with no intervening therapy; no confirmed partial or complete response to prior anti-PD1 agents; no prior receipt of CTLA-4 inhibitor; Zubrod performance status 0-2; no active brain metastases; no history of autoimmune pneumonitis or colitis requiring steroids or interruption of therapy; and adequate organ function. Prior receipt of BRAF/MEK inhibitors is permitted. Subjects are randomized 1:3 to ipi 3mg/kg q3wk x4 doses or ipi with nivo 1mg/kg q3wk x4 doses followed by nivo 240mg q2wk (21 planned on ipi; 63 on ipi+nivo). Tumor biopsy and blood for correlative studies are taken prior to enrollment and at Day 28-35 on study. Tumor assessments are performed every 12 weeks for 1 year and treatment is continued while clinical benefit persists with a final survival follow-up at 2 years. The combination will be considered superior to single-agent ipi if PFS is doubled from 3 to 6 months with one-sided alpha of 0.1 and power of 0.9. As of January 2018, 5 of 84 planned subjects have enrolled. Clinical trial information: NCT03033576.

TPS9598 Poster Session (Board #423b), Mon, 1:15 PM-4:45 PM

A phase II study of study of bevacizumab (BEV) in combination with atezolizumab (ATEZO) in pts (pts) with untreated melanoma brain metastases (BEAT-MBM). *First Author: Gustavo Schvartsman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immunotherapy (IO) has significantly improved survival for many pts with metastatic melanoma. However, the majority of trials excluded pts with MBM. Recently, combination of nivolumab and ipilimumab (IPI) showed objective response rate (ORR) of up to 55%, but pts with symptomatic disease still do poorly and usually are not candidates for IO due use of high dose steroids. Additionally, there is a concern for increased perilesional edema, which can lead to neurologic symptoms. BEV has widely been used as a "steroid-sparing agent" with remarkable success in controlling intracranial edema. Moreover, studies have implicated elevated angiogenic markers as predictors of poor outcome with IO by limiting effector T-cell trafficking and activity. Clinically, BEV has been shown to improve the outcome of IO and has indeed increased expression of favorable chemokines in the tumor microenvironment, improving ORR when added to IPI. Moreover, the combination of BEV and ATEZO, a PD-L1 inhibitor, produced remarkable responses in renal cell carcinoma. We therefore hypothesized that combining BEV and ATEZO will be more effective and have an improved toxicity profile in MBM. **Methods:** This phase II study will evaluate the intracranial safety and efficacy of BEV + ATEZO by ORR (iRANO criteria) in pts with untreated or progressive MBM who have not been exposed to PD-1/PD-L1 inhibitors. We will accrue 40 pts, divided in two cohorts: cohort A (25 asymptomatic pts); and cohort B (15 pts that are either mildly symptomatic, or asymptomatic, but requiring a low dose of systemic steroids (no higher than 4 mg/day of PO dexamethasone or equivalent). BEV will be given at 15 mg/kg and ATEZO at 1200 mg flat dose, both IV every 3 weeks until progression or death. Efficacy will be assessed by MRI of the brain and systemic imaging every 2 cycles. Continuous monitoring for toxicity and futility will be performed and assumes an ORR of 45% (96% power to detect a 25% difference from historical control of 20%). Effects of BEV + ATEZOL on correlative immune markers will be studied. This study is open for enrollment. Clinical trial information: NCT03175432.

TPS9599 Poster Session (Board #424a), Mon, 1:15 PM-4:45 PM

A randomized phase II study of anti-PD1 antibody [MK-3475 (Pembrolizumab)] alone versus anti-PD1 antibody plus stereotactic body radiation therapy in advanced merkel cell carcinoma (Alliance A091605). *First Author: Jason J. Luke, University of Chicago Comprehensive Cancer Center, Chicago, IL*

Background: Merkel cell carcinoma (MCC) is a rare cutaneous malignancy associated with ultraviolet light exposure, advanced age and infection with the Merkel cell polyomavirus (MCP). Historically, median survival in the metastatic setting was approximately 9.6 months with radiation and platinum- based chemotherapy as the foundations of treatment. More recently, outcomes have been markedly improved with the development of PD1/L1 antibodies. Durable response rates have been observed ranging from 30-50%, depending on line of therapy, that are independent of PDL1 or MCP status, mutation burden or tumor-infiltrating lymphocytes. A large preclinical literature and some clinical observations support the hypothesis that radiation may augment the systemic efficacy of immunotherapy (abscopal effect) through increased antigen presentation, T-cell priming, and interferon gamma associated signaling. No clinical studies to date have directly tested this hypothesis. **Methods:** This is an NCTN supported (Alliance for Clinical Trials in Oncology, SWOG and NRG Oncology) open-label phase II study comparing pembrolizumab with pembrolizumab plus stereotactic body radiation therapy to a single lesion in advanced MCC. The study randomizes patients 1:1 with eligibility including no prior therapy in the metastatic setting, ≥2 sites of RECIST measurable disease, ECOG performance status 0-2 and no autoimmunity or immunosuppression. The primary endpoint is progression-free survival in non-irradiated lesions (abscopal), with secondary endpoints evaluating response rate, overall survival and toxicity. Translational biospecimens, including archival tumor tissue (for PDL1, TMB, gene expression profiling and other analyses), serum and peripheral blood mononuclear cells and fecal microbiome samples, are being collected for analysis. The study is open to accrual via the Cancer Trials Support Unit (CTSU) of NCI to any NCTN group member site. Recruitment is on-going (target 96 patients). Clinical trial information: NCT03304639.

TPS9600 Poster Session (Board #424b), Mon, 1:15 PM-4:45 PM

A randomized phase III study of duration of anti-PD-1 therapy in metastatic melanoma (STOP-GAP): Canadian Clinical Trials Group study (CCTG) ME.13. *First Author: Tara D. Baetz, Division of Medical Oncology, Queen's University, Kingston, ON, Canada*

Background: Efficacy of the anti-PD -1 agents has been demonstrated in metastatic melanoma in phase I-III trials. During the development of these trials there was no optimal duration of treatment identified. Trials stopped therapy due to unacceptable side effects, investigator's choice, at a specific time point typically at 24 months of therapy or at disease progression. Clinical reports suggest that stopping treatment early due to toxicity may not adversely impact efficacy. In addition, there is evidence that retreatment with immunotherapy may be clinically effective. Unnecessary long term therapy may result in a higher risk of toxicity, diminished quality of life (QoL) and will impact the cost-effectiveness of the therapy. We hypothesize that treatment to maximum tumour response will result in non-inferior overall survival with better QoL, less toxicity and lower cost than continuous therapy. **Methods:** This is a large, simple randomized phase III trial evaluating the duration of anti-PD-1 therapy in metastatic/unresectable melanoma. Consenting patients must be eligible to receive anti- PD-1 inhibitor as standard of care. Patients are randomized 1:1 to either standard 24 months of therapy in the absence of disease progression versus treatment until maximum tumour response (MTR) with retreatment at the time of progression. MTR is determined by at least two radiologic measurements three months apart. Eligibility criteria are broad to reflect a "real world" patient population. Data collection is streamlined to focus on key endpoints. The primary endpoint is overall survival. Secondary endpoints are PFS, response rate, adverse event rate, health related QoL and economic analysis. Patients are stratified based on line of therapy, stage of disease, BRAF status, LDH level, prior use of adjuvant therapy, anti-PD -1 inhibitor selected and the presence of CNS metastases. The trial will enroll 550 patients with 275 in each arm. It is expected that accrual will last 5.5 years. Currently 78 patients have been enrolled. Clinical trial information: NCT02821013..

TPS9601 Poster Session (Board #425a), Mon, 1:15 PM-4:45 PM

Trial in progress: A phase 2 study of intratumor pil-12 plus electroporation in combination with intravenous pembrolizumab in patients with stage III/IV mealanoma progressing on either pembrolizumab or nivolumab treatment (PISCES). *First Author: Robert Hans Ingemar Andtbacka, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Immunotherapy and targeted therapies have significantly changed the treatment landscape for advanced melanoma over the past few years. However, despite the addition of these new therapeutic strategies, a lack of response or disease progression continues to occur in a significant fraction of patients (~60%). Pembrolizumab (anti-PD-1 antibody) for the treatment of advanced melanoma confers a 33% objective response rate (ORR). Intratumoral plasmid IL-12 (tavokinogene telseplasmid; tavo) with electroporation (IT-tavo-EP) is a gene-based immunotherapeutic approach that forces localized expression of the proinflammatory cytokine IL-12, which converts both treated and untreated lesions from poorly immunogenic/low T-cell infiltrating tumors unlikely to respond to anti-PD-1 therapy into highly inflamed immunologically active lesions. The purpose of this study is to evaluate the tolerability and efficacy of pembrolizumab plus IT-tavo-EP in Stage III/IV melanoma patients who have progressed or are progressing on approved checkpoint inhibitors, and to assess the immunomodulatory effects of therapy **Methods:** OMS-I103 (PISCES) is a phase 2, multicenter, open-label trial of IT-tavo-EP with pembrolizumab in patients with stage III/IV melanoma who are progressing on either pembrolizumab or nivolumab. The primary objective is best ORR by RECIST v1.1 at 24 weeks determined by independent reviewers. A Simon 2-stage minimax design is employed. In Stage 1, up to 23 eligible patients will be enrolled and treated with IT-tavo-EP to the accessible lesions on Days 1, 5 and 8 every 6 weeks with IV pembrolizumab (200 mg) on Day 1 of each 3-week cycle for 24 weeks. If the predesignated threshold is reached in Stage 1, ($N > 3$ /23) enrollment for Stage 2 will include an additional 25 patients (total of 48 patients). The study is enrolling in the US and Australia. Clinical trial information: NCT03132675.

TPS9602 Poster Session (Board #425b), Mon, 1:15 PM-4:45 PM

Multicenter phase I/IIa study using T cell receptor gene therapy in metastatic melanoma. *First Author: Maartje W. Rohaan, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Since the introduction of targeted therapy and checkpoint inhibitors, the historically poor prognosis of patients with unresectable stage IIIc/IV melanoma has greatly improved, with now known 2-year survival rates of 46-64%. However, a substantial group of patients, for example those with metastatic uveal melanoma, have poor response rates upon these therapies with no alternative approved therapy yet available. Adoptive transfer of T cell receptor (TCR) gene modified T cells is a modality to create a large pool of tumor reactive T cells. Responses of clinical significance have been seen in preclinical and clinical trials when targeting the melanocyte differentiation antigens gp100 and MART-1. The primary aim of our study is to explore the feasibility, safety and objective response rate of the adoptive transfer of autologous T cells modified with a MART-1 specific TCR, preceded by non-myeloablative (NMA) chemotherapy. **Methods:** In this phase I/IIa study, a total of 25 patients $\geq$ 18 years of age, with irresectable stage IIIc/IV melanoma (cutaneous, melanoma of unknown primary, mucosal and uveal melanoma) who have failed previous standard treatments, are HLA-A2 positive and have MART-1 and MHC class I expressing tumors, will be included. Patients will undergo leukapheresis to isolate autologous T cells, which will be transduced with a retroviral vector encoding the 1D3HMCys MART-1 TCR and expanded *ex vivo*. Patients will receive NMA chemotherapy and a single intravenous infusion with MART-1 TCR transduced T cells in a dose escalating regimen after evaluation of toxicity and efficacy. Primary endpoints are the feasibility of MART-1 specific TCR therapy in terms of delivery of this sequence of treatment in metastatic melanoma patients, safety according to CTCAE 4.0 and objective response rate according to RECIST 1.1. Secondary endpoints are the 1-year progression free survival, median overall survival and the efficacy of induction of tumor specific T cell responses measured in peripheral blood and tumor biopsies. Enrollment started in March 2012 in The Netherlands Cancer Institute and will be continued in a 2-stage Simon design. Clinical trial information: NCT02654821.

TPS9603 Poster Session (Board #426a), Mon, 1:15 PM-4:45 PM

Reversing resistance to PD-1 blockade by combination of talimogene laherparepvec (T-VEC) with pembrolizumab (pembro) in advanced melanoma patients following progression on a prior PD-1 inhibitor: SWOG S1607 (NCT#02965716). *First Author: Siwen Hu-Lieskovan, UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: A significant number of patients do not respond to PD-1/L1 blockade because there are no pre-existing tumor antigen-specific T-cells in their tumors ready to attack the cancer. We hypothesize that this lack of sufficient immune activation can be addressed by a combination therapy with an immune activating oncolytic virus such as T-VEC. Intralesional administration of T-VEC, a modified herpes simplex virus type-1, can selectively replicate in tumor tissue and stimulate a local and systemic antitumor immune response. **Methods:** This is a Phase 2 study of T-VEC plus pembro in patients with advanced melanoma whose disease progressed after prior therapy with a PD-1/L1 inhibitor. The primary endpoint is durable response rate. Secondary objectives include objective response rate in the injected, non-visceral non-injected and visceral lesions, progression free survival, overall survival and toxicity. Translational objectives include difference in T-cell infiltrate in responding vs non-responding tumors. Key eligibility criteria include unresectable melanoma; anti-PD-1/L1 based therapy must be the immediate previous line of treatment within 56 days prior to registration; no confirmed partial or complete response to prior anti-PD1 agents; Zubrod performance status 0-2; no active brain metastases; no history of autoimmune disease or toxicity requiring steroids; and adequate organ function. Subjects in cohort A must have at least one measurable visceral lesion; in cohort B subjects must not have visceral lesion. Subjects will receive intratumoral injection of T-VEC 1 million PFU/ml for cycle 1 followed by 100 million PFU/ml from cycle 2 to 36 (one cycle equals 21 days). Pembro 200mg IV will be given every 21 days. Tumor biopsy and research blood are taken at baseline and while on treatment at Day 28 (both injected and non-injected lesions). Tumor assessments are performed every 12 weeks, and treatment is continued while clinical benefit persists for up to 2 years. A total of 36 subjects will be enrolled in cohort A and 25 subjects in cohort B, with a Simon 2 stage design. Clinical trial information: NCT02965716.

TPS9604 Poster Session (Board #426b), Mon, 1:15 PM-4:45 PM

Determining optimal sequencing of anti-PD-1 and BRAF-targeted therapy: A phase II randomised study of neoadjuvant pembrolizumab with/without dabrafenib and trametinib (D+T) in BRAF V600 mutant resectable stage IIIb/c/d melanoma (NeoTrio trial). *First Author: Maria Gonzalez, Melanoma Institute Australia, North Sydney, Australia*

Background: BRAF targeted and CTLA-4/PD-1 immunotherapies have high response rates and improve survival for patients (pts) with metastatic melanoma, however, most still die of this disease. It is hypothesised the activated cytotoxic T cell infiltrate that occurs early during treatment with BRAF/MEK inhibitors is potentiated by adding checkpoint inhibitors, resulting in improved response and survival. While trials combining BRAF/MEK inhibitors and anti-PD-1/L1 antibodies are underway in the metastatic setting, the neo-adjuvant (neo-adj) setting provides an opportunity to test different treatment schedules in small cohorts of pts. Tissue and blood biomarkers can be drawn at several timepoints and correlated to clinical and pathological endpoints to explore mechanisms of response, biomarkers of efficacy, and to select the best schedules to take forward to larger-scale trials. **Methods:** Eligible pts with BRAF V600 mut, stage IIIB/C/D, resectable and measurable (RECIST 1.1) melanoma are evenly assigned to 3 cohorts (n = 60). All pts undergo complete macroscopic resection (RES) at wk 12 and receive neo-adj therapy for 12 wks preceding RES, followed by 40 wks of adjuvant (adj) therapy. Cohort 1 receive sequential therapy with D+T for 2 wks, then 4 pembrolizumab (pembro) doses until wk 12, and 3 wkly pembro after RES. Cohort 2 receive concurrent D+T and 3 wkly pembro before and after RES. Cohort 3 receive 3 wkly pembro for the entire treatment course. Pembro is given at a flat dose of 200mg. Ultrasound of known disease areas is undertaken during the neo-adj period. CT and FDG PET/CT are used to measure response and exclude progression in the neo-adj phase, and to monitor for recurrence during adj and post treatment phases. Blood and tumour samples are collected at baseline, wk 1, 4 and 12. The primary endpoint is the complete pathological response rate at RES following 12 wks of therapy. Secondary endpoints include RECIST response, metabolic response, OS, RFS, safety/tolerability, surgical outcomes, quality of life, and biomarker analysis. First patient enrolled 29Nov2017. Clinical trial information: NCT02858921.

TPS9605 Poster Session (Board #427a), Mon, 1:15 PM-4:45 PM

ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in merkel cell carcinoma patients with clinically detected lymph node metastases; NCT03271372. *First Author: Shailender Bhatia, University of Washington Fred Hutchinson Cancer Center, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. MCC with clinically detected lymph node (LN) metastases is associated with high risk of systemic recurrence despite initial surgical therapy and/or radiation therapy (RT). Adjuvant cytotoxic chemotherapy is not associated with overall survival benefit in stage III MCC and there is a strong unmet need for effective adjuvant systemic therapy. Clinical investigation of PD-1/PD-L1 blockade in patients with metastatic MCC is associated with remarkable improvement in clinical outcomes with response rates > 50% in a chemotherapy-naïve setting. This notable benefit from PD-1 blockade in stage IV MCC, along with the recent success with adjuvant PD-1 blockade in stage III melanoma, together provide strong rationale for investigating avelumab, an anti-PD-L1 antibody, for adjuvant systemic therapy in MCC patients with high risk of recurrence. **Methods:** The ADAM (Adjuvant Avelumab in Merkel) trial is an investigator-sponsored, phase 3, multi-center, double-blinded and placebo-controlled study. We plan to enroll 100 MCC patients with clinically or radiologically detected LN metastases treated definitively with surgery (with or without adjuvant RT). Patients will be randomized (1:1) to receive either avelumab or placebo administered IV at a dose of 10mg/kg every 15 days for the first 4 months, then once monthly for the next 4 months, and then once every 4 months. Treatment will end 2 years after starting the study drug, or upon recurrence of disease, unacceptable toxicity, or study withdrawal. The primary endpoint is relapse-free survival. Secondary endpoints include overall survival, disease-specific survival, distant metastasis-free survival, and safety and tolerability. Exploratory endpoints include tissue and blood-based biomarkers and AMERK (Anti-Merkel polyomavirus) serology as a recurrence predictor in a prospective, multi-center setting. The ADAM trial represents the first-ever phase 3 trial in MCC and is a major academic collaboration across several US cancer centers. Clinical trial information: NCT03271372.

TPS9606 Poster Session (Board #427b), Mon, 1:15 PM-4:45 PM

Multicenter phase 2 study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO) (OpACIN-neo). *First Author: Elisa A. Rozeman, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The outcome of high risk stage III melanoma patients (pts) is poor, with a 5 year overall survival (OS) rate of < 50%. Adjuvant (adj) high dose IPI significantly improves 5 year progression free survival (PFS) and OS and adj NIVO improves the median PFS even more. In stage IV pts, the combination of IPI and NIVO improves response rates (RR) and PFS compared to monotherapy, but at cost of higher toxicity. Neo-adjuvant (neoadj) treatment may be a favorable approach as immune checkpoint inhibition (ICI) is of greatest value at the moment of TCR triggering and therefore dependent on the amount of antigen. The phase Ib OpACIN study compared neoadj versus adj IPI plus NIVO. The pathological RR (pRR) was 80% in the neoadj arm, and to date after a median follow-up of 24 months, none of the responders has relapsed, while 4/10 pts have relapsed in the adj arm. Moreover, pts in the neoadj arm expanded more tumor-resident TCR clones than adj treated pts. Neoadj IPI+NIVO was feasible, but toxicity was high with 90% grade 3/4 immuun-related adverse events (irAE) in both arms. This raises the question whether neoadj IPI plus NIVO can be alternatively scheduled to reduce toxicity but preserve efficacy. **Methods:** The aim of the multi-center phase 2 OpACIN-neo trial is to identify an optimal neoadj combination scheme of IPI and NIVO. 90 pts with resectable stage III melanoma will be randomized 1:1:1 between three different combination schemes of IPI and NIVO (Arm A: 2x IPI 3mg/kg plus NIVO 1mg/kg q3wks, Arm B: 2x IPI 1mg/kg plus NIVO 3mg/kg q3wks, Arm C: 2x IPI 3mg/kg q3wks directly followed by 2x NIVO 3mg/kg q2wks). All pts will undergo surgery at week 6. Primary endpoints are rate of grade 3 and 4 irAEs, pRR, and radiologic RR according to RECIST 1.1. Major inclusion criteria are: ≥1 measurable lymph node metastases (according to RECIST 1.1) that can be biopsied, no history of in-transit metastases in the last 6 months, and naïve for ICI. Baseline biopsies and blood samples (week 0, 6, 12) will be taken. An interim analysis was planned after 13 pts had been accrued to each arm (according to the Simon stage-2 design). Pre-specified activity goals for the first stage of accrual were met; until now 56 of 90 pts have been enrolled. Clinical trial information: NCT02977052.

TPS9607 Poster Session (Board #428a), Mon, 1:15 PM-4:45 PM

Confirmatory trial of non-amputative digit preservation surgery in subungual melanoma: JCOG1602 (J-NAIL study). *First Author: Yasuhiro Nakamura, Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan*

Background: Subungual melanomas (SUMs) are rare, comprising only 2–3% of all cutaneous melanomas in the Caucasian population and 8.7–20% of all cutaneous melanomas in the Asian and African populations. The excision margin for SUM remains controversial, and although amputations at various bone levels have been proposed, more proximal amputation levels have not improved prognoses. In addition, the prognosis for patients with SUM does not depend on the amputation level, but rather on the time from initial diagnosis to surgery. Furthermore, non-amputative digit-preservation surgery has been performed for SUMs in situ and < = 0.5 mm-thick. A recent study has indicated that not all patients with invasive SUMs histologically showed invasion to the underlying distal phalanx, and digit-preservation surgery can be applied to such patients without compromising prognosis. This trial is designed to investigate the efficacy and safety of digit preservation surgery in SUMs without bone invasion. **Methods:** Eligible patients are less than 80 years old, with stage I, II, or III SUM without evidence of tumor invasion to the underlying distal phalanx on preoperative radiograph. Eligible patients receive digit preservation surgery. Sentinel node biopsy is performed for patients without regional lymph node enlargement. Regional lymph node dissection is performed for patients with regional lymph node enlargement. The primary endpoint is major relapse-free survival (major RFS), which do not include local recurrence as an event; and the secondary endpoints are overall survival, digit-preservation survival, relapse-free survival, local relapse-free survival, partial relapse-free survival, and incidence of adverse events. We anticipate that the expected 5-year major RFS of historical control of amputation surgery is 77%, and that of non-amputative digit preservation surgery will decrease the major RFS by less than 10%. The planned sample size is 85 patients to provide power of 70% and on-sided alpha of 10%. Planned accrual period is 5.5 years and a follow-up period is 5 years. The trial began in November 2017 and two patients have been enrolled as of January 2018. Clinical trial information: UMIN000029997.

TPS9608 Poster Session (Board #428b), Mon, 1:15 PM-4:45 PM

SWOG S1512: A phase II and pilot trial of pembrolizumab in patients with resectable or unresectable desmoplastic melanoma (DM). *First Author: Kari Lynn Kendra, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: DM is characterized by high collagenous stroma and a high mutational burden. A retrospective review demonstrated a 70% RR to anti-PD1 -in 60 patients with metastatic melanoma. Surgery for locally advanced DM often results in large resections in exposed areas of the body. Determining the capability of reducing the tumor size and surgical defects is of clinical interest. Evaluating the correlation of T cell infiltrate, TCR clonality, and the impact of pre-existing adaptive immune response with clinical response is of potential predictive interest. **Methods:** This prospective study evaluates neoadjuvant pembrolizumab in patients with resectable DM (phase 2) and pembrolizumab in patients with unresectable DM (pilot). The primary endpoint of cohort A (resectable DM) is pathologic complete response rate (pCR). Secondary endpoints: ORR at 9 weeks, OS at 9 weeks, and toxicity. The primary endpoint of cohort B (unresectable DM) is CR. Secondary endpoints: PFS and OS. Translational objectives for both cohorts: evaluate the association between mutational load (whole exome sequencing) and pCR, examine relationships between T-cell infiltration and response, and assess the difference in TCR clonality in responders and non-responders. Key eligibility criteria include no prior systemic therapy and adequate organ function. In addition (cohort A) patients must have resectable disease. Cohort A: pembrolizumab 200 mg IV q 3wk x 3, followed by resection. Cohort B: pembrolizumab 200 mg IV q3wk. Blood for correlative studies: prior to initiation of pembrolizumab. For both cohorts, biopsies will occur pre-treatment, prior to C2, and at the time of resection (cohort a). Tumor assessments are performed at baseline and at week 9. Cohort B: tumor assessments continue every 9 weeks. Cohort A: if >5 patients demonstrate a pCR, further study is warranted (alpha of 4.6%, power of 90.2%). Cohort B: ≥ 3 patients demonstrating a CR warrants further study (true CR is 5%, power is 82%). As of January 2018, accrual = 5. Funding: NIH/NCI grant awards U10CA180888 and U10CA180819; and in part by Merck, Sharpe & Dohme, Corp. Clinical trial information: NCT02775851.

10000 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Omega-3 fatty acid use for obese breast cancer patients with aromatase inhibitor-related arthralgia (SWOG S0927). *First Author: Sherry Shen, Columbia University Medical Center, New York, NY*

Background: Although aromatase inhibitors (AIs) prolong survival in postmenopausal women with breast cancer (BC), AI arthralgia can lead to discontinuation. Obese patients have higher rates of AI arthralgia than non-obese patients. Omega-3 fatty acid (O3-FA) treatment for AI arthralgia has produced mixed results. We performed an exploratory analysis to evaluate whether the effects of O3-FAs are associated with body mass index (BMI). **Methods:** SWOG S0927 was a randomized placebo-controlled trial of O3-FA use for AI arthralgia. Post-menopausal women with stage I–III BC taking an AI were randomized to 24 weeks of O3-FAs or placebo. Brief Pain Inventory (BPI) pain scores and serum were assessed at baseline, 6, 12, and 24 weeks. Global change in joint pain was assessed with scores ranging from -3 for "very much worse" to +3 for "very much better" than baseline. **Results:** Among the 249 participants, 139 had BMI $<$ 30 (56%) and 110 had BMI $\geq$30 (44%). Patients with BMI $\geq$30 had higher rates of diabetes (19% vs. 8%, p= 0.009) and hypertension (53% vs. 31%, p= 0.0005), were more likely to have $\geq$2 cardiovascular risk factors (33% vs. 17%, p= 0.009), and had lower HDL levels (49.9 vs. 60.3, $p<$ 0.0001). O3-FA use was associated with significantly reduced triglyceride levels at 12 weeks compared with placebo in patients with BMI $\geq$30 (-22.42 vs. +1.59, p= 0.03), but not in those with BMI $<$ 30 (p= 0.12, interaction p= 0.09). Among patients with BMI $\geq$30, O3-FA use was associated with a 2.89-point decrease in BPI worst pain score after 24 weeks compared to a 1.49-point decrease with placebo use (p= 0.02), whereas there was no significant difference between O3-FAs and placebo in those with BMI $<$ 30 (p= 0.40, interaction p= 0.05). Trends were similar using global change in joint pain for O3-FA use compared to placebo (BMI $\geq$30, +0.98 vs. +0.48 respectively, p= 0.05; BMI $<$ 30, +0.57 vs. +0.50 respectively, p= 0.80), though the interaction was not statistically significant (p= 0.22). **Conclusions:** In BC patients with BMI $\geq$30, O3-FA use was associated with significantly reduced AI arthralgia and significantly lower triglyceride levels compared to placebo. If confirmed, O3-FA use may lead to improved AI adherence in this subset of BC patients. Clinical trial information: NCT01385137.

10001 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

The effect of acupuncture versus cognitive behavior therapy on insomnia in cancer survivors: A randomized clinical trial. *First Author: Jun J. Mao, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Insomnia is a common and debilitating disorder experienced by up to 60% of cancer survivors. We evaluated the effectiveness of acupuncture versus cognitive behavior therapy for insomnia (CBT-I). **Methods:** We conducted a randomized clinical trial of acupuncture vs. CBT-I among 160 post-treatment cancer survivors with clinically diagnosed insomnia disorder. Acupuncture involved stimulating body points with needles. CBT-I included sleep restriction, stimulus control, cognitive restructuring, relaxation training, and education. The intervention duration was eight weeks (primary end point) with a follow up assessment at 20 weeks. Insomnia severity, measured by the Insomnia Severity Index, was the primary outcome. **Results:** The mean age of participants was 61.5 years, 57% (n = 91) were women, and 29.4% (n = 47) were non-white. At the end of treatment, acupuncture reduced insomnia severity by 8.3 points (95% CI 7.3-9.4), compared to 10.9 points (95% CI 9.8-12.0) for CBT-I, with CBT-I being the more effective treatment overall (2.6, 95% CI 1.1 – 4.1, P = 0.0007). Patients with mild insomnia were significantly more likely to respond to CBT-I than acupuncture (85% vs. 18%, p $<$ 0.0001); however, patients with moderate to severe insomnia had similar response rates to CBT-I and acupuncture (75% vs. 66%, p = 0.26). Both groups had few mild adverse events and maintained improvements up to 20 weeks. Both groups also had similar improvement in quality of life in physical health (p = 0.46) and mental health (p = 0.44) during the study. **Conclusions:** While both acupuncture and CBT-I resulted in clinically meaningful and durable effects among cancer survivors with insomnia, CBT-I was more effective, especially among patients with mild insomnia symptoms. Patients and oncology clinicians can use these findings to inform their choice of insomnia treatment. Clinical trial information: NCT02356575.

LBA10003 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Improving communication with older patients with cancer using geriatric assessment (GA): A University of Rochester NCI Community Oncology Research Program (NCORP) cluster randomized controlled trial (CRCT). *First Author: Supriya Gupta Mohile, University of Rochester Medical Center, Rochester, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 2:00 p.m. ET on Friday, June 1, 2018, and in the *Annual Meeting Proceedings* online supplement to the June 20, 2018, issue of the *Journal of Clinical Oncology*. On site at the Meeting, this abstract will be printed in the Sunday edition of *ASCO Daily News*.

10004 **Oral Abstract Session, Sun, 8:00 AM-11:00 AM**

Symptom burden in hospitalized patients with curable and incurable cancers. *First Author: Richard Newcomb, Massachusetts General Hospital, Boston, MA*

Background: Inpatient supportive care interventions are targeted to patients with advanced solid tumors due to perceived higher symptom burden. Yet, few studies have characterized symptom prevalence in hospitalized patients with curable cancers. We aimed to describe and compare symptom burden and palliative care utilization in hospitalized patients with curable and incurable cancers to determine the allocation of such supportive care resources. **Methods:** We conducted a single center study of 1549 patients (238 curable hematologic, 239 curable solid, 123 incurable hematologic, 949 incurable solid cancers) who experienced an unplanned hospitalization between 9/14-4/17. On admission, we assessed patients' physical symptoms (Edmonton Symptom Assessment System) and psychological distress (Patient Health Questionnaire-4 and Primary Care PTSD Screen). **Results:** The median number of moderate to severe symptoms reported by patients with curable hematologic, curable solid, incurable hematologic, and incurable solid cancers were 5 [3-6], 5 [3-7], 5 [4-6], and 6[4-7], respectively. Most patients reported moderate to severe fatigue (83.6%, 82.9%, 81.3%, 86.9%). Table 1 depicts rates of psychological distress. In adjusted analyses patients with incurable solid cancers reported higher symptom burden (β = 7.6, P $<$ 0.01), depression (β = 0.4, P = 0.01), and anxiety (β = 0.3, P = 0.03) symptoms, but no difference in PTSD symptoms. Among patients in top quartile of symptom burden, palliative care was consulted in 16.2%, 7.9%, 23.8%, and 49.6% (P $<$ 0.01) of patients with curable hematologic, curable solid, incurable hematologic, and incurable solid cancers, respectively. **Conclusions:** Hospitalized patients with solid and hematologic cancers experience substantial physical and psychological symptoms regardless of the curability of their illness. Palliative care is rarely consulted for highly symptomatic patients with curable cancers. Inpatient supportive care interventions should target the needs of all highly symptomatic patients with cancer.

Symptoms	Curable Hematologic	Curable Solid	Incurable Hematologic	Incurable Solid
Depression	15.2%	14.2%	21.4%	18.1%
Anxiety	11.8%	13.4%	15.0%	19.3%
PTSD	13.1%	13.0%	13.2%	13.3%

10005 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Randomized trial of a symptom monitoring intervention for hospitalized patients with cancer. *First Author: Charn-Xin Fuh, Massachusetts General Hospital, Boston, MA*

Background: Hospitalized patients with cancer experience a high symptom burden, which is associated with poor health outcomes and increased healthcare utilization. We conducted a pilot randomized trial to assess the feasibility and preliminary efficacy of a symptom monitoring intervention to improve symptom management in hospitalized patients with advanced cancer. **Methods:** We randomly assigned patients with advanced cancer and unplanned hospitalizations who were admitted to the oncology service to a symptom monitoring intervention or usual care. Patients in both arms daily self-reported their symptoms (Edmonton Symptom Assessment System and Patient Health Questionnaire-4) via tablet computers. Patients assigned to the intervention had their symptom reports presented graphically with alerts for moderate/severe symptoms during daily team rounds. We defined the intervention as feasible if participants completed > 75% of their daily symptom assessments. We also observed daily team rounds to determine how often clinicians discussed and developed a plan to address patients' symptoms. We used regression models to assess intervention effects on patients' symptoms throughout their hospital stay and readmission risk. **Results:** From 10/26/16-6/30/17, we randomized 150 patients (81.1% enrollment rate; median age = 64.0 [22.7-92.8]; 40.7% female). The most common cancers were gastrointestinal (36.7%) and lung (22.0%). Patients completed 89.4% of their daily symptom assessments. Clinicians discussed 60.4% of the symptom reports and developed a plan during rounds to address patients' symptoms 20.8% of the time. Compared with usual care, patients assigned to the intervention had a greater proportion of days with lower psychological distress (B = 0.12, P = .008). Intervention patients experienced improvements in their average symptom scores for drowsiness (B = -0.54, P = .033) and dyspnea (B = -0.43, P = 0.009). Intervention patients had lower risk of readmissions (hazard ratio = 0.68, P = .221), although this difference was not significant. **Conclusions:** This symptom monitoring intervention is feasible and demonstrates encouraging preliminary efficacy for improving patients' symptoms and risk for readmissions. Clinical trial information: NCT02891993.

10006 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Does timing of palliative care consults impact end-of-life health services utilization in pancreatic cancer patients? *First Author: Nizar Bhulani, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Early palliative care consult can influence end of life health care utilization in controlled clinical trials. However, the effect in large scale, real world setting is not known. We explored the effect of early vs. late palliative care consult on end of life health care utilization in Medicare patients with pancreatic cancer. **Methods:** Pancreatic cancer patients diagnosed between 2000 - 2009 with palliative consults were identified using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Early palliative care was defined as a consult received in the first 4 weeks of diagnosis. Patients older than 66 years, with survival more than 3 months and known date of death were included. Trend of palliative care consults and health services utilization was studied for patients with early vs late palliative care consults. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC). **Results:** Out of the 1966 patients with palliative care consults, 840 (43%) received early palliative care. On univariate analysis, age, sex, state of residence and stage at diagnosis were associated with early palliative care consult ($p < 0.001$). On multivariate analysis, patients with early palliative care consults were more likely to be women, older than 85 years and have stage 4 disease. Race and state of residence were not associated with early vs late palliative care consult. Patients with early palliative care had lower number of visits to the ED (2.4 vs. 3.0 $p < 0.001$) and lower cost of ED care ($3043 vs. $4117, $p < 0.001$). Early palliative care patients were admitted less frequently to the ICU compared to late palliative care patients (0.68 vs. 0.94, $p < 0.001$) and the duration of Intensive care unit stay was shorter (3.0 days vs 3.7 days, p 0.04). Cost of ICU care was not statistically different between both the groups. **Conclusions:** In this claims analysis of elderly pancreatic cancer patients, those with early palliative care had lower health care utilization as measured by ED and ICU stay. This provides real world evidence to support oncology societies' recommendations for early integration of palliative care.

10007 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Patient (Pt) and oncologist (MD) discordance in goals of care in end of life (EOL) decision making. *First Author: Sara L Douglas, Case Western Reserve University-Nursing and Case Comprehensive Cancer Center, Cleveland, OH*

Background: Providing EOL care that is in accordance with Pt goals of care is an essential component of quality care. Because discordance between the attitudes of Pt and physician can undermine optimal EOL care, identification of disagreements regarding goals of care is important, particularly in the context of advanced disease. **Methods:** This was a longitudinal design study. Adult Pts with Stage IV gastrointestinal (GI) or lung cancer were eligible. Each Pt and MD were surveyed at study enrollment and every 3 months for 15 months or until the Pt died. The primary variables of interest were the Pt and MD identified goals of care and what the MD believed to be the Pt's goal of care, using a visual analog scale (VAS). Scores on the VAS ranged from 0 (comfort, quality of life) to 100 (survival, length of life). Discordance was defined as an absolute difference > 40 on the VAS. **Results:** Between January 2015 and July 2017, 378 Pts were enrolled. Refusal rate was 27.5%; attrition rate 8.1%. 168 Pts (44%) died and their results are presented. Mean age was 64 years (range = 36-88 years); 66% had GI and 34% had lung cancer. Mean time from enrollment to death was 6.5 months (range = 3 - 15 months). At the last assessment prior to Pt death, 32% of the Pt-MD pairs had discordant goals (> 40 points different). In 60% of these cases, the Pt had more survival focused goals while in 40% of cases the MD had more survival focused goals. Also, 77% of Pt-MD pairs with discord at enrollment still had discord at the last assessment before death ($p < .001$). In comparing what the MD believed to be the Pt's goal of care with the Pt's actual goal of care at death, there was discord in 27% of the pairs. The correlation between MDs' own identified goals for Pts and what MDs identified as the Pts' goals was large ($r = .71$, $p < .001$). **Conclusions:** These data suggest that communication between Pts and MDs is suboptimal regarding goals of care at the EOL. Interventions to improve the explicit discussion of mutual goals of care over time between MDs and Pts are needed in order to ensure that patients receive EOL care consistent with their goals.

10008 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Understanding factors contributing to geographic variations in end-of-life expenditures. *First Author: Nancy Lynn Keating, Harvard Medical School, Boston, MA*

Background: Health care spending at the end of life varies across geographic areas and yet is not associated with improved outcomes. The factors underlying these variations are poorly understood. We assessed the extent to which geographic variation in end-of-life spending for advanced-stage cancer patients is explained by differences in patient sociodemographic factors, clinical factors, patient beliefs, physician beliefs, and availability of services. **Methods:** Using data from the prospective, multi-regional CanCORS study, we studied 1132 patients with advanced-stage lung and colorectal cancer diagnosed in 2003-2005 who died before 2013. We linked patient and physician survey data, medical record data, and Medicare data, and we characterized Medicare spending in the last 30 days of life. After assessing differences in patient factors/beliefs, physician beliefs, and availability of services across areas that differed based on Dartmouth Atlas measures of intensity of end-of-life spending, we used mixed effects linear regression with random area effects to assess the area-level variance in spending in the last 30 days of life in our cohort and the proportion of that variance explained with sequentially adding groups of explanatory variables. **Results:** The mean (SD) expenditures in the last 30 days of life were $13,664 ($17,563). Physicians in higher-spending areas reported less knowledge and comfort caring for dying patients and less positive attitudes about hospice (all $P < .05$). Higher-spending areas had more physicians, a lower percentage of primary care providers, and fewer hospices/10,000 persons. Physician beliefs and availability of services each explained 45-60% of the variation in end-of-life expenditures; area-level patient beliefs did not contribute to area-level variations. **Conclusions:** Physicians' beliefs and area-level availability of services but not patients' beliefs were important factors explaining geographic variations in intensity of end-of-life spending for patients with advanced-stage cancer. Physician training and strategic allocation of services may have potential for decreasing unwarranted variation in care at the end of life for patients with advanced-stage cancers.

10009 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Patient-defined goals and preferences among older adults with cancer starting chemotherapy (CT). *First Author: Enrique Soto Perez De Celis, City of Hope, Duarte, CA*

Background: Older adults with cancer facing decisions with competing health outcomes may favor maintaining quality of life (QOL), independence, or cognition over prolonging survival. The goal of this study was to elicit preferences among outcomes from older adults starting CT. **Methods:** This is a secondary analysis of an ongoing prospective study aimed at identifying and addressing vulnerabilities in older adults (age ≥65) starting CT (NCT02517034). Patients completed 3 tools assessing preferences in health outcomes: 1) *Health Outcomes Tool:* rates the relative importance of 4 outcomes (survival, function, freedom from pain, and freedom from symptoms) using a visual analog scale (VAS); 2) *Now vs. Later Tool:* rates the relative importance of QOL at 3 times: today,1 year (y) in the future , and 5y in the future using a VAS; and 3) *Attitude Scale:* rates subjects' agreement with statements related to outcomes. We measured the proportion of patients reporting other outcomes being "as important" or "more important" than survival and studied their characteristics. **Results:** 121 patients (median age 71y, 47% male, 72% Stage IV, 31% gastrointestinal cancer) were included. 52% had poor physical function, 50% needed help with instrumental activities of daily living (e.g. cooking or transportation), and 73% had poor social support. On the *Health Outcomes Tool*, 44% rated other outcomes as more important than survival. On the *Now vs. Later* tool, 59% considered current QOL more/as important as QOL at 1y, and 58% considered current QOL more/as important as QOL at 5y. On the Attitude Scale, 58% agreed/strongly agreed with: "*I would rather live a shorter life than lose my ability to take care of myself*"; and 81% agreed/strongly agreed with: "I*t is more important to me to maintain my thinking ability than to live as long as possible*". Patients with good physical function and/or good social support were more likely to consider survival as the most important outcome, regardless of stage. **Conclusions:** Half of older patients rated other outcomes (particularly cognitive ability) as being more important than survival. Eliciting which outcomes are the most important for older patients can help define treatment goals and improve shared decision-making.

10010 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Quality of life (QoL) in older patients (pts) with cancer and prognostic factors for QoL decline. *First Author: Lore Decoster, UZ Brussel, Brussels, Belgium*

Background: QoL is an important outcome parameter for older pts with cancer. This study aims to investigate baseline QoL and its evolution during treatment in older pts with cancer and to determine prognostic factors for QoL decline. **Methods:** A prospective Belgian multicentre (n = 22) study was performed. Pts ≥70 years with a malignant tumor and abnormal G8 screening tool (≤14/17) underwent geriatric assessment (GA) and baseline QoL evaluation using the European Organization for Research and Treatment Quality of Life Questionnaire core 30 (EORTC QLQ-C30) Global Health Status Scale, with follow up at 2-3 months. QoL change was defined as the difference between follow-up and baseline QoL score and categorized in three groups: decline (< -10), improvement (> 10) and no change (≥-10 and ≤10). Uni- and multivariate regression was performed to determine factors associated with baseline QoL and with QoL decline (level of significance at p = 0.05). **Results:** 3673 pts with abnormal G8 and QoL data available at both time points were included in the present analysis. In multivariate analysis, baseline QOL was significantly worse with decreasing age, poor ECOG-PS (≥2 vs 0/1), higher stage (reference stage I) and abnormal geriatric domains such as functional status by instrumental activities of daily living, pain, fatigue, mental status and nutritional status. Pts with tumors of the digestive system, gynaecological system and thorax presented statistically lower baseline QoL compared to pts with breast cancer, (reference group) (p = 0.030; p = 0.017 and p = 0.017 respectively). During the course of treatment (n = 2972), an improvement in QoL was observed in 1037 pts (35%) and a decline in 838 pts (28.2%). In multivariate analysis, stage, baseline pain and fatigue, malnutrition and absence of comorbidities were prognostic for QoL decline **Conclusions:** Our study demonstrates that QoL improves in 1/3 of older pts with cancer during treatment, indicating that these pts can benefit from cancer treatment. On the other hand, QoL declines in 1/4 of older pts during cancer treatment and we identified prognostic factors for QoL decline in these pts. Directed interventions against pain, fatigue and malnutrition may subsequently improve QoL for these pts.

10011 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Relationship between preoperative geriatric frailty and need for postoperative intensive care unit admission and subsequent short- and long-term mortality. *First Author: Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The relationship between age-related impairments in geriatric surgical patients and the need for postoperative intensive care unit (ICU) admission and subsequent outcomes is largely unknown. **Methods:** Since 2015, Memorial Hospital surgical services have referred cancer patients age 75+ to the Geriatrics Service for preoperative evaluation including the eRFA (Shahrokni et al., JNCCN, Feb 2017). The eRFA has 13 items: the Karnofsky Performance Scale, basic and instrumental activities of daily living, Timed Up and Go test, history of falls, social activity level, social support, distress level, depression, cognitive impairment, polypharmacy, weight loss, and number of comorbid conditions. In order to develop a scoring system , we performed a univariate & multivariate analysis of the correlation between these variables, the frequency of ICU admission, and the likelihood of 12-month mortality among ICU survivors. **Results:** 1164 patients (median age 79) were evaluated prior to surgery after which 53 patients (4.6%) were admitted to the ICU. Five eRFA factors were associated with ICU admission: > 4 comorbid conditions, weight loss > 10 pounds, polypharmacy, limited social activity, and high distress level. The median number per patient of these 5 impairments in our cohort was 2. In a univariate analysis, frail patients (> 2 of 5 impairments) were more likely to be admitted to the ICU than fit patients (≤2 of 5 impairments (OR = 3.42, p < 0.001). The correlation persisted after adjusting for age, gender, ASA performance status, duration of surgery, and preoperative albumin level (OR = 2.87, p = 0.013). The one year mortality of patients not needing ICU care was 1.8% for fit patients and 5.7% for frail patients. The one year mortality of patients needing ICU care was 9.4% for fit patients and 20.4% for frail patients. **Conclusions:** Frail patients are at higher risk for postoperative ICU stay compared to fit patients. 1 out of 5 frail patients age 75+ dies within 1 year after ICU stay. Future studies should assess the effectiveness of interventions aimed to improve the long-term outcomes of geriatric ICU survivors.

10012 Clinical Science Symposium, Mon, 1:15 PM-2:45 PM

Randomized trial of a pharmacy intervention for older adults with cancer. *First Author: Margaret Ruddy, Massachusetts General Hospital, Boston, MA*

Background: Oncology clinicians often struggle with managing medications and vaccinations in older adults with cancer. We sought to demonstrate the feasibility and preliminary efficacy of integrating pharmacists into the care of older adults with cancer to enhance medication management and administration of appropriate vaccinations. **Methods:** We enrolled patients age ≥65 years with breast, gastrointestinal (GI), or lung cancer receiving first-line chemotherapy and randomly assigned them to the pharmacy intervention or usual care. Patients assigned to the intervention met with a pharmacist during their second or third chemotherapy infusion. The pharmacist performed medication reconciliation, obtained vaccination history and made recommendations to the care team. We obtained information about patients' medications and vaccinations via patient-report and from the electronic health record (EHR) at baseline and week 4. We determined the number of discrepant medications, defined as the difference between patient-report and the EHR; and categorized medications as potentially inappropriate, based on Beers Criteria as determined by non-intervention pharmacists blinded to group assignment. We defined the intervention as feasible if > 75% of patients enrolled in the study and attended the visit with the pharmacist. **Results:** From 1/17/17-10/27/17, we randomized 60 patients (median age = 71.5 years [range 65.1-91.5]; 32 [53.3%] female; 39 [65.0%] retired; cancer types: 27 [45.0%] GI, 21 [35.0%] lung, and 12 [20.0%] breast). We enrolled 80.1% of patients approached, and 96.6% of patients assigned to the intervention attended the pharmacist visit. At week 4, patients assigned to the intervention had higher vaccination rates for pneumonia (67.9% vs 40.0%, P = .040) and influenza (67.9% vs 23.3%, P = .001). Compared with usual care, intervention patients had fewer discrepant (5.8 vs 8.3, P = .081) and potentially inappropriate (3.5 vs 4.8, P = .069) medications at week 4, although the differences were not statistically significant. **Conclusions:** Integrating pharmacists into the care of older adults with cancer is feasible with encouraging preliminary efficacy for enhancing medication management and improving patients' vaccination rates. Clinical trial information: NCT02871115.

10013 Poster Discussion Session; Displayed in Poster Session (Board #1), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Impact of cancer on employment and finances in young adult (YA) survivors. *First Author: Tyler Garrett Ketterl, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: YA survivors face challenges unique from those survivors of childhood cancer or older adults. The potential impact of cancer or its treatment upon employment and financial burden in YAs are not fully known. **Methods:** Eligibility included diagnosis of malignancy between ages 18-39, 1-5 years from diagnosis and ≥1 year from therapy completion. Participants were randomly selected from tumor registries of 7 participating sites and asked to complete an online patient reported outcomes survey. Diagnostic/treatment data were abstracted from medical records. **Results:** Subjects included 872 survivors, 72.3% female, grouped into 4 diagnostic categories: breast (n = 209), thyroid (n = 104), lymphoma (n = 91), and other (n = 332) including brain tumors. Most survivors (736, 84.4%) reported working for pay at some time between diagnosis and survey completion and 517 (70.2%) reported a physical component to their job and that their cancer/treatment interfered with their ability to perform the physical (58.6%) or mental (54.2%) job tasks required. Males were more likely to be working for pay any time after diagnosis (OR1.6, 95% CI 1.0-2.5, p = 0.05). Survivors treated with surgery alone were less likely to have impairments limiting their ability to perform physical (OR 0.5 95% CI 0.3-0.7, $p < 0.005$) or mental tasks (OR 0.4, 95% CI of 0.3-0.5, $p < 0.005$) at work compared to those treated with chemotherapy +/- radiation. 56.6% reported taking extended paid or unpaid time off from work, or made a change in their hours, duties or employment status and 95.6% of those reported this was related to their cancer/treatment. Unpaid time off from work was taken by 286 survivors (38.9%) with 107 (37.4%) of those taking > 6 months unpaid time off. Survivors in the "other diagnosis" category were significantly more likely to have taken unpaid time off work (OR of 1.5, 95% CI 1.0-2.2, p = 0.015). Nearly 1/3 of all survivors reported that they/their family borrowed money or went into debt because of cancer/treatment; 47.2% with debt borrowed > $10,000 and 13 (4.9%) reported bankruptcy. **Conclusions:** In YA survivors, cancer/treatment has a significant impact on the physical and mental activities of their jobs and many report ongoing work limitations > 1 year from therapy completion.

10014 Poster Discussion Session; Displayed in Poster Session (Board #2), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Predictors of long-term follow-up care (LTFU) among survivors of adolescent and young adult (AYA) cancers: A population-based study in the IMPACT cohort. *First Author: Dalia Kagramanov, The Hospital for Sick Children, Toronto, ON, Canada*

Background: AYA cancer survivors are at elevated risk for developing therapy-related adverse health outcomes and require life-long risk-adapted health care. We determined the location and providers of LTFU care received by a population-based cohort of survivors and explored the demographic, disease and treatment factors that predict care received. **Methods:** We conducted a retrospective study using multiple linked administrative health databases in Ontario, Canada. Five-year AYA cancer survivors were identified from the IMPACT cohort, which consists of all AYA who were 15-20.9 years of age at diagnosis of one of six specified cancers in Ontario between 1992-2010. We defined four models of care: specialized survivor clinic; general oncology clinic; primary care physician; no regular care. Specialized survivor clinic attendance was only available to those treated at a paediatric cancer centre. Separate Poisson regression models determined attendance rates, adjusting for demographic, disease and treatment characteristics. **Results:** The cohort consisted of 1574 survivors (1066 treated at adult centres; 508 treated at paediatric centres). Median follow-up from five-year survival was 8.7 years (95% CI, 4.3-13.9 years). Over their follow-up, the highest level of care accessed by survivors was: survivor clinic (16.7%), oncology clinic (47.3%), PCP (9.3%), no regular care (26.7%). Among those eligible for the specialized survivor clinics, greater attendance was observed in females, those younger at diagnosis, living closer to a clinic, and those treated with Bone-Marrow Transplant. Specialized clinic attendance decreased by 19% with every 2-years of follow up. In contrast, the risk of receiving no regular care among all survivors was highest in males and increased by 20% with every 2-years of follow-up. **Conclusions:** Despite the need for risk-based care, most eligible AYA survivors do not attend specialized clinics, and almost one-third receives no regular care, with lack of care increasing over time. Strategies are needed to ensure that the maximum number of survivors receive life-long risk-based care.

10015 Poster Discussion Session; Displayed in Poster Session (Board #3), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Risk of chronic comorbidities in survivors of adolescent and young adult cancer (AYA). *First Author: Chun Chao, Kaiser Permanente Southern California, Pasadena, CA*

Background: Data needed to develop age-appropriate survivorship care guidelines for AYA cancer are lacking. Using a retrospective cohort design, we described risk of chronic comorbidities in AYA cancer survivors. **Methods:** 6,778 two-year survivors of cancers diagnosed at age 15-39y at Kaiser Permanente Southern California between 2000-2012 were included. A non-cancer comparison group (N = 87,737) was matched to cancer survivors (1:13) on age, sex and calendar year. New onset of comorbidities listed in Table 1 was ascertained using ICD-9 diagnosis codes, laboratory values, medication prescription and cause of death in the electronic health records through end of 2014. Incidence rate and incidence rate ratio (IRR) from Poisson regression adjusting for age, sex, race/ethnicity were derived for each comorbidity. Within cancer survivors, multivariable Poisson regression was used to evaluate the associations between chemotherapy exposures (mutually adjusted) and risk of selected comorbidities. **Results:** Median age at cancer diagnosis was 33y; 35% were male; 42% were non-Hispanic white. The most common cancer types were thyroid (16%), breast (16%) and melanoma (10%). Comparison with non-cancer subjects: see Table 1. Within cancer survivors: chemotherapy exposure was associated with multiple comorbidities. The largest IRR was found for methotrexate use and avascular necrosis (AN) (IRR = 15.5); followed by ifosfamide and chronic kidney disease (IRR = 8.3); and bleomycin and pulmonary fibrosis (IRR = 4.7). **Conclusions:** These data provide basis for identifying high-risk individuals for population-based targeted surveillance.

IRR for cancer survivors in reference to non-cancer comparisons.

	IRR	95% Confidence Interval	
Heart Failure	2.6	1.8	3.8
Coronary Artery Disease	1.6	1.1	2.3
Stroke	3.2	2.4	4.3
Dyslipidemia	1.3	1.2	1.4
Hypertension	1.4	1.2	1.5
Premature Ovarian Failure	2.9	1.6	5.3
Diabetes	1.5	1.3	1.7
Thyroid Disorders	2.1	1.8	2.4
Hearing Loss	1.7	1.3	2.1
Vision Loss	1.4	0.7	2.5
Asthma	1.2	1.0	1.4
COPD	2.3	1.3	4.2
Severe Depression/Anxiety	1.4	1.2	1.6
Chronic Liver Disease	2.4	2.0	2.8
Renal Failure	2.5	2.1	3.0
Avascular Necrosis	8.3	4.6	14.9
Fractures	2.1	1.6	2.8
Joint Replacement	3.9	2.4	6.2
Osteoporosis	5.8	3.7	8.9

10016 Poster Discussion Session; Displayed in Poster Session (Board #4), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Scrambler therapy for established chemotherapy-induced neuropathy: A randomized phase II trial. *First Author: Charles L. Loprinzi, Mayo Clinic, Department of Oncology, Rochester, MN*

Background: Pilot data support that Scrambler therapy may benefit patients with Chemotherapy-induced peripheral neuropathy (CIPN). **Methods:** Patients with CIPN for at least 3 months were eligible if the patient had finished previous neurotoxic chemotherapy. They needed to have CIPN-related tingling or pain of at least 4/10 during the week prior to registration. Patients were randomized to receive Scrambler therapy versus TENS (trans-electrical nerve stimulation), for 2 weeks. Patient- reported outcomes were utilized, including the EORTC CIPN 20 instrument, the Subject Global Impression of Change (GIC) scale, and a number of 0-10 numerical analog scales regarding applicable symptoms. After each treatment day, and weekly for 8 more weeks, patients were asked whether they would recommend their therapy to others. The primary chosen endpoint was the percentage of patients who achieved more than 50% reduction in pain or tingling scores (based on which item was selected most problematic at baseline for each patient), from baseline values, after 2 weeks of therapy. The proportion of patients with ≥50% reduction in symptom scores were estimated and compared using the chi-square test. The areas under the curves (AUC) were compared using the t-test. **Results:** 50 patients were randomized, 25 per arm. Data are provided in the Table. P values are provided, understanding that this is not a well-powered phase III trial. **Conclusions:** These results support that Scrambler therapy decreases CIPN symptoms, to a moderate degree. Further exploration of this approach is indicated. Clinical trial information: NCT01290224.

Item (higher scores are better)	Scrambler	TENS	P-value
≥50% reduction in selected pain/tingling scores, at 14 days	40%	20%	0.06
≥50% reduction in pain scores, at 14 days	56%	28%	0.04
≥50% reduction in tingling scores, 14 days	48%	24%	0.08
14 day AUC pain reduction from baseline	25	16	0.08
14 day AUC tingling reduction from baseline	24	13	0.08
14 day AUC GIC neuropathy symptoms rating	17	5	0.001
14 day AUC GIC pain rating	13	4	0.004
14 day AUC GIC overall QOL rating	14	4	0.006
10 week AUC pain reduction from baseline	11	13	0.72
10 week AUC GIC neuropathy symptoms rating	7	3	0.09
10 week AUC GIC pain rating	5	2	0.16
10 week recommendation of therapy to other patients (mean)	82%	39%	0.0001

10017 Poster Discussion Session; Displayed in Poster Session (Board #5), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Randomized, double-blind, phase III trial of monosialotetrahexosylganglioside versus placebo in GI cancer patients with oxaliplatin induced peripheral neurotoxicity (TJMUCH-GI-001). *First Author: Zhou Likun, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy Tianjin Medical University, Tianjin, China*

Background: Neurotoxicity is the most common dose-limiting toxicity of oxaliplatin. There is no treatment for cumulative sensory neuropathy. This trial is designed to study the efficacy of Monosialotetrahexosylganglioside (GM1) in GI cancer patients with oxaliplatin-induced peripheral neurotoxicity (OIPN). **Methods:** In this single center (TJMUCH),double-blind, phase III trial, patients were randomized in a 1:1 ratio to receive GM1 or placebo. Patients with OIPN persisting during or after oxaliplatin-based chemotherapy were eligible. The patients who remained on oxaliplatin after enrollment, received concurrent placebo or GM1 x 7 days with each chemotherapy cycle. The patients who stopped taking oxaliplatin, were treated with placebo or GM1 x 14 days every 3 weeks. GM1 was dosed at 60mg daily for every 3-week or 40mg daily for every 2-week schedule. Trial was continued until visual analogy score (VAS) decreased by ≥30% or stayed unchanged after two more treatments beyond completion of oxaliplatin. The primary endpoint was reduction of modified EORTC QLQ-CIPN20(MCIPN20) score by ≥30%. Secondary endpoints were improvement of VAS by ≥30%, CTCAE grade by≥1. Patients who received ≥1 treatment cycle were included in the analysis. Chi-square tests were used for statistical analysis. **Results:** From May 2015 to Dec 2017, 73 patients were enrolled in GM1 and 72 in placebo arm. 39 (53%) patients in GM1 and 10 (14%) in placebo arm achieve ≥30% reduction in MCIPN20 (RR = 3.85, 95% CI, 2.08-7.11, P < 0.0001). 36 (49%) patients in GM1 and 16 (22%) in placebo arm had ≥30% improvement of VAS (RR = 2.22, 95% CI,1.36-3.623, P = 0.001). The median treatment cycles of GM1 was 2 (range,1-7). Majority of patients in both arms (89% in GM1 and 83% in placebo) continued receiving oxaliplatin on the trial. There were no significant differences in CTCAE and acute neurotoxicity grading between the two arms. There was no ≥G3 GM1 related adverse events. **Conclusion:** GM1 effectively reduces OIPN in GI cancer patients. The observed clinical benefit is independent of oxaliplatin discontinuation. Trial: NCT02486198 (Drug was afforded by Qilu Pharmaceutical Co., Ltd, China). Clinical trial information: NCT02486198.

10018 Poster Discussion Session; Displayed in Poster Session (Board #6), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Pretreatment physical activity to predict short- and long-term chemotherapy-induced peripheral neuropathy (CIPN) in a nationwide longitudinal study of paclitaxel for breast cancer. *First Author: Ian Kleckner, University of Rochester Medical Center, Rochester, NY*

Background: CIPN is a dose-limiting toxicity with no established treatments and limited knowledge of risk factors. Exercise during chemotherapy may mitigate CIPN, but it is unknown whether pre-treatment physical activity protects against CIPN. This secondary analysis examines whether physical activity before paclitaxel predicts short- and long-term CIPN symptom severity. **Methods:** 200 women with non-metastatic breast cancer (52±10 years) receiving paclitaxel with curative intent rated their CIPN (0-10 severity of numbness/tingling in the past week) three times—within 1 week pre-paclitaxel, and within 1 month and 6 months post-paclitaxel. We used linear regression to test whether pre-paclitaxel patient-reported physical activity (Aerobic Center Longitudinal Study) predicted CIPN symptoms (either within 1 month or 6-months post-paclitaxel) controlling for pre-paclitaxel neuropathy, age, BMI, diabetes (yes/no), and cumulative paclitaxel dose. **Results:** CIPN symptom severity increased significantly from pre- to post-paclitaxel (+3.6 units; $p < 0.001$) and from pre- to 6-month follow-up (+2.08; $p < 0.0001$). This is a high level of development of CIPN considering that a 0.5-unit change is clinically significant. Each additional 15 min/day of physical activity pre-paclitaxel was associated significantly less severe CIPN symptoms at post-paclitaxel (-0.5; $p = 0.0002$) and 6 months follow-up (-0.25; $p = 0.09$). Each additional 10 years of age was associated with significantly more severe CIPN symptoms at post-paclitaxel (+0.8, $p < 0.0001$) and 6-month follow-up (+0.9; $p < 0.0001$) controlling for pre-paclitaxel neuropathy, physical activity, BMI, diabetes, and paclitaxel dose. **Conclusions:** Breast cancer patients who are more physically active pre-paclitaxel experience less severe CIPN immediately and 6 months post-paclitaxel. Physical activity may be especially important for older patients because CIPN severity increases with age. Clinicians prescribing paclitaxel should ask patients about pre-treatment physical activity levels because it may lead to greater treatment tolerability.

10019 Poster Discussion Session; Displayed in Poster Session (Board #7), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Efficacy and safety of additional olanzapine to ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting: A randomized, double-blind, placebo-controlled, crossover study. *First Author: Veerisa Vimolchalao, Division of Oncology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: Currently, the antiemetic regimen consisting of dexamethasone, palonosetron plus a NK-1 antagonist or olanzapine is recommended in prevention of chemotherapy induced nausea and vomiting (CINV) for highly emetogenic chemotherapy (HEC). However, palonosetron and NK-1 antagonists are costly and not accessible for all Thai patients. We sought to evaluate efficacy and safety of the additional olanzapine to ondansetron and dexamethasone for CINV prevention in patients receiving HEC. **Methods:** We randomly assigned chemotherapy-naïve patients receiving either anthracycline-cyclophosphamide or high dose cisplatin (≥50 mg/m^2) regimen, to receive olanzapine or placebo in addition to ondansetron and dexamethasone. All subjects were crossed over to another arm on second-cycle chemotherapy. The primary endpoint was complete response (CR) rate defined as no vomiting and no use of rescue drugs. **Results:** At first cycle, CR was 69% among the 32 patients receiving olanzapine and 25% among the 32 patients receiving placebo, $p < 0.001$. CR was significantly better with olanzapine than with placebo in acute phase (0-24 h) (75% vs. 31%, $p < 0.001$) and delayed phase (24-120 h) (69% vs. 43%, $p = 0.038$). In analysis after two crossover antiemetic regimens, CR was improved in olanzapine group compared to placebo group in acute phase (72% vs. 33%, $p < 0.001$), delayed phase (67% vs. 38%, $p < 0.001$) and overall period (67% vs. 25, $p < 0.001$). In crossover analysis using visual analog score (VAS), the patients with olanzapine had lower mean VAS in nausea (1.28 vs. 3.05, $p < 0.001$) and fatigue (3.5 vs. 4.58, $p < 0.001$) but higher mean VAS in appetite (2.5 vs. 1.55, $p = 0.003$) and sleepiness (3.26 vs. 2.2, $p < 0.001$). There were no grade 3 and 4 antiemetic-drug-related toxicities. Mean QT interval change did not different between two groups (-4.30 ms vs. -1.86 ms, $p = 0.69$). The olanzapine combination was preferable to placebo in 52 of 60 patients ($p < 0.001$). **Conclusions:** Without the NK-1 antagonists, the additional olanzapine to ondansetron and dexamethasone significantly improved CINV prevention and was safe in patients receiving HEC.

10020 Poster Discussion Session; Displayed in Poster Session (Board #8), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Treating anorexia in people with advanced cancer. a randomised, double blind, controlled trial of megestrol acetate, dexamethasone or placebo. *First Author: David Christopher Currow, University of Technology Sydney, Sydney, Australia*

Background: This multi-site, double blind, parallel arm, fixed dose phase III study compared megestrol acetate 480 mg/day, dexamethasone 4 mg/day and placebo for their net short-term effect on appetite and quality of life (QoL) in people with advanced cancer **Methods:** Inpatients or outpatients seeing a palliative care team with anorexia for ≥2 weeks with a score ≤4 on a 0-10 numeric rating scale (NRS; 0 = no appetite, 10 = best possible appetite) were recruited. Participants were randomised to receive megestrol 480 mg, dexamethasone 4 mg or placebo daily for up to 4 weeks. Primary response assessment occurred at day 7, and responders were defined as having more than a 25% improvement in NRS compared to baseline. **Results:** There were 190 people randomised (megestrol acetate n = 61; dexamethasone n = 67, placebo n = 62). At week 1 (primary endpoint), 79·3% of participants in the megestrol group, 65·5% in the dexamethasone group and 58·5% in the placebo group (p = 0·067) were responders. No differences in weight, performance status or quality of life were reported. Treatment emergent adverse events occurred in the majority of participants (90·4%), and included altered mood and insomnia. Hyperglycemia was more frequent in people on dexamethasone. **Conclusions:** Although there was little difference between treatment groups for the primary or secondary effectiveness endpoints, there was a consistent trend in secondary endpoints favouring megestrol acetate than dexamethasone or placebo. Subgroup analyses indicate megestrol acetate may be more effective in maintaining body weight for subjects whose appetite responded. Clinical trial information: ACTRN12608000405314.

10021 Poster Discussion Session; Displayed in Poster Session (Board #9), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Retrospective cohort study comparing hydration protocols with or without mannitol in patients treated with cisplatin (HYDRA study). *First Author: Nathalie LeTarte, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, QC, Canada*

Background: Various hydration protocols have been used to mitigate acute kidney injury (AKI) induced by cisplatin. The use of mannitol remains controversial however recent studies suggested that mannitol has a protective effect against cisplatin-induced nephrotoxicity. **Methods:** This is a retrospective observational study including patients who received at least one dose of cisplatin between September 2010 and December 2016 at the Centre Hospitalier de l'Université de Montréal. After approval by our IRB, we compared the risk of all grade AKI between hydration protocols with or without mannitol (12.5 g if cisplatin < 75 mg/m^2 or 25 g if cisplatin ≥ 75 mg/m^2). Patients received a total of 3 or 4 L of fluids (D5/0.45 NS or NS) according to the cisplatin dose. AKI was evaluated by comparing baseline serum creatinine (SCr) to the highest SCr levels between each cycle. **Results:** Of 1932 patients identified, 1821 were included in this study of which 658 received mannitol whilst 1163 received hydration alone. The risk of all grade AKI was significantly lower in the mannitol group for patients with lymphoma, gynecologic, upper gastrointestinal and urinary tract malignancies. No difference was seen for head and neck, lung, germ cell and others cancer (see table I). In the subgroup of patients receiving cisplatin < 75 mg/m^2, mannitol reduced all grade AKI for head and neck (HR 0.37 [95% CI 0.2 – 0.8]), lung (HR 0.56 [95% CI 0.3 – 0.98], upper GI (HR 0.15 [95% CI 0.1 – 0.5]) and urinary tract cancer (HR 0.14 [95% CI 0.1 – 0.5]). **Conclusions:** Hydration protocols containing mannitol were associated with a significantly lower risk of all grade AKI compared to hydration alone. Therebefore, mannitol should be added to hydration protocol with cisplatin especially those with doses < 75 mg/m^2.

All grade AKI for mannitol vs non-mannitol hydration.

Malignancies	Hazard Ratio [95% CI]	p value
Head and Neck (N = 543)	0.99 [0.7–1.5]	p = 0.99
Lung (N = 456)	0.73 [0.5–1.1]	p = 0.096
Gynecologic (N = 333)	0.50 [0.3–0.94]	p = 0.033
Upper GI (N = 128)	0.32 [0.1–0.8]	p = 0.009
Urinary tract (N = 80)	0.29 [0.1–0.7]	p = 0.005
Lymphoma (N = 63)	0.33 [0.2–0.8]	p = 0.008
Germ cell cancer (N = 69)	1.15 [0.3–4.4]	p = 0.836
Other (N = 149)	1.29 [0.6–2.7]	p = 0.508

10022 Poster Discussion Session; Displayed in Poster Session (Board #10), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Survival of advanced cancer patients (ACP) receiving early inpatient palliative care (PC) compared to standard oncologic care (SOC) without palliative care. *First Author: Fay J. Hlubocky, University of Chicago Medicine, Chicago, IL*

Background: Palliative care has been described as significantly enhancing ACP quality of life, symptom control, and reducing healthcare costs. Increasing evidence has shown improved outcomes for hospitalized ACP including discharge status, transitions to end-of-life care, and overall morality. **Methods:** An ACP cohort receiving either PC or SOC between Jan 2015-Dec 2015 were retrospectively analyzed for potential predictors associated with discharge and death. Demographics, diagnosis, discharge status, and survival from the time of discharge were compared between groups. Univariate and multivariate analyses were performed (e.g. log-rank survival and Cox proportional hazards regression). **Results:** Of a total of 810 patient encounters, 468 were admitted to PC and 342 to SOC. In comparison with SOC, PC were more likely to be: younger (61.1±13.2 v. 62.5±13.0, p = 0.02); AA (48% v. 36%, p = 0.0045); female (50% v. 40%, p = 0.005); shorter length of inpatient stay(5.7± 4.9 v. 6.2±6.5, p = 0.01). Compared with SOC, ACP receiving PC were more likely to be discharged to: home (55% v.45%, p = 0.01); healthcare facilities (e.g. skilled nursing, inpatient rehabilitation) (36.1% v. 20%, p = 0.04); and hospice (home and inpatient) (7.7% v 5.8%, p = 0.02). PC had overall greater median survival from the time of discharge (106.8±99.95 v. 73.8±61.93, p = 0.03) compared to SOC. PC were less likely to die during admission compared to SOC (4.7% v. 6.8%, p = 0.01) and 1.2 times more likely to be discharged home (p < 0.0001). Home discharge was associated with longer survival (ratio = 0.34; 95%CI, p = 0.002). For PC, multivariate logistic regression revealed younger age (< 50) (p < 0.001); female gender (p = 0.004); and AA ethnicity (p = 0.003) was associated with home discharge. Primary cancer diagnosis (p = 0.0001) and disease severity (p = 0.0034) were independently associated with greater likelihood of death. **Conclusions:** Results from this simultaneous care program reveal a unique model of care such that early inpatient PC benefits younger and underserved ACP with distinct clinical characteristics and survival, with improved outcomes, compared to those receiving SOC.

10023 Poster Discussion Session; Displayed in Poster Session (Board #11), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Association between phase angle and survival in patients with advanced cancer admitted to an acute palliative care unit (APCU). *First Author: David Hui, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Many complex healthcare decisions in the last weeks and days of life are dependent on accurate prediction of survival. Phase angle, a novel measure of cellular function, has been found to be prognostic in patients with months of survival; however, its utility has not been examined in patients with weeks/days of survival. We determined the association between phase angle and survival in advanced cancer patients admitted to an APCU. **Methods:** In this prospective cohort study, we assessed phase angle with bioelectric impedance analysis in consecutive patients with advanced cancer admitted to our APCU. Survival analysis was conducted using the Kaplan Meier method, log rank test and multivariate Cox regression analysis, adjusting for established prognostic factors including the Palliative Prognostic Score and delirium. We identified the optimal phase angle cutoff using the Contal and O'Quigley method. Subgroup analysis was conducted in patients without peripheral edema. **Results:** Among 204 patients, the median overall survival was 10 days (95% confidence interval 8-11 days). 74 (36%) did not have edema. The median phase angle was 3.7° for the entire cohort and 3.9° for the no edema cohort. In univariate analysis, a low phase angle was associated with decreased survival for the entire cohort (≤3° vs. > 3°, median survival 7 vs. 10 days; P = 0.045) and for the no edema cohort (5 vs. 18 days; P < 0.001). In multivariate Cox regression analysis adjusting for known prognostic factors, phase angle was not significant for the entire cohort but remained significant in the no edema cohort (hazard ratio 2.46, 95% confidence interval [CI] 1.14, 5.31; P < 0.001). Specifically, phase angle ≤3° had an accuracy of 86% (95% CI 77%-93%) for 3 day survival among patients without edema, with a sensitivity of 50%, specificity of 90%, positive predictive value of 30%, negative predictive value of 95% and positive likelihood ratio of 5.2. **Conclusions:** We identified phase angle as a novel, independent prognostic factor even among patients with a short survival. Phase angle ≤3° was predictive of impending death within 3 days. Our findings suggest that phase angle may be best used among patients without edema.

10024 Poster Discussion Session; Displayed in Poster Session (Board #12), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Comprehensive evaluation of place of death for patients with hematological malignancies, 1999-2015. *First Author: Fumiko Ladd Chino, Duke University Radiation Oncology, Durham, NC*

Background: Patients with hematologic malignancies (HM) are more likely to receive aggressive care at the end of life than patients with solid tumors, and less often utilize hospice care. However, most prior research in this area is Medicare-based (only patients ≥65), or limited to hospice reporting, thus more comprehensive US-based analyses are needed. **Methods:** CDC WONDER contains death certificate data for all US counties and is maintained by the National Center for Health Statistics. Place and year of death was obtained for all HM deaths from 1999- 2015, as well as sociodemographic information. Place of death was dichotomized to death at home or hospice facility, vs other location. Data from 2015 was used to test for disparities in place of death associated with sociodemographic variables or primary cancer on univariate (UVA) and multivariate (MVA) logistic regression. **Results:** In the study period, there were 951,435 deaths due to HM. 26.1% of HM deaths were in those aged < 65. HM inpatient deaths decreased from 54.6% in 1999 to 38.2% in 2015, while home (25.9 to 32.7%) and hospice facility deaths (0 to 12.1%) increased (p < 0.001). On MVA of all cancers, including solid tumors, patients with HM had the lowest odds of home or hospice facility death (OR 0.56, 95% CI 0.55-.057). Compared to any other cancer type, in 2015 patients with HM were 65% more likely to die in the hospital (38.2% HM vs 23.2% non-HM) and 25% less likely to die at home (32.7% HM vs 43.6% non-HM) (both p < 0.001). On MVA of HM cancers, older age (40-64: OR 1.57, 95%CI 1.35-1.82 and 65+: OR 2.29, 95%CI 1.97-2.65), being married (OR 1.44, 95%CI 1.44-1.73) and having myeloma (OR 1.32, 95%CI 1.25-1.39) were associated with death in home or hospice facility, while being black (OR 0.71, 95%CI 0.66-0.77), Asian (OR 0.55, 95%CI 0.48-0.64) or Hispanic (OR 0.83, 95% CI 0.76-0.90) or having a chronic leukemia (OR 0.81, 95%CI 0.76-0.87) had decreased odds of dying at home or hospice. **Conclusions:** Despite a 30% decrease in hospital deaths over time, patients with HM remain more likely than solid tumor patients to die in the hospital, and disparities exist along age, racial, and ethnic lines. Continued efforts are needed to improve the provision of quality end-of-life care in hematology.

10025 Poster Session (Board #13), Mon, 1:15 PM-4:45 PM

Hospice use among Medicare fee-for-service (FFS) or managed-care organization (MCO) enrollees with leukemia and myeloma. *First Author: Adam J. Olszewski, The Warren Alpert Medical School of Brown University, Providence, RI*

Background: Hospice services are "carved out" of Medicare MCO contracts and covered by FFS Medicare. This financially incentivizes MCOs to enroll their patients (pts) in hospice early, and may affect survival outcomes. We compared the use of hospice at the end of life (EOL) and associated overall survival (OS) among MCO and FFS Medicare beneficiaries with hematologic cancers, who are known to underuse hospice and need effective strategies to improve their EOL care. **Methods:** From the linked Surveillance, Epidemiology, and End Results-Medicare database, we selected pts with acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or myeloma who died in 2007-2011. We identified their MCO/FFS status before death, hospice use at EOL, and disenrollment from hospice before death. We compared binary outcomes in multivariable robust Poisson models, reporting relative risk (RR) adjusted for multiple sociodemographic characteristics. OS from diagnosis was compared in Cox models, reporting adjusted hazard ratios (HR) with 95% confidence intervals (CI). **Results:** Among 24,118 pts (median age 78 y, 43% women), 25% were enrolled in a MCO at EOL. MCO enrollees were 17% more likely to use hospice than pts with FFS Medicare (RR, 1.17; 95%CI, 1.14-1.21), consistent across histologies (Table). They were also less likely to use hospice services for < 3 days (RR, 0.82; 0.75-0.89). We found no difference in adjusted OS (HR, 0.98; 0.95-1.01), or in the rate of early hospice disenrollment (RR, 1.07; 0.91-1.27) between MCO and FFS enrollees. **Conclusions:** Compared with FFS enrollees, MCO enrollees with leukemia or myeloma use hospice more frequently and for longer, without any decrease in survival. Enhanced care coordination in MCO may contribute to more meaningful use of hospice among pts with these cancers, suggesting a novel strategy for improving quality of care at EOL in hematology.

	AML	CLL	Myeloma
N	7,347	6,847	9,924
Hospice at EOL, MCO / FFS	54% / 47%	50% / 45%	55% / 48%
RR (95%CI)	1.18 (1.12-1.24)	1.15 (1.08-1.22)	1.18 (1.12-1.23)
< 3 days on hospice, MCO / FFS	19% / 25%	18% / 20%	17% / 21%
RR (95%CI)	0.74 (0.64-0.87)	0.89 (0.74-1.06)	0.85 (0.74-0.98)
HR for OS (95%CI)	1.01 (0.95-1.08)	0.94 (0.88-1.00)	0.98 (0.94-1.04)

10026 Poster Session (Board #14), Mon, 1:15 PM-4:45 PM

Aligning goals of care with aggressiveness at end of life (EOL). *First Author: Sara L Douglas, Case Western Reserve University-Nursing and Case Comprehensive Cancer Center, Cleveland, OH*

Background: Aggressiveness of care at EOL should be aligned with the patient's (Pt) goals of care that ideally are established in collaboration with the oncologist (MD). This is particularly important for Pts with advanced disease. **Methods:** A longitudinal study was conducted. Adult Pts with Stage IV gastrointestinal (GI) or lung cancer were eligible. Each Pt and MD were surveyed at study enrollment and every 3 months for 15 months or until the Pt died. The primary variables of interest were the Pt and MD identified goals of care using a visual analog scale (VAS). Scores on the VAS ranged from 0 (comfort, quality of life) to 100 (survival, length of life). Individual scores > = 70 indicated a strong preference for prolonging survival and presumably a willingness to undergo aggressive interventions. Scores < = 30 indicated a strong preference for comfort care and presumably a willingness to forgo aggressive interventions. Aggressiveness of care was assessed using standard indicators (e.g. > 1 hospitalization in last 30 days of life, hospice stay < 3 days, etc.). **Results:** Between January 2015 and July 2017, 378 Pts were enrolled. Refusal rate was 27.5%; attrition rate 8.1%. 168 Pts (44%) died and their results are presented. Mean age was 64 years (range = 36-88 years); 66% had GI and 34% had lung cancer. Mean time from enrollment to death was 6.5 months (range = 3-15 months). As seen in Table 1, when there was strong agreement between Pt and MD on goals (either survival or comfort) the patient received levels of aggressiveness of care that were reflective of the goals. For example, when Pt and MD agreed on the goal of survival, 90% received at least 1 indicator of aggressive treatment. **Conclusions:** These data confirm the importance of aligning Pt and MD goals of care. When there are differences in goals, regardless of whether the Pt or MD identified comfort as the priority, Pts are at risk for receiving care that is not congruent with their preferences and goals of care.

	Survival Pt > MD	Survival MD > Pt	Survival Agreement	Comfort Pt > MD	Comfort MD > Pt	Comfort Agreement
% of Subjects (n = 168)	17.3%	11.3%	5.95%	19.6%	23.8%	12.5%
Hospice LOS: Md	12.5	15	2	12	13	20.5
No Aggressive Tx (%)	75%	63%	10%	66%	64%	81%

10027 Poster Session (Board #15), Mon, 1:15 PM-4:45 PM

Impact of palliative care consults on racial disparity in do-not resuscitation (DNR) orders at an urban safety net hospital. *First Author: Nizar Bhulani, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Previous studies have suggested that racial disparities exist for DNR orders in cancer patients. We examined racial differences in DNR orders for pancreatic cancer patients in an urban setting safety net hospital with a high proportion of black patient population. **Methods:** Retrospective analysis was conducted of pancreatic cancer patient records seen at the Parkland Health and Hospital System, Dallas between 1/1999 - 9/2016. Cancer cases and receipt of palliative care were identified from prospectively maintained registries. Demographics, cancer characteristics, DNR order, were abstracted. All statistical analysis was done using IBM SPSS version 24. **Results:** A total of 455 pancreatic cancer patients were included; mean age was 61 years, 227 (50%) were female, 228 (50%) were white and 202 (44%) were black, 277 (61%) received a palliative care, and 29 (6.4%) had at least one ICU admission. There was no statistically significant difference in palliative care consults between whites and black patients. Do-Not-Resuscitate (DNR) order was placed for 140 (30.8%) patients within 60 days of death. DNR status was significantly associated with cancer stage, admission to the ICU and receiving a palliative care consult ($p < 0.001$). There was no difference in the rate of DNR order between white and black patients, 29.7% (68/229) white patients and 32.2% (65/202) black patients ($p = 0.71$). Additionally, age, sex, cancer site or histology were not associated with DNR order. **Conclusions:** In this single institution study of pancreatic cancer patients there was no racial disparity in DNR orders. This can be explained by a high rate of palliative referrals (61%) and a safety net system which improves access to care. Additional studies are needed to understand determinants of DNR order use. Systems based changes, such as early integration of palliative care and increased access to health services can reduce racial disparities in DNR status of minority cancer patients.

10028 Poster Session (Board #16), Mon, 1:15 PM-4:45 PM

End of life care in gynaecological cancer patients: A population-based study of cancer deaths from the Swedish Register of Palliative Care. *First Author: Kristina Lindemann, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway*

Background: The quality of end of life care for gynecological cancer patients in Europe is unknown. Patient age may affect of end of life care. **Methods:** Patients who died expectably from gynaecological cancer between 2013 and 2015 were identified in the population-based Swedish Register of Palliative Care (N = 2,970). We investigated if age-dependent differences were present with respect to twelve indicators of palliative care quality. Patients were categorized in five predefined age groups. Odds ratios (OR) with 95% confidence intervals (CIs), adjusted for type of end-of-life care unit where appropriate, were calculated using logistic regression, with the oldest group (≥85 years) as reference. **Results:** Age-dependent differences in implementation rate were present for three out of 12 end-of-life care quality indicators, some of which were progressively less well met with each increment in age group. Compared to elderly cancer patients, younger patients (40-59 years) were more often informed about imminent death, (OR, 2.29; 95% CI, 1.41-3.71; p = 0.001). They were also more likely to be cared for by a specialised palliative care service (OR, 5.02; 95% CI, 3.78-6.65;p < 0.001). There was no difference between age groups in the assessed for the presence and severity of pain, injections prescribed as needed against pain, nausea, anxiety or death rattle. However, younger patients were more likely to receive fluids via enteral tube or intravenously during last 24 hours of life (OR, 4.86; 95% CI, 3.174-7.445; p = 0.001). **Conclusions:** Elderly gynaecological cancer patients are at high risk to die without the care of specialized palliative care services. Still, also institutions outside specialized care seem to increasingly adhere to palliative care quality guidelines.

10029 Poster Session (Board #17), Mon, 1:15 PM-4:45 PM

Multicenter randomized controlled trial for advanced cancer patients receiving parenteral nutrition (PN) versus oral feeding (OF): Results of AlimK study. *First Author: Carole Bouleuc, Institut Curie, Paris, France*

Background: The decision to use PN in patients with advanced cancer is controversial. There is lack of high evidence level demonstrating its interest and safety in this population. In case of refractory cachexia, PN interest would be to improve health-related quality of life (HRQoL) and to reduce certain symptoms caused by food intake without significant toxicity. AlimK (NCT02151214) study was performed to address this gap. **Methods:** We planned a prospective multicenter randomized controlled parallel-group phase IV trial, with a Zelen single-consent design for randomization. Intervention arm received PN whereas control arm were pursuing OF alone. Primary objective assessed PN influence on HRQoL deterioration free survival (HRQFS) of one of the 3 targeted scores of the EORTC QLQ-C15-PAL: global HRQoL, physical functioning and fatigue. HRQFS was defined as a definitive deterioration of 10 points at least compared to the baseline score, or death. A p-value < 0.0166 was considered statistically significant (Bonferroni adjustment) to ensure an overall bilateral alpha risk of 5%. Key secondary endpoints included overall survival (OS) and safety. **Results:** Between 07/2012 and 03/2017, 148 cancer patients were enrolled in 13 French cancer centers. Informed consent was obtained for 111 patients: 48 (43%) in PN arm and 63 (57%) in OF arm. PN was refused by 8/48 (18%) patients. Among all patients, 98% were metastatic with life expectancy less than one year and 97 % were still on anticancer treatment. Patients were malnourished with median weight loss over 6 months of -8.20 (range -26.5; 10). There was a trend favoring HRQFS in the OF group for global HRQoL (HR = 1.31 95%CI, 0.88-1.94, p = 0.18), physical functioning (HR = 1.58, 95% CI, 1.06-2.35 p = 0,024) and fatigue (HR = 1.19, 95%CI, 0.80-1.77 p = 0.34). Median OS was 3.12 (95%CI 2.27-4.14) months in OF arm vs 1.97 (1.18-3.06) in PF arm. There was a higher total adverse events in PN arm (52%) than in OF arm (41%). **Conclusions:** In this study PN did not provide clinical benefit for advanced cancer patients with numerically reduced OS and increased toxicity. More data will be shown about tolerance of PN and influencing factors on HRQoL scores. Clinical trial information: NCT02151214.

10030 Poster Session (Board #18), Mon, 1:15 PM-4:45 PM

Impact of patient reported functional limitation on overall survival in older adults undergoing autologous hematopoietic cell transplant (AutoHCT). *First Author: Mariam T. Nawas, University of California San Francisco, San Francisco, CA*

Background: The optimal means of assessing fitness for AutoHCT in older adults with hematologic malignancies is unknown. Few studies have evaluated the impact of patient reported function on AutoHCT outcomes. **Methods:** Comprehensive geriatric assessment (GA) including the FACT-BMT quality of life tool was administered to 184 patients ≥50 years old (median 61, range 50-75) at a median of 21 days prior to AutoHCT (range 1-186 days). Associations between GA/QOL metrics and post-transplant outcomes were evaluated using Cox regression. **Results:** The indication for AutoHCT was multiple myeloma / amyloid in 139 patients (76%), lymphoma in 39 patients (21%) and acute leukemia in 6 patients (3%). Median progression-free survival (PFS) was 28 months, and median overall survival (OS) was not reached (median follow up time 23 months). Both PFS and OS were significantly associated with 5 GA components: limitation in instrumental activities of daily living (IADL), patient reported Karnofsky performance status (KPS), and FACT physical, functional and BMT subscale scores (Table). In multivariate analysis, each GA component was adjusted for known prognostic factors (age, provider reported KPS, disease status, comorbidity index). Three components – IADL limitation, patient reported KPS, and FACT-BMT physical subscale score – remained predictive of both PFS and OS. Age was not associated with PFS or OS. **Conclusions:** In patients ≥50 years old undergoing AutoHCT, limitation in any one of three patient reported measures of functional status is independently associated with inferior PFS and OS, even when adjusting for known prognostic factors. Importantly, chronologic age is not associated with outcomes in this population.

Measure		Univariate HR (p value)	Multivariate HR (p value)
Any IADL limitation	PFS	1.94 (0.003)	1.76 (0.02)
	OS	2.99 (0.003)	2.68 (0.02)
Patient reported KPS (per decile)	PFS	0.80 (0.004)	0.78 (0.01)
	OS	0.69 (0.004)	0.74 (0.06)
FACT physical score	PFS	0.94 (0.001)	0.96 (0.02)
	OS	0.91 (0.001)	0.93 (0.03)
FACT functional score	PFS	0.95 (0.02)	0.96 (NS)
	OS	0.91 (0.008)	0.94 (NS)
FACT BMT score	PFS	0.96 (0.02)	0.97 (NS)
	OS	0.93 (0.01)	0.96 (NS)

10031 Poster Session (Board #19), Mon, 1:15 PM-4:45 PM

Randomized clinical trial of telephoned-based physical activity intervention in onco-geriatric patients. *First Author: Haritz Arrieta, Department of Physiology, University of the Basque Country (UPV/EHU), Leioa, Bizkaia, Spain, Leioa (Bizkaia), Spain*

Background: Cancer in older patient favors the loose of physical function. Physical activity could be a key factor to diminish the age and cancer-related decline. **Methods:** We conducted a multicenter open-label 12-month randomized clinical trial with two parallel arms. Onco-geriatric patients with histological confirmation for lymphoma or carcinoma requiring curative treatment were included. Participants were randomly assigned to an intervention (IG) or usual care group (UCG). The IG received individualized phoned physical activity advice. Subjects in the UCG received a booklet with the current national recommendations in physical activity. **Results:** 301 participants were eligible and randomized. The loose of physical function measured by the Short Physical Performance Battery (SPPB) was experienced likewise in both the IG and the UCG at one year. However, after two years significantly less participants within the IG than the UCG declined in the SPPB score among breast cancer participants ($P = .006$), females ($P = .019$), and those with normal nutritional status ($P = .040$). Linear mixed models showed similar results in both the IG and the UCG in the SPPB, gait speed, the level of physical activity measured using the self-reported International Physical Activity Questionnaire, and verbal fluency at baseline and after three, six, twelve, eighteen and twenty four months (NS). Both the IG and the UCG showed similar results for falls, hospitalization, institutionalization, and death at one and two years (NS). **Conclusions:** Telephone-based physical activity intervention were not effective to reduce the functional decline at one year, but significant differences in favor of the IG were observed over two years among females with breast cancer and good nutrition subgroups. Clinical trial information: NCT01432067.

10032 Poster Session (Board #20), Mon, 1:15 PM-4:45 PM

The value of inflammatory markers in predicting overall survival in older adults with cancer. *First Author: Tomohiro F. Nishijima, New York University, New York, NY*

Background: The widely studied inflammatory markers, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and lymphocyte monocyte ratio (LMR), are associated with survival outcomes in patients with various cancers. However, little is known about the value of these markers in older cancer patients, especially in relation to traditional prognostic factors, such as age and Karnofsky Performance Status (KPS), and a geriatric assessment (GA) derived scale that is predictive of overall survival (OS) [Nishijima, J Geriatr Oncol. in press]. **Methods:** Our sample includes 144 patients age ≥ 65 years with solid tumor (Carolina Senior Registry NCT01137825) who completed a GA within 3 months of their date of diagnosis in 2010 - 2014 and had pretreatment CBC with differential. Patients were followed for death from any cause for a median of 2.5 years, during which 54 patients died. NLR was dichotomized at the upper limit of normal 3.5 [Forget, BMC Res Notes 2017] while PLR and LMR were dichotomized at the median. The 3-item GA-derived prognostic scale (score ranging 0-3) consisted of (1) "limitation in walking several blocks", (2) "limitation in shopping", and (3) "≥ 5% unintentional weight loss in 6 months". Univariable and multivariable Cox proportional hazards models evaluated whether NLR, PLR and LMR were independently predictive of OS. **Results:** Median age was 72 years, 53% had breast cancer, 27% had stage 4 cancer, 14% had KPS < 80, 11% received less intensive treatment than standard treatment for stage and 39% had NLR > 3.5. In the univariable survival analyses, higher NLR (hazard ratio (HR) = 5.08, 95% CI; 2.85-9.07, $p < 0.001$, 2-year OS; 43% vs 86%), higher PLR (HR = 2.10, 95% CI; 1.20-3.67, p = 0.009, 2-year OS; 60% vs 79%) and lower LMR (HR = 2.11, 95% CI; 1.21-3.66, p = 0.008, 2-year OS; 58% vs 80%) were associated with poor OS. Only NLR remained a significant predictor of OS (HR = 2.16, 95% CI; 1.10-4.25, p = 0.025) after accounting for cancer type, stage, age, KPS, treatment intensity and GA-derived prognostic scale. **Conclusions:** NLR > 3.5 was found to be predictive of poorer OS in older adults with cancer, independent of GA-derived prognostic scale and traditional prognostic factors; further validation in external datasets is warranted.

10033 Poster Session (Board #21), Mon, 1:15 PM-4:45 PM

Patient-reported psychosocial needs and psychological distress: the influence on survival in geriatric oncology patients. *First Author: Bonnie Leung, BC Cancer - Vancouver Centre, Vancouver, BC, Canada*

Background: Little is known about how psychosocial factors and distress affect geriatric oncology patients and their survival. The study goals were: review patient-reported needs from all cancer types; identify factors associated with increased risk for psychological distress, defined as moderate to severe anxiety (ANX) and depression (DEP); and determine whether ANX and DEP are independent prognostic variables for patients ≥65 years. **Methods:** All patients ≥65 years, referred to BC Cancer from 2011 – 2016 who completed the Psychosocial Screen for Cancer (PSSCAN-R) and the Canadian Problem Checklist (CPC) within 6 m of cancer diagnosis were included in the study. Baseline demographics and disease characteristics were collected retrospectively. Univariate analysis using the X^2 test were used to compare patient groups. OS was calculated using the Kaplan Meier method and compared using the log rank test. MVA conducted using Cox-regression analysis. **Results:** 26, 323 patients were included in the analysis. Baseline characteristics: female 50%; age 65-69 29%, 70-79 46%, ≥80 27%; GI 20%, Breast 18%, GU 16%, Lung 16%, Other 29%; M0 66%, M1 19%, MX 15%. Patients presenting with ANX and DEP were more likely to be female, be aged 65 to 69, have lung cancer and metastatic disease (p-values < 0.001). Patients reporting emotional, informational, physical, and social/family problems or needs were more likely to present with ANX and DEP ($p < 0.001$). Median OS ANX 34 m vs no symptoms 43 m ($p < 0.001$) and DEP 31m vs no symptoms 43m ($p < 0.001$). MVA including age, sex, M status, ANX, DEP showed all variables were statistically significant; increasing age HR 1.05, male vs female HR 1.11, M1 vs M0 HR 3.62, ANX vs no symptoms HR 1.30, DEP vs no symptoms HR 1.50. **Conclusions:** Geriatric oncology patients who are female, are aged 65-69, have metastatic disease or lung cancer are at risk for distress. ANX and DEP are independent prognostic variables, negatively impacting survival. This vulnerable cohort of geriatric oncology patients should receive psychological support and follow up to better improve survival.

10034 Poster Session (Board #22), Mon, 1:15 PM-4:45 PM

Is there a role for older-patient-specific cancer clinical trials? A pooled analysis of 2277 older patients in adjuvant breast cancer trials (Alliance A151715). *First Author: Dyda Dao, Mayo Clinic, Rochester, MN*

Background: Breast cancer incidence increases with age, but older patients tend to be underrepresented in clinical trials. To address this underrepresentation, this study examined the role of older-patient-specific trials – defined as those designed explicitly for older cancer patients. **Methods:** This study focused on patients 65 years of age or older (younger patients in age-unspecified trials were excluded). It included all Alliance phase III adjuvant breast cancer trials conducted from 1985-2012, encompassing older-patient-specific trials (CALGB 49907 and NCCTG 89-30-52; the latter was the only hormonal trial) and age-unspecified trials (CALGB 40101, NCCTG 9831, CALGB 9741, CALGB 9344, and CALGB 8541). Comparisons were based on trial type (older-patient-specific *versus* age-unspecified). **Results:** 2277 older patients were included (1014 from older-patient-specific trials; 1263 from age-unspecified trials). The cohort of older-patient-specific trials compared to the cohort of age-unspecified trials comprised a greater percentage of patients 75 year of age or older: 26% *versus* 6% ($p < 0.0001$) with a median age (range) of 72 years (65, 89) and 68 years (65, 84), respectively, ($p < 0.0001$). Median overall survival (OS) was comparable: 12.8 years (95% confidence interval (CI): 11.9-13.7 years) and 13.5 years (95% CI: 12.9-14.1 years) in older-patient-specific trials and age-unspecified trials, respectively. After adjusting for age, estrogen receptor status, tumor size, and positive lymph nodes, OS remained comparable (hazard ratio 0.9; 95% CI: 0.8-1.0; (referent: older-patient-specific trials; performance score excluded from the model due to missing data)). Similar conclusions were reached for recurrence-free survival. Older-patient-specific trials had lower grade 2-5 adverse event rates (68% versus 73%; $p = 0.03$). Sensitivity analyses with only chemotherapy trials (NCCTG 89-30-52 excluded) yielded similar findings. **Conclusions:** Older-patient-specific trials appear to help address the underrepresentation of older patients in cancer clinical trials. Support: UG1CA189823, U10CA180821, U10CA180882

10035 Poster Session (Board #23), Mon, 1:15 PM-4:45 PM

Geriatric comanagement and surgical outcomes of older cancer patients. *First Author: Armin Shahrokni, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Perioperative Geriatric Comanagement may improve surgical outcomes of older frail cancer patients. We present our 3 year experience with perioperative geriatric comanagement & the electronic Rapid Fitness Assessment (eRFA) at Memorial Hospital (MH). **Methods:** Since 2015, MH surgical services referred cancer patients age 75+ to the Geriatrics Service for preoperative evaluation including the eRFA (Shahrokni et al, JNCCN, Feb 2017). The eRFA score (0 to 13) is based on 1 point for impairments in the Karnofsky Performance scale score, dependency for basic and instrumental activities of daily living, Timed Up and Go test, history of fall, limited social activity, poor social support, presence of distress, depression, and cognitive impairment, polypharmacy, weight loss, and > 4 comorbid conditions. These patients were then co-managed by the geriatrics and surgical services while hospitalized. We compared the short- and long-term surgical outcomes of frail patients with fit patients. **Results:** 2291 patients (median age 79) had perioperative geriatric comanagement in 2015-17 with 1175 (51.3%) requiring hospitalization after surgery (average length of stay = 7days). The median eRFA score was 5 (IQR 3-8). 30 day minor & major surgical complications, emegrnecy room visit, readmission & mortality did not differ between frail patients (eRFA > 5) & fit patients (eRFA ≤5) in both the in- and out-patient surgical groups. Among patients requiring hospital stay, frailty was associated with a longer average length of stay (frail vs. fit; 7.7 vs. 6 days, $P < 0.001$). Frailty was associated with the higher likelihood of dying in 12 months after outpatient surgical procedure (OR = 5.27, $p < 0.001$) or inpatient surgical procedure (OR = 2.20, $p = 0.002$). **Conclusions:** Perioperative co-management by geriatricians & surgeons leads to similar short term outcomes between frail and fit patients. Future studies should assess the impact of prolonged geriatric comanagement on long-term outcomes of older cancer patients after surgery.

10036 Poster Session (Board #24), Mon, 1:15 PM-4:45 PM

Geriatric assessment to predict hospitalization frequency and long-term care utilization in older adult cancer survivors. *First Author: Grant Richard Williams, University of Alabama at Birmingham, Birmingham, AL*

Background: Geriatric assessments (GA) assess physiologic age in older adults; however, the association between GA identified impairments and long-term healthcare utilization in older cancer survivors remains unknown. Our objective was to evaluate whether a GA performed at cancer diagnosis was predictive of hospitalizations and long-term care [LTC] utilization in older adult cancer survivors. **Methods:** Older adults within the Carolina Senior Registry (NCT01137825) with GA performed between 3 months before and up to 6 months after diagnosis were included (n = 125). Patients with fee-for-service coverage were linked to Medicare claims. Hospitalizations and LTC utilization (skilled nursing or assisted living) were identified up to 5 years after their diagnosis, death, or 12/31/2013. GA risk measures (prefrail/frail status, impaired Instrumental Activities of Daily Living [IADL], limitations in climbing stairs, prolonged Timed Up and Go [TUG], > 5% unintended weight loss) were assessed in separate Poisson models estimating the relative risk (RR) for hospital and long-term care visits, controlling for person-time, age, and Charlson comorbidity score. **Results:** Participants median age of 74 years, majority female (80%), and white (89%). Most common malignancies were breast (64%) and lung cancer (8%); predominantly early stage disease (stage 0-III = 77%). During follow-up 41 (33%) participants were hospitalized and 20 (16%) received LTC. Prefrail/frail status (RR 2.5, $p < 0.001$), IADL impairment (RR 5.47, $p < 0.001$), and limitations in climbing stairs (RR 2.94, $p < 0.001$) were associated with increased hospitalizations. Prefrail/frail status (RR 1.86, $p < 0.007$), IADL impairment (RR 4.58, $p < 0.001$), presence of falls (RR 6.73, $p < 0.001$), prolonged TUG (RR 5.45, $p < 0.001$), and limitations in climbing stairs (RR 1.89, $p < 0.005$) were associated with LTC utilization. **Conclusions:** GA identified impairments were associated with increased hospitalizations and LTC utilization among older adults with cancer. GA-focused interventions, such as physical and occupational therapy, should be employed to potentially reduce long-term adverse health care utilization in this vulnerable population.

10037 Poster Session (Board #25), Mon, 1:15 PM-4:45 PM

Phase 2 randomized study of a walking intervention for radiation-related fatigue among older breast cancer patients receiving radiation. *First Author: Noam Avraham VanderWalde, Department of Radiation Oncology, University of Tennessee Health Science Center/West Cancer Center, Memphis, TN*

Background: This study's purpose is to determine if an exercise intervention can decrease fatigue in older women receiving radiotherapy (RT) for breast cancer. **Methods:** A phase 2 randomized study was conducted in women age $\geq$ 65 years with breast cancer receiving adjuvant RT. After informed consent, women were randomized to the intervention arm; the Walk with Ease (WWE) pamphlet, or the usual care arm (UC); a document describing the benefit of moderate exercise. Prior to RT patients completed an objective assessment of physical function using the Short Physical Performance Battery (SPPB), and questionnaires to assess fatigue, physical function, and other fatigue-related symptoms. All assessments were repeated at last week of radiotherapy and 1 month follow up. The primary outcome was change in fatigue as measured by the Total Disruption Index (TDI) of the Fatigue Symptom Index (FSI) over time. Secondary outcomes include change in level of activity (based on self-reported walking log), change in physical function as measured by the SPPB, and change in fatigue related symptoms. A Repeated Measures Mixed Linear Model was used to describe the change in outcomes over time. **Results:** Of the 54 patients accrued, 50 had complete data. Median age was 69 years (range 65-84). With the exception of hormone status, the baseline criteria were similar between study arms. Longitudinal modeling revealed no significant change over time in TDI between the two arms (p-value = 0.79). However, these models revealed that increasing walking over time was associated with lower levels of fatigue ($p = 0.04$). Number of minutes walking per week increased in both arms (45 min/wk baseline to 432 min/wk end of RT, $p < 0.01$) and physical function improved statistically over time in both arms ($p < 0.01$) and both remained improved at follow up (p-value = 0.01 and < 0.01 respectively). **Conclusions:** This study demonstrated no benefit in fatigue with the WWE program. However, women in both arms increased their walking and had improved physical function during and following RT. Increased walking was statistically associated with lower fatigue scores during and after radiotherapy in this older group of women with breast cancer. Clinical trial information: NCT02434367.

10038 Poster Session (Board #26), Mon, 1:15 PM-4:45 PM

Anti-PD1 antibodies in late elderly advanced melanoma patients: A retrospective multicentre study. *First Author: Francesco De Rosa, Immunotherapy, Cell Therapy and Biobank, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy*

Background: advanced age is associated with comorbidities and impairment of the immune system: these aspects may influence efficacy and tolerability of immune checkpoint inhibitors. Limited data suggest that anti-PD1 antibodies in advanced melanoma are equally effective in patients (pts) aged over 65 years; however, the information on late elderly pts ($>$ 75 years) is still lacking, as comorbidities and logistic reasons often exclude them from clinical trials. **Methods:** we retrospectively reviewed clinical records of late elderly advanced melanoma pts treated in any line with an anti-PD1 agent (nivolumab or pembrolizumab) at our institutions to investigate efficacy and toxicity in a real practice setting. Clinical response was assessed according to RECIST criteria; toxicity was assessed according to CTCAE 4.0. Survival was estimated according to Kaplan-Meier method. **Results:** we identified 161 pts fulfilling inclusion criteria (68 M, 93 F). Median age was 79 (range 75-93); 110 pts (68%) had multiple comorbidities including history of other cancers (25 pts) and autoimmune/inflammatory disorders (13 pts). Eighty-eight pts received nivolumab, 73 pembrolizumab; basal LDH was elevated in 76 pts (47.2%). Fourteen pts (8.7%) obtained a complete response and 44 (27.3%) a partial response; additional 30 patients (18.6%) obtained a stable disease. Median overall survival was 8.71 months; normal LDH was significantly associated with better prognosis (14.45 vs 6.08 months; $P = 0.016$). Fifty-five pts have died; 48 of them because of progressive disease and the others for comorbidities. In our series treatment was well tolerated: only 5 pts had severe (G3-4) toxicity and no treatment-related death was reported. Adverse events were managed with corticosteroids and no pt needed additional immunosuppressive agents. **Conclusions:** anti-PD1 antibodies seem equally effective and well tolerated even in late elderly advanced melanoma pts, whose access to treatment should not be restricted solely because of advanced age.

10039 Poster Session (Board #27), Mon, 1:15 PM-4:45 PM

Examining progression free survival (PFS), overall survival (OS), and toxicities of palbociclib in a geriatric population. *First Author: Katherine Clifton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: A recent FDA pooled analysis of patients treated with CDK4/6 inhibitors showed a trend towards improved PFS in the geriatric population, although this was not statistically significant. The study found more grade 3-4 events in the geriatric population, however the overall adverse event rate was low. The objective of this study was to analyze PFS, OS, dose reductions, dose delays and toxicity in a geriatric population receiving palbociclib as standard of care. **Methods:** Patients with metastatic breast cancer receiving palbociclib in any line of therapy were identified from a cohort of 845 pts at MDACC. Clinical, demographic, comorbidities, recurrence and survival data were collected. Dose delays, dose reductions, and toxicities were retrospectively extracted from the medical record. Data was analyzed using Fischer's exact test for categorized variables and T test/Wilcoxon rank-sum test for continuous variables. PFS and OS were analyzed using the Kaplan Meier method. **Results:** 605 pts who met eligibility criteria were included. Pts receiving palbociclib on clinical trial were excluded. 160 pts were $\geq$ 65 years-old and 92 pts were $\geq$ 70 years-old. Pts $\geq$ 70 had a significantly increased number of dose reductions ($p = 0.03$) and dose delays ($p = 0.02$) compared to the younger pts. Pts $\geq$ 70 had significantly lower baseline GFR ($p < 0.0001$) and higher Charleston Comorbidity index ($p < 0.0001$). There was no significant increase in toxicity rate, including neutropenic fever, infections, or hospitalizations, in the $\geq$ 70 cohort ($p = 0.3$). The $\geq$ 70 cohort had a significantly improved PFS as compared to the younger cohort ($p = 0.02$). This was also true when an age cut-off of $\geq$ 65 was used ($p = 0.009$). There was no difference in OS in either cohort (age $\geq$70 $p = 0.4$, age $\geq$ 65 $p = 0.9$). **Conclusions:** Palbociclib was well tolerated in the geriatric population. Interestingly, the geriatric population was found to have improved PFS. Palbociclib has been shown to restore senescence signaling. Further studies are warranted to investigate if palbociclib may work synergistically with already enhanced senescence pathways in the geriatric population.

10040 Poster Session (Board #28), Mon, 1:15 PM-4:45 PM

Impact of age on outcomes with PD-(L)1 blockade in patients (Pts) with non-small cell lung cancer (NSCLC). *First Author: Morgan Lichtenstein, Massachusetts General Hospital, Boston, MA*

Background: As the population ages, it has become increasingly important to understand the risks and benefits of novel agents among older adults with cancer. Immunotherapy (IO) has revolutionized the treatment of advanced NSCLC, but less is known about the activity of PD-(L)1 blockade in older adults ($\geq$70 years). In these pts, immunosenescence may theoretically blunt the effectiveness of anti-PD-(L)1 therapy and/or alter its toxicity profile. We sought to assess the impact of age on clinical outcomes and rates of IO-related toxicities in pts with advanced NSCLC treated with anti-PD-(L)1. **Methods:** We retrospectively evaluated all pts with NSCLC at our institution treated with IO between 1/2013 and 10/2017. To assess progression-free survival (PFS) and overall survival (OS) across age groups, we performed Kaplan-Meier and Cox regression models adjusted for sex, ECOG, comorbidity, stage at diagnosis (dx), time since dx with metastatic disease, and lines of treatment prior to IO. IO-related toxicities, steroid use, and hospitalizations were also compared. **Results:** Of 245 pts, 141 (58%) were $<$ 70 years and 104 (42%) were $\geq$70 years old. Compared with younger pts, older pts had higher comorbidity scores (6.9 vs 6.6, $p = 0.024$), worse ECOG scores (1.4 vs 1.2, $p = 0.011$), and lower stage at dx (stage 4: 50% vs 75%, $p < 0.001$). Older and younger pts had similar median PFS (2.6 vs 2.0 months, $p = 0.14$) with PD-(L)1 blockade; multivariable models demonstrated equivalent PFS across age groups (HR: 0.81, $p = 0.19$). Older pts had a worse median OS (8.6 vs 14 months, $p = 0.10$). After adjusting for key confounders, however, multivariable models demonstrated no significant difference in OS by age (HR = 1.4 $p = 0.070$). Overall, 102 (42%) pts experienced IO-toxicities with no significant difference by age (41% vs 44%, $p = 0.69$). Thyroiditis (17%), pneumonitis (10%), and dermatitis (9%) were most common. Toxicity-associated steroid use (26% vs 25%, $p = 1.0$) and IO-related hospitalizations (12% vs 10%, $p = 0.68$) did not differ between age groups. **Conclusions:** Older pts with NSCLC experienced similar toxicity and survival compared to younger pts receiving PD-(L)1 blockade, suggesting that IO may be a viable treatment option for the geriatric population.

10041 Poster Session (Board #29), Mon, 1:15 PM-4:45 PM

Predicting chemotherapy toxicity and death in older adults with colon cancer: Results of MOST (Massilia Oncologic Senior Tests) study. *First Author: Frédérique Retornaz, Centre Gérontologique de Marseille, Marseille, France*

Background: Older patients with colon cancer are more vulnerable to chemotherapy toxicity and early death. Establishing simple scores specific for colon cancer (cc) patients able to predict severe chemotoxicity or early death is needed to select the best appropriate treatment. **Methods:** This prospective multicenter study included cc patients aged ≥ 70 years receiving first-line adjuvant or metastatic chemotherapy. Five frailty markers (FM) : nutrition, physical activity, mobility, energy, grip strength), six domains of CGA (functional status, comorbidities, falls, nutrition, cognition, depression) and laboratory parameters were collected at admission. Logistic or Cox regression was used to examine at 500 days the association between FM, CGA, laboratory parameters and grade 3-4 toxicity or death, respectively. **Results:** 93 patients (mean age 78.8 years, range 70-90) received adjuvant (32, 34.4 %) or metastatic (61, 65.6 %) chemotherapy. During the first 500 days grade 3-4 toxicity occurred in 49 (53.3 %) and 23 (26.7 %) died. Multivariate logistic regression identified polychemotherapy, albuminemia < 32 g/L, abnormal grip strength and C-reactive protein > 11 mg/L (odds ratio: 6.85, 2.79, 2.40, 1.43, respectively) as independent predictors of toxicity. Cox regression identified metastasis, alkaline phosphatases > 100 IU/ml, age > 82 years, sex (female), and abnormal grip strength (hazard ratio: 7.99, 3.45, 3.31, 3.2, 1.18, respectively) as independent predictors of premature death. The predictive model for grade 3-4 toxicity combined (polychemotherapy x 3) + (albuminemia x 2) + (abnormal grip strength x 1.5) + C-reactive protein, cut-off > 3. The predictive model for premature death combined (metastasis x 5) + (age x 2.5) + alkaline phosphatases + sex + abnormal grip strength, cut-off > 6. Characteristics of both models are : Clinical trial information: NCT02148731. **Conclusions:** These two simple and efficient scores will help clinicians to better identify cc older patients with increased risk of toxicity and/or premature death.

Risk	AUC ROC curve (± SD)	95 % CI	*P*	Sensitivity (%)	Specificity (%)
Toxicity	0.747 ± 0.052	0.647-0.832	< 0.0001	71.4	72.1
Death	0.908 ± 0.032	0.826-0.960	< 0.0001	87.0	81.0

10042 Poster Session (Board #30), Mon, 1:15 PM-4:45 PM

Prevalence and clinical correlates of vulnerable status using the Vulnerable Elders Survey 13 (VES-13) in newly diagnosed adult non-Hodgkin lymphoma (NHL) patients: A LEO cross-sectional analysis. *First Author: Angelo Fama, Mayo Clinic, Rochester, MN*

Background: The VES-13 is a self-reported tool designed to identify people at risk of functional decline and death. We evaluated the prevalence of vulnerable (VUL) status in newly diagnosed NHL patients, overall, and by age, gender and clinical features. **Methods:** We used pre-treatment data from 1194 NHL patients consented 7/2015 to 7/2017 into the Lymphoma Epidemiology of Outcomes (LEO) cohort study (NCT02736357). Patients with a VES-13 score ≥3 were classified as VUL. χ^2 tests and unconditional logistic regression were used to identify correlates of VUL. **Results:** The median age was 62 years (range 18-94), 44% were ≥65 years, and 61% were male. Overall, 22% (268/1194) of the patients were classified as VUL, with a prevalence of 18% (117/666) for age < 65 years and 29% (151/528) for age ≥65 years. The prevalence of VUL status was higher in women vs men (26% vs 20%, p = 0.009), performance status ≥2 vs 0-1 (74% vs 19%, p < 0.0001), any B-symptoms (36% vs 19%, p < 0.0001), stage III-IV vs I-II (24% vs 20%, p = 0.11), ≥2 vs 0-1 comorbidities (41% vs 19%, p < 0.0001) and subtype (p = 0.0003, DLBCL 30%). All of these patterns were similar in analyses stratified on age 65 years. In a multivariable model, age (OR = 1.02 per year, 95% CI 1.01-1.04), female gender (OR = 1.6, 95% CI 1.2-2.2), PS ≥2 (OR = 8.1, 95% CI 4.5-14), B-symptoms (OR = 2.2, 95% CI 1.5-3.1), ≥2 comorbidities (OR = 2.5, 95% CI 1.7-3.8) and DLBCL subtype (OR = 2.0, 95% CI 1.3-3.1) were all predictors of VUL status. As physicians were unaware of the VES-13 score, we next evaluated VUL status by anthracycline (ATC) use as initial therapy (not accounting for dosing) in DLBCL cases. 89% of VUL patients (83/93) received an ATC compared to 90% of patients not classified as VUL (198/221; p = 0.93). **Conclusions:** Over 20% of newly diagnosed NHL patients were classified as VUL, including 18% < 65 years, highlighting the need for functional assessment of patients across a wider age spectrum. VUL status correlated with more adverse prognostic factors. The initial use of ATC not accounting for dosing/dose reduction in the treatment of DLBCL did not differ by VUL status. Future work will evaluate VES-13 with patient outcomes.

10043 Poster Session (Board #31), Mon, 1:15 PM-4:45 PM

Utilizing a practical tablet-based modified geriatric assessment in clinic for older adults with multiple myeloma (MM). *First Author: Nitya Nathwani, Judy and Bernard Briskin Center for Multiple Myeloma Research, Department of Hematology and Hematopoietic Cell Transplantation, Duarte, CA*

Background: More than 60% of patients diagnosed with MM are > 65 years old and at greater risk for treatment toxicity. Comprehensive geriatric assessment predicts toxicity and survival but is difficult to add to already stressed clinical workflow. We have previously demonstrated feasibility of a tablet-based modified geriatric assessment (mGA). Here, we provide a final report of impact on decision-making and treatment outcomes. **Methods:** In this multi site study, patients with MM > 65 years old completed a tablet-based mGA in clinic just prior to an oncology visit to discuss a treatment decision. Using the International Myeloma Working Group (IMWG) frailty model, a summary score, along with selected other GA and clinical data, was displayed to oncology providers at the beginning of the clinical visit. **Results:** 166 patients enrolled. Most were white (76%, n = 127) and male (56%, n = 93); mean age was 72 years (SD6.46; range 61-95). Based on IMWG criteria, patients were fit (39%, n = 64), intermediate fit (33%, n = 55) or frail (28%, n = 47), and 69% of providers agreed/strongly agreed that the mGA influenced the treatment recommendations for the patient. Treatments selected were more intensive for fit patients, while frail patients received lower intensity, with a reduced number of agents or a different route of administration (χ^2 = 20.81 (4), p < .0001). There was a significant association between fit status and transplant eligibility, with more fit patients being transplant eligible (χ^2 = 20.81 (6), p = .007). Outcome follow-up at 3 months on 144 patients indicated 39% (n = 56) of patients had a dose modification after the initial assessment and 18% (n = 26) discontinued therapy earlier than planned; 19.4% (n = 28) had a CTCAE grade 3-5 hematologic toxicity and 22% (n = 31) had a grade 3-5 non-hematologic toxicity, most commonly fatigue. Rates of toxicity were similar between patients considered fit, intermediate fit and frail. **Conclusions:** Results of a mGA presented to a provider at the point of care influenced treatment decisions. Most patients continued the prescribed therapy at 3 months, with relatively low rates of grade 3-5 toxicity. Further study is needed to compare outcomes with standard care. Clinical trial information: NCT03068637.

10044 Poster Session (Board #32), Mon, 1:15 PM-4:45 PM

Association between participation in religious activities and depression and anxiety in older patients with cancer. *First Author: Yu Cao, City of Hope, Duarte, CA*

Background: Older patients (pts) with cancer are at risk for depression and anxiety, which are often under-recognized. Participation in religious activities has been associated with better mental health in pts with cancer; however, data are conflicting and few studies focus on older pts. This study explores associations between participation in religious activities and depression and anxiety in older pts with cancer. **Methods:** This is a secondary analysis of a prospective study of pts age ≥ 65 with cancer. Prior to starting a new line of chemotherapy, pts self-reported if they felt depressed (yes/no on a 1-Question Yale Depression Screen) or anxious (score ≥ 6 on a 0-10 Likert Scale). Participation in public (e.g. church) and private (e.g. prayer) religious activities was measured via the Duke University Religion Index. High (≥ weekly public AND ≥ daily private), middle (≥ weekly public OR ≥ daily private), and low (< weekly public AND < daily private) religious participation groups were defined. Univariate and multivariate logistic regression analyses were conducted evaluating associations between participation in religious activities and depression and anxiety. **Results:** Of 458 pts (mean age 72 [range 65-91]; 57% female, 55% non-Hispanic white), with 31% GI, 19% breast, and 18% GU cancers, the majority (75%) had stage IV disease. Twenty-four percent (N = 110) reported anxiety, and 21% (N = 97) depression. Thirty-five percent (N = 161) reported ≥ weekly public, and 45% (N = 208) ≥ daily private religious activity. Both groups tended to report less anxiety (OR 0.66, p = 0.08; OR 0.68, p = 0.08, respectively); neither group was less likely to report depression (OR 0.79, p = 0.33; OR 1.05, p = 0.83, respectively). Combined, the high religious participation group (27.5%; N = 126) reported less anxiety on univariate (OR 0.59, 95% CI 0.35-0.99, p = 0.04) and multivariate (OR 0.51, 95% CI 0.28-0.92, p = 0.03) analyses, adjusting for age, gender, race, education, number of comorbidities, physical function, and social support, but not less depression (p = 0.46). **Conclusions:** Among older pts with cancer, participation in both public and private religious activities is associated with less anxiety, but not less depression.

10045 Poster Session (Board #33), Mon, 1:15 PM-4:45 PM

Prognostic benefit of taking statin and/or metformin in elderly patients with advanced non-small cell lung cancer: A nationwide population-based epidemiologic study. *First Author: Yun-Gyoo Lee, Division of Hematology/Oncology, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*

Background: Comorbidities including dyslipidemia, diabetes and coronary heart disease are frequently found in elderly patients with advanced non-small cell lung cancer (NSCLC). Taking statin and/or metformin attenuates chronic inflammations, and could affect cancer outcomes. We aimed to evaluate prognostic impact of taking statin and/or metformin on survival in elderly patients with advanced NSCLC. **Methods:** Patients ≥ 70 years with advanced NSCLC incident from 2007 to 2012 were identified using reimbursement claims from Korea's National Health Insurance Service Database, and exposures to statin and/or metformin were also documented. Cox proportional-hazards model and propensity score matched analysis were used to estimate the impact of drug exposures on overall survival (OS). **Results:** Excluding 976 treated by upfront anti-EGFR, 7298 receiving palliative chemotherapy were included: statin preparations were taken in 13.0%, metformin preparations in 13.8%, both in 3.5%, and neither in 76.6%, respectively. Median OS of statin + / metformin +, statin + / metformin –, statin - / metformin +, and statin - / metformin – users was 14.5, 12.9, 11.4 and 9.9 months respectively. By multivariate analyses, metformin was not statistically significantly associated with improved OS in statin non-user (HR 0.99; 95% CI 0.91-1.08; p= 0.819) and statin user (HR 0.99; 95% CI 0.85-1.16; p= 0.898) group. However, use of statin, regardless of metformin, was associated with improved OS (HR 0.80; 95% CI 0.74-0.86; $p< 0.001$). In propensity-matched cohort, survival benefit was noted not by use of metformin (HR 0.97; 95%CI 0.85-1.11; p= 0.661), but by use of statin (HR 0.83; 95%CI 0.73-0.95; p= 0.007). There was no significant effect modifier. **Conclusions:** We found that the about one-quarter of elderly NSCLC patients were taking statin and/or metformin. Exposures to statin could be the independent prognostic factor for better survival in elderly advanced NSCLC patients.

10046 Poster Session (Board #34), Mon, 1:15 PM-4:45 PM

The effect of a geriatric oncology (GO) evaluation on treatment (Tx) decisions for older patients (pts) with cancer in Mexico. *First Author: Haydee Cristina Verduzco-Aguirre, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Ciudad De México, Mexico*

Background: GO evaluations may lead to improvements in the care of older adults with cancer, but their effect on Tx decisions in everyday clinical practice needs further research. Our goal was to describe the effect of GO evaluations on Tx decisions in the first GO clinic implemented in Mexico. **Methods:** The records of 173 pts aged ≥65 years (y) referred to our GO Clinic before active Tx initiation from 05/15 to 10/17 were reviewed. Pts were screened with a validated tool (G8; Soubeyran et al, 2011); those deemed vulnerable (score ≤14) underwent a full geriatric assessment; and Tx recommendations were sent to the treating oncologist. We measured the proportion of patients in which there was agreement between GO recommendations and final Tx decisions, and assessed whether agreement increased in cases in which the treating oncologist's notes mentioned the GO evaluation. **Results:** Median age was 79 y (range 64-97). 37% of pts had genitourinary and 32% gastrointestinal malignancies; 42% were stage IV. Proposed Tx before GO evaluation included palliative chemotherapy (CT) (32%), curative surgery/radiotherapy (31%), and neo/adjuvant CT (19%). A recommendation to administer standard Tx was made in 47% of cases, less intensive Tx in 32%, and best supportive care (BSC) in 20%. The treating oncologist's final Tx decision matched the GO recommendation for 81% of pts, and GO recommendations were mentioned in the treating oncologist's notes in 62% of cases. Agreement between the treating oncologist & GO clinic was higher when BSC was recommended (94%), followed by standard Tx (77%), and less intensive Tx (75%). Agreement between the treating oncologist & GO clinic was 84% when the GO evaluation was mentioned, compared to 75% when it wasn't (p = 0.16). In pts for which less intensive Tx was recommended (n = 56), agreement was 84% when the GO evaluation was mentioned, compared with 56% when it wasn't (p = 0.04). **Conclusions:** Agreement between GO recommendations and final Tx decisions was high, especially for cases in which BSC was recommended. Including GO evaluations in everyday clinical practice may provide useful information to guide oncologists caring for older pts, particularly when considering less intensive therapy.

10047 Poster Session (Board #35), Mon, 1:15 PM-4:45 PM

Inflamm-aging and the need to consider age in cytokine-patient-reported outcome (PRO) relationships: The case of acute myeloid leukemia (AML). *First Author: Shabbir M.H. Alibhai, University Health Network, Toronto, ON, Canada*

Background: Cancer-related fatigue (CRF) and poor quality of life (QOL) remain major problems in adults with AML during and after active treatment. Prior studies have linked cytokines to these PROs but have not examined age as a modifier. Ageing is associated with chronic inflammation which may alter the cytokine-PRO relationship. **Methods:** 213 patients age 18 or older who underwent intensive chemotherapy for AML were assessed at up to 4 time points (pre-treatment, 1 month, 6 months, 12 months). PROs were assessed with validated self-report questionnaires (FACT-F, EORTC QLQ-C30 global health) and blood was analyzed in duplicate for a panel of 32 cytokines using multiplexed protein immunoassays (Meso Scale Diagnostics). Log-transformed and centred cytokine values were regressed in models against CRF and QOL in separate models adjusting for age, gender, time, remission status, and haemoglobin. Models were stratified by age (< 60, 60+) and model and partial R^2 values were calculated. **Results:** 498 sets of cytokine measurements were available for analysis. For CRF, the model R^2 was 20.6%, with cytokines explaining 7.8% of the variance. For QOL, the model R^2 was 25.7%, and cytokines accounted for 7.8% of the variance. When stratified by age (< 60 versus 60+ years or older), the proportion of variance in CRF explained by the multivariable model and by cytokines collectively was greater in younger patients (34.1% for the entire model and 17.9% for cytokines) than older adults (21.7% and 14.4%, respectively). The interaction term was significant (p = 0.002). The three most influential cytokines were TNF-α, MCP-4, and IL-15 in younger adults and MIP-1a, TARC, and IL-7 in older adults. Similar differential results by age group were seen for global QOL (interaction term $p < 0.001$). **Conclusions:** Cytokines explain a significantly larger amount of variation in both CRF and QOL in younger patients with AML compared to older patients. Specific culprit cytokines also appear to be different. This suggests that cytokine-targeted therapies (drug or non-drug) may need to differ in younger versus older adults but requires verification in other tumour types.

10048 Poster Session (Board #36), Mon, 1:15 PM-4:45 PM

The impact of a positive cognitive impairment screen on conversations between patients, caregivers, and oncologists: A UR NCORP randomized study. *First Author: Allison Magnuson, University of Rochester Medical Center, Rochester, NY*

Background: The prevalence of CI and the utility of CI screening for community oncology practices are not well established. We used two tools to screen for CI in older patients (pts) enrolled onto a cluster randomized controlled trial and explored how CI screening influences conversations about cognition (CAC) between older pts, their caregivers, and oncologists. **Methods:** Pts aged ≥70 with advanced cancer were recruited (URCC 13070; PI: Mohile). CI screen, including Mini-Cog (MC) (normal/abnormal) and Blessed Orientation Memory Concentration Test (BOMC) (scored 0-28), were included in a Geriatric Assessment (GA). Practices were randomized to usual care (UC) vs GA intervention (GA summary provided to oncologists). Audio-recorded clinical encounters were transcribed by 2 blinded coders who coded CAC with a priori scheme as follows: cognition discussed (Y/N), type of concern, who initiated. MC and BOMC were compared and receiver operating characteristic (ROC) analyses identified BOMC score that best predicted abnormal MC. **Results:** Mean age was 77 (range 70-93); 2.2% screened positive by BOMC using standard score of ≥11 and 33.5% had abnormal MC. Pts with abnormal MC were more likely to have impaired activities of daily living (ADL) (34 vs 24%), Instrumental ADL (64 vs 52%), Timed Up and Go (47 vs 34%) and positive depression screen (28 vs 19%), ($p < 0.05$ for all). CAC occurred in 22% of encounters and were more common in the intervention arm (OR 4.64, 95%CI: 2.98- 7.21, $p < 0.001$). Differences in CACs were most notable for pts with abnormal MC (71% in intervention group vs 16% in UC, $p < 0.001$). Oncologists were more likely to be the initiator of CACs in the intervention arm (90% vs 57%, $p < 0.001$). The most common concerns were memory (54%) and comprehension (15%). A BOMC cutoff ≥4 was optimal for predicting abnormal MC (AUC = .73, sensitivity 59%, specificity 74%). **Conclusions:** In community oncology practices, 1/3 of older pts screen positive for CI and were more likely to have other GA impairments. Providing oncologists with results of a CI screen increases CACs. A lower BOMC cutoff predicted abnormal MC, consistent with studies in non-cancer pts where lower BOMC score predicted more mild CI.

10049 Poster Session (Board #37), Mon, 1:15 PM-4:45 PM

Development and temporal validation of a practical prognostic scoring system (ONCOGERIATRIC INDEX -OGI) based on the comprehensive geriatric assessment to predict early death in elderly cancer patients: A 892 patients cohort study. *First Author: Jurema Telles O Lima, IMIP - Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil*

Background: Recognizing prognostic factors is important when evaluating elderly people with cancer to decide the appropriate treatment. The Oncogeriatric Index (OGI) was developed to predict early death (in 6 months) among elderly people with cancer, based on the Karnofsky Performance Status Scale, the Mini Nutritional Assessment and the Charlson Comorbidity Index. OBJECTIVES: To temporarily validate the OGI.**Methods:** We used a prospective cohort of cancer patients aged 60 or + years for GA n 605 (2015-2017) [training set]; 2016–2017: n 291 [validation set]) was performed during a six-month follow-up. Epidemiologic data and CGA (using 12 scales) before oncologic treatment were collected. The outcome was ED (within first 180 days). Cox's proportional hazards model was used for the selection of prognostic factors. A prognostic score, the Onco Geriatric Index (OGI), was constituted of the number of abnormal CGA scales. Overall survival was estimated using the Kaplan–Meier method, and survival curves were compared using the log rank test. Predictive performance (calibration and discrimination) was determined. **Results:** There were 41 deaths among the 291 admitted patients. Patients who had three altered scales had 23.5 times higher risk of dying, adjusted for age, primary site of cancer and tumor staging (HR = 23.5, 95% CI 7.0-78.4, $p < 0.001$); those with two, 6.9 times (HR = 6.8, 95% CI 2.4-40.1, $p < 0.001$); and those with one, 3.1 fold (HR = 3.1, 95% CI 1.2-7.9, p = 0.020). The numbers of deaths predicted by the OGI were similar to those occurred, as well as a 6-month overlap of survival curves for each of the groups in the derivation and validation cohort, demonstrating that this prognostic model had an adequate predictive performance. **Conclusions:** Geriatric Index (OGI) is valid to evaluate elderly people with cancer in order to identify those at higher risk for early death.

10050 Poster Session (Board #38), Mon, 1:15 PM-4:45 PM

Diagnosing deficits in quality of life and providing tailored therapeutic options: Results of a randomized trial including 220 patients with colorectal cancer. *First Author: Monika Klinkhammer-Schalke, Tumor Center Regensburg, Institute of Quality Management and Health Services Research of the University of Regensburg, Regensburg, Germany*

Background: There have been increasing efforts to develop interventions that improve patients` quality of life (QoL) in routine cancer care. The Tumor Center Regensburg has designed and implemented an intervention consisting of the systematic diagnosis and tailored therapy of QoL. The efficacy of this intervention has been demonstrated in a randomized trial of patients with breast cancer. To generalize and strengthen the external validity of these findings, this intervention system was applied to a cohort of patients with colorectal cancer. **Methods:** In a 2-arm randomized controlled trial, 2x110 patients with primary colorectal cancer were recruited in four colorectal cancer centers and randomized into an intervention group (IG) or a control group (CG). QoL (EORTC QLQ-C30 and QLQ-CR29) was measured in both arms before clinical discharge and at the 3-, 6-, 12-, and 18-months routine follow-up. A network of local healthcare providers of QoL therapy was established that encompassed physiotherapy, psychotherapy, pain therapy, social support, nutrition, stoma care, and fitness. In the IG, the treating physician received printouts of QoL results (QoL profile including 15 scales). If a need for QoL therapy was diagnosed (cutoff < 50 points in scales of 0-100), specific QoL therapies were recommended. In the CG, QoL was also measured, but the treating physician neither received QoL profiles nor recommendations on QoL therapy. **Results:** At clinical discharge, a need for QoL therapy was diagnosed in 92% (96/104) of IG patients and in 85% (88/104) of CG patients. At 12 months (primary endpoint), the intervention had reduced the rate of patients with a need for QoL therapy to 50% (41/82) compared to 66% (57/87) in CG (χ^2-Test p = .041, number needed to treat (NNT) = 7). **Conclusions:** Patients with primary colorectal cancer benefited from the intervention with QoL diagnosis and therapy in terms of faster improvement of their QoL during the first year after surgery. The NNT was exactly the same as for patients with breast cancer, indicating high external validity of these results. Clinical trial information: NCT02321813.

10051 Poster Session (Board #39), Mon, 1:15 PM-4:45 PM

Patient and provider preferences for physician roles in breast cancer survivorship care. *First Author: Archana Radhakrishnan, University of Michigan, Ann Arbor, MI*

Background: Adoption of team-based models for cancer survivorship has lagged in part due to uncertainty around which physician—oncologist or primary care provider (PCP)—should lead which elements of delivery. We assessed patient, oncologist, and PCP preferences for who leads multiple aspects of survivorship after primary breast cancer treatment. **Methods:** SEER data from LA and Georgia was used to identify and survey women newly diagnosed with breast cancer between 2014-15 (N = 3672, 70% response rate). Participants identified their oncologist (N = 491) and PCP (N = 518) who were also surveyed (61.9% oncologist, 60.8% PCP response rates). Patients and providers were each asked their preference (oncologist- vs. PCP-led) for which physician should lead cancer-related (mammograms) and non-cancer related survivorship care (other cancer screenings, general preventive care and comorbidity management). Distributions of patient and provider preferences was tabulated for each of the four services. The level of overall agreement amongst all three (%) was then calculated for each service (N = 237 triads). **Results:** Agreement within patient-oncologist-PCP triads for physician role preferences (Table) was highest for follow-up mammograms (81% of triads, majority preferred oncologist-led care) and comorbidity management (81% of triads, majority preferred PCP-led care), and intermediate for general preventive care (62% of triads, majority preferred PCP-led care). Agreement was lowest for other cancer screenings (32% of triads): 95% of patients, 62% of oncologists, and 57% of PCPs preferred oncologists lead other cancer screenings. **Conclusions:** Breast cancer patients, oncologists, and PCPs largely agreed on who should lead follow-up mammograms and comorbidity management, but disagreed most on who should direct other cancer screenings during survivorship. Targeting efforts to clarify physician roles, especially for cancer vs. non-cancer related care, will be important to maximize the quality of team-based models of survivorship care.

N = 237 Triads	Follow-up mammograms	Other cancer screenings	General preventive care	Comorbidity management
Prefer oncologist-led (%)				
Patients	95	95	19	11
Oncologists	97	62	13	2
PCPs	89	57	10	6

10052 Poster Session (Board #40), Mon, 1:15 PM-4:45 PM

E-cigarette use among patients of smoking-related cancers in the United States. *First Author: Oladimeji Akinboro, Boston University Medical Center, Boston, MA*

Background: The prevalence of e-cigarette use, and its impact on smoking cessation, among cancer survivors in the United States is unknown. We sought to estimate the prevalence of e-cigarette use, and examine its associations with cigarette smoking and quit attempts among survivors of smoking-related cancer survivors in the United States. **Methods:** We obtained data from the 2014-2016 annual cycles of the National Health Interview Survey. Our study sample comprised 2,561 adults with self-reported lifetime histories of at least one smoking-related cancer. We calculated the prevalence rates of e-cigarette use among survivors of smoking-related cancers. Using a multivariable logistic regression model, we examined independent associations of cigarette smoking history with e-cigarette use while adjusting for sociodemographic and other patient variables that were associated with e-cigarette use from the bivariate analyses. Survey weights were applied in estimating the population-based prevalence rates, odds ratios (OR), and 95% confidence intervals (CI). **Results:** The prevalence of e-cigarette use among survivors of smoking-related cancers was 3.31% (95% CI 2.39%, 4.56%). Those aged 18-44 years had the highest rates of e-cigarette use of any age group (7.26%; 95% CI 2.80%, 11.72%; p-value for age: < 0.001). No associations were seen between e-cigarrete use and gender, race, presence of other smoking-related comorbidities, or duration of survival. Current cigarette smokers were 31 times as likely as never smokers to use e-cigarettes (OR 31.48; 95% CI 4.54, 218.16). Among current smokers, no association was seen between e-cigarette use and either the number of quit attempts or smoking cessation counselling by health professional in the prior year. **Conclusions:** E-cigarette use was highest among current smokers and relatively young survivors of smoking related cancers. The lack of association between e-cigarette use and smoking quit attempts supports observations that e-cigarettes do not increase smoking quit rates. This is concerning, and highlights the need for further studies to define the impact of e-cigarette use on smoking cessation, and long-term outcomes of survivors of smoking-related cancers.

10053 Poster Session (Board #41), Mon, 1:15 PM-4:45 PM

Efficacy of haloperidol versus olanzapine for control of chemotherapy induced nausea and vomiting. *First Author: Soniya Dulal, National Academy of Medical Sciences (NAMS), Bir hospital, Kathmandu, Nepal*

Background: Prevention of chemotherapy induced nausea and vomiting (CINV) is an essential part of cancer care. In resource scarce countries like Nepal, determining anti-emetic combinations of highest value is of utmost importance. The purpose of the study was to compare the efficacy and toxicity of Olanzapine (OLN) (a higher cost drug) and Haloperidol (HAL) (a lower cost drug) in the prevention of CINV in patients (pts) receiving highly emetogenic chemotherapy (HEC) in a developing country. **Methods:** An IRB approved randomized phase II trial was performed in chemotherapy-naive pts receiving cisplatin $\geq$70 mg/m^2 or cyclophosphamide $\geq$ 500 mg/m^2 and doxorubicin $\geq$ 50 mg/m^2. Pts were randomized to receive OLN 10 mg orally on day 1 to 4 or HAL 1 mg orally on day 1 and 0.5 mg BID on days 2 to 4. Both groups received ondansetron (OND) 16 mg and dexamethasone (DEX) 12 mg intravenously on day 1. Use of additional antiemetics for CINV refractory to assigned treatment arm was permitted. From day 1 to day 5, pts recorded their nausea using the Edmonton Symptom Assessment Scale (ESAS). They also recorded their daily episodes of vomiting (number and when) and the use of additional antiemetics. The primary endpoint was complete nausea prevention (CNP) (ESAS - 0). The secondary endpoint was complete emesis prevention (CEP) without the use of additional antiemetics. **Results:** Sixty pts consented and were randomized, 30 in each arm. There was no difference in CNP during the overall period (day 1-5 post chemotherapy) between OLN and HAL (66.6% vs 70%; p = 0.78). In both the acute period (24 hours post chemotherapy) and delayed period (day 2-5 post chemotherapy) CNP was similar between OLN and HAL (acute - 83.3% vs. 80.0%; delayed - 66.6% vs. 73.3%). No difference was identified in the rate of CEP during the overall period (80% OLN vs. 76.6% HAL; p = 0.75) nor in the acute period (93.3% OLN vs. 90% HAL) or delayed period (83.3% OLN vs. 83.3% HAL). No difference in toxicities was noted between treatment arm. **Conclusions:** In this study, HAL was comparable to OLN in the control of CINV with no statistically significant difference in the primary and secondary endpoints suggesting it is the higher value option in pts receiving HEC in a resource scarce country.

10054 Poster Session (Board #42), Mon, 1:15 PM-4:45 PM

Pilot trial of epidermal growth factor (EGF) ointment for the patients with epidermal growth factor receptor (EGFR) inhibitor related skin side effects. *First Author: Sung Yong Oh, Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea, Republic of (South)*

Background: The efficacy of the EGFR inhibitors has been demonstrated in non-small cell lung cancer (NSCLC), pancreatic cancer (PC) and colorectal cancer (CRC). Dermatological reactions can cause significant physical and psycho-social discomfort to patients. In present study, we evaluated the efficacy of EGF ointment on EGFR inhibitor related skin side effects (ERSEs) **Methods:** this was placebo-controlled double blind, multicenter, phase III trial. The patients diagnosed as NSCLC, PC, or CRC who were treated with EGFR inhibitors (e.g. erlotinib, gefitinib, cetuximab). Only patients with Grade $\geq$2 ERSEs according to the NCI-CTCAE v. 4.03 were enrolled. The patients were randomized to 3 groups; A (placebo) group, B (1ppm concentration of EGF ointment), or C (20ppm of EGF ointment). The response to study drug was defined as follows: (1) Grade 2, 3, or 4 ERSEs downgraded to $\leq$Grade 1 or (2) Grade 3 or 4 ERSEs downgraded to Grade 2 and persisting for at least two weeks. The quality of life (QoL) was evaluated with SKINDEX-16. **Results:** Between Jun 2015 and Sep 2017, final efficacy evaluation included 80 patients. Palmar plantar erythrodysesthesia was main symptomatic ERSEs of PC, Rash/Acne was main symptomatic ERSEs of NSCLC and CRC. According to the definition of effectiveness, response to EGF study drug of A (placebo), B (1ppm), or C (20ppm) were 44.4%, 61.5%, and 77.8%, respectively (P= 0.0424). They had been observed linear correlation between different EGF concentration groups (P= 0.0119). The QoL results of the SKINDEX-16 were analyzed as an overall score and three domain scores (including symptoms, emotions and functioning), and reported as mean value. Mean $\pm$ standard deviation (SD) score change from baseline to maximum response of A (placebo), B (1ppm), or C (20ppm) were -5.16 $\pm$ 8.62, -11.74 $\pm$ 14.16, and -18.58 $\pm$ 17.70, respectively (P= 0.0078). Comparing with placebo group, emotions (P= 0.005) and functions (P= 0.044) score domains were much improved by EGF containing group. **Conclusions:** Based on the results, the EGF ointment is effective for ERSEs compared with placebo. The EGF ointment evenly improved all kinds of symptoms and QoL of patients with ERSEs. Clinical trial information: NCT02284139.

10055 Poster Session (Board #43), Mon, 1:15 PM-4:45 PM

Effect of comorbidities on outcomes in colorectal cancer (CRC) survivors. *First Author: Colleen A Cuthbert, University of Calgary, Calgary, AB, Canada*

Background: The effect of comorbidities on outcomes in cancer survivors has not been evaluated in detail, but this can inform survivorship care. We aimed to evaluate comorbid medical conditions, causes of death (COD), and the effect of these conditions on survival among CRC survivors in a Canadian province. **Methods:** A population-based cohort study using administrative data. Patients were diagnosed with stage I-III CRC from 2004 to 2015. ICD-10 codes were used to categorize COD. CRC patients were divided into 5 mutually exclusive comorbid groups: cardiovascular disease (CVD), diabetes (DM), both cardiovascular disease and diabetes (CVD+DM), other comorbidities (OC), and no comorbidities. Kaplan Meier and Cox proportional hazards models were used to evaluate survival, adjusting for age, cancer stage, and treatment. **Results:** We evaluated 12,265 patients. Median age 67.3(range 18-104) years, 56.2% men, 61.8% colon cancer, 38.8% stage III disease, and 36.8% Charlson comorbidity index $\geq$1. There were 1153 (9.4%), 1711(13.9)%, 515(4.2%), and 1141(9.3%) patients in the CVD, DM, CVD+DM and OC groups, respectively. Mean follow-up was 3.8 years. Median overall survival (mOS) was 8.6 (CI 8.3-8.9) years in the entire cohort. Among those who died (N = 3964), 51.2% and 39.3% were due to CRC and other causes, respectively. CVD was a common non-CRC COD (17.1%). In comparison to those with no comorbidities, patients with CVD+DM fared the worst (mOS 3.3 [2.8-3.7] years; adjusted HR for death, 2.27, 95% CI 2.0-2.6, p $<$ 0.001) (see Table). For stage III disease, the percentage receiving curative intent (surgery + adjuvant) treatment was different (p $<$ .001) across groups (31.7% in CVD+DM, 37.6% in CVD, 66.7% in DM, and 57.4% in OC). **Conclusions:** Specific comorbid medical conditions are associated with increased risk of death from CRC and non-CRC causes. Undertreatment was associated with comorbidity profile and may be a driver of worse CRC survival in these patients. Engagement of primary care and other specialty providers earlier in the survivorship trajectory is warranted.

Group	mOS	HR (95% CI)	P value
No comorbidities	10.8 yrs	referent	
CVD	4.2 yrs	1.98 (1.7-2.1)	$<$ .001
DM	7.3 yrs	1.33 (1.2-1.5)	$<$ .001
CVD+DM	3.3 yrs	2.27 (2.0-2.6)	$<$ .001
OC	6.0 yrs	1.61 (1.5-1.8)	$<$ .001

10056 Poster Session (Board #44), Mon, 1:15 PM-4:45 PM

Cardiometabolic risk in childhood cancer survivors: A Children's Oncology Group study. *First Author: Emma Lipshultz, Dana-Farber Cancer Institute, Boston, MA*

Background: Childhood cancer survivors (CCS) are at increased risk of cardiovascular (CV) disease. We assessed the burden of potentially modifiable cardiometabolic risk factors among young adult CCS vs population-matched controls. **Methods:** CCS who enrolled on Pediatric Oncology Group protocols 9404, 9425, 9426, and 9754 from 1996-2001 with acute lymphoblastic leukemia/lymphoma, Hodgkin lymphoma, and osteosarcoma were prospectively assessed for prevalence of obesity, hypertension, dyslipidemia, diabetes, and lifestyle habits (smoking, physical activity) in CCS vs an age-, sex-, and ethnicity-matched 2013 NHANES population. We then estimated Framingham and PDAY general CV risk scores for both groups, and for CCS we also estimated CV risk scores published by the Childhood Cancer Survivor Study (CCSS). **Results:** Compared with NHANES (n = 591), CCS (n = 109; 43% female, mean age 28y; 16y since diagnosis; mean doxorubicin dose 286 mg/m^2; 39% chest radiation, mean 23 Gy; 54% dexrazoxane exposed) had similar rates of obesity (26 vs 30%, p = .73), hypertension (35 vs 31% p = .46), hyperglycemia (12 vs 18%; p = .17), dyslipidemia (49 vs 46%; p = .55), and metabolic syndrome (ATP3 criteria: 12 vs 17%; p = .19). More CCS met Centers for Disease Control & Prevention's guidelines for physical activity (69 vs 45%; p $<$ .001) and fewer reported a history of smoking (27 vs 45%; p = .002). Results were similar among CCS recruited from sites with $>$ 50 vs $<$ 50% participation in this analysis. Because of lifestyle differences, Framingham and PDAY risk scores were generally higher for NHANES vs CCS. Applying the CCSS risk scores, 39% of CCS were at moderate risk of ischemic heart disease, and $>$ 95% at moderate or high risk for heart failure corresponding to a 9-12% predicted incidence of these conditions by age 50. **Conclusions:** Young adult CCS exhibited similar cardiometabolic profiles as NHANES. With more favorable lifestyle habits, CCS had lower predicted CV risk per general risk models but a high proportion had moderate or greater risk of CV disease predicted by the CCSS risk models. Further analyses are needed to determine the impact of dexrazoxane on CCS-specific CV risk. However, the favorable lifestyle habits of this cohort provide cause for optimism.

10057 Poster Session (Board #45), Mon, 1:15 PM-4:45 PM

Patient characteristics and long-term outcomes beyond the first 6 months after a diagnosis of cancer-associated thrombosis. *First Author: Robert Adam Schmidt, Department of Internal Medicine, University of British Columbia, Vancouver, BC, Canada*

Background: Cancer associated thrombosis (CAT) is a common complication of malignancies. However, little is known about the clinical course of CAT beyond the initial treatment period of 3 to 6 months. This information is important for clinicians and patients to inform their decision regarding duration of anticoagulation. **Methods:** Health records from 523 consecutive patients managed at the Vancouver General Hospital Thrombosis clinic for CAT (excluding catheter-related thrombosis) between 2013 and 2015 were reviewed; 327 were alive at 6 months post initial CAT diagnosis. Patient and cancer characteristics, objectively documented recurrent venous thromboembolism (rVTE), clinically relevant bleeding (CRB), and overall mortality of this "survivor" cohort over month 6 to 24 are described. **Results:** In the 6 month survivor cohort, patients were followed for a median of 605 days (range 1 to 730) and 85.9% had at least 24 months of follow-up or died. Patient characteristics at at 6 months are summarized (Table). Anticoagulation was continued in 68.8%, with a median duration of 93 days; 54.3% of patient-days were on anticoagulation. In the 6 to 24 months after the initial CAT diagnosis, there were 34 rVTE in 30 patients (9.2%; 95% CI 6.3 - 12.8) and 16 CRB in 14 (4.3%; 95% CI 2.4 – 7.1) patients, corresponding to 2.9 rVTE per 100 patient-days and 1.4 CRB per 100 patient-days of follow-up. Twenty-one (61.8%) rVTE events and 11 CRB episodes (68.8%) occurred on therapeutic anticoagulation. Over the 18 months, 141 (43.1%; 95%CI 37.7 – 48.7) patients died. Causes of death were cancer (80.9%), rVTE (1.4%), bleeding (2.8%), other (7.8%), and unknown (7.1%). Three fatal bleeds and 2 fatal rVTE occurred while on anticoagulation. **Conclusions:** Patients with CAT who are alive at 6 months after VTE diagnosis remain at high risk of rVTE, CRB and death.

Patient characteristics at 6 months after initial CAT diagnosis

Median Age, year	63.8
Male, %	48.3
≥2 comorbidities, %	25.1
Cancer Site, %	
Upper GI	13.5
Hematologic	19.3
Lower GI	15.0
Lung	12.8
Gynecological	13.8
Breast	7.3
GU	4.3
Prostate	4.9
Brain	3.4
Other	5.8
Metastatic disease,* %	56.0
Cancer treatment, %	64.7

*among patients with solid tumours (n = 259).

10058 Poster Session (Board #46), Mon, 1:15 PM-4:45 PM

Pharmacokinetic (PK) modeling of serum platinum to reveal extent of long-term exposure and associated comorbidities after cisplatin treatment. *First Author: Omar El Charif, The University of Chicago, Chicago, IL*

Background: Platinum (Pt) is detectable for years after cisplatin treatment completion, but few studies have examined the extent of long-term exposure to Pt and associated co-morbidities. **Methods:** Eligible testicular cancer survivors (TCS, n = 633) given 300 or 400 ± 15 mg/m^2 cisplatin underwent lab tests and extensive audiometry, and completed questionnaires at follow-up (median 5 y, range 1-35). Since subject-level PK parameters cannot be estimated in cross-sectional designs, we regressed log(Pt) on dose and follow-up time in the entire cohort. Each subject's PK trait was defined as the deviation from the average concentration-time curve (the residual). High values indicate Pt levels exceeding the expected value, i.e. slower elimination. The Pt reference interval (RI) used (central 95% of 147 non-Pt exposed patients) was 8-47 ng/L (JALM 2016; 1:2, 143). Linear regression at $\alpha = 0.05$ was used for associations with co-morbidities. Hearing loss was quantified as the geometric mean of thresholds: 4-12 kHz (JCO 2016; 34, 2712). Sensory neuropathy was self-reported using EORTC-CIPN20. Cardiovascular (CV) burden was defined as angina, angioplasty, stroke, DVT, PE, CAD, and/or MI $>$ 1 month after therapy. Serum Pt, LDL, HDL, and creatinine (used to estimate creatinine clearance [CrCl] with the Cockroft-Gault formula) were measured. **Results:** Only 35 TCS (5.6%) were within the RI (median follow-up for this group: 20 y, range: 10-35). The estimated time to reach RI upper limit was 18 and 21 y after 300 and 400 mg/m^2 cisplatin respectively (time to RI median: 46 and 57 y). The Pt PK phenotype was strongly negatively associated with CrCl ($p < 10^{-9}$), and positively associated with age ($p < 10^{-8}$), neuropathy ($p = 0.002$; age-adjusted $p = 0.04$), and HDL (age-adjusted $p < 0.001$). When adjusted for age, no associations were apparent with LDL, CV burden, or hearing loss. **Conclusions:** Circulating Pt persists for decades and may contribute to adverse outcomes. We previously showed that hearing loss, but not neuropathy, is associated with cumulative cisplatin dose. In conjunction with our findings here, this suggests differential kinetics of ototoxicity and neurotoxicity.

10059 Poster Session (Board #47), Mon, 1:15 PM-4:45 PM

Risk factors for the development of atrial fibrillation on ibrutinib treatment. *First Author: Robert William Lentz, Northwestern University Internal Medicine, Chicago, IL*

Background: Ibrutinib is a Bruton's tyrosine kinase inhibitor used for treating B-cell malignancies. The incidence of atrial fibrillation/flutter (AF) while on ibrutinib is reported to be 6-16%. The risk factors for incident AF while on ibrutinib are poorly defined. **Methods:** Charts were retrospectively reviewed to include patients treated with ibrutinib for any indication between July 2012 and July 2016. Those with existing AF were excluded. ECGs were manually reviewed to document AF. Patients were followed until incident AF, end of the medical record, end of ibrutinib treatment, or August 2017. Statistical analysis used chi-square and t-tests. **Results:** Of the 168 patients included, median age was 65.7 years, 70.2% were men, 68.5% were white, 60.7% had chronic lymphocytic leukemia, 13.1% had Waldenstrom macroglobulinemia, 11.3% had mantle cell lymphoma, and 14.9% had other cancer types. The incidence of AF was 11.9% after a median of 153 days of ibrutinib treatment. The median follow-up time for those without incident AF was 489 days. Age, coronary artery disease (CAD), heart failure (HF; systolic, diastolic, or either), and moderate/severe mitral regurgitation (M/S MR) were significantly different between patients with and without incident AF. Table 1 includes all evaluated parameters. Of those with HF or M/S MR, 45% and 100%, respectively, developed incident AF. **Conclusions:** In this large retrospective study, the incidence of AF on ibrutinib was higher in patients with older age, CAD, systolic or diastolic HF, and M/S MR. Every patient with M/S MR developed AF. Patients with these risk factors should be counseled on the risk of AF and monitored closely. An echocardiogram to evaluate for structural heart disease prior to initiating ibrutinib should be considered.

Risk factors for incident AF.

	No incident AF (n = 148)	Incident AF (n = 20)	p value
Body mass index, kg/m^2	27.9	28.3	0.758
Age, years, median	**65.4**	**69.1**	**0.038**
Male (n = 118)	68.9%	80.0%	0.309
CAD (n = 27)	**13.5%**	**35.0%**	**0.014**
Hypertension (n = 78)	45.3%	55.0%	0.413
Hyperlipidemia (n = 92)	52.7%	70.0%	0.145
Diabetes mellitus (n = 35)	20.3%	25.0%	0.625
HF (n = 20)	**7.4%**	**45.0%**	**1.12×10^{-6}**
Systolic HF (n = 10)	**3.4%**	**25.0%**	**0.0001**
Diastolic HF (n = 10)	**4.1%**	**20.0%**	**0.005**
M/S MR (n = 3)	**0%**	**15.0%**	**1.99×10^{-6}**

10061 Poster Session (Board #49), Mon, 1:15 PM-4:45 PM

A longitudinal assessment to evaluate the impact of higher body mass index on cancer-related fatigue in breast cancer patients receiving chemotherapy. *First Author: Julia Ellen Inglis, University of Rochester Medical Center, Rochester, NY*

Background: Obesity and weight gain post-chemotherapy leads to increases in all-cause mortality, inflammation, and decreased quality of life but little is known about how obesity contributes to cancer-related fatigue (CRF). Inflammation is also associated with cancer-related fatigue (CRF). We conducted a secondary analysis of a large prospective, nationwide study to assess the impact of obesity on CRF levels in breast cancer patients. **Methods:** Female breast cancer patients (N = 565, aged 53±10.61) completed the multidimensional fatigue symptom inventory (MFSI) and the symptom inventory (SI) to measure CRF symptoms at baseline pre-chemotherapy (T1), post-chemotherapy (T2), and six months post-chemotherapy (T3) as part of a longitudinal study for cognitive impairment. Height and weight were collected at T1 and subjects were categorized based on BMI: Obese (OB: ≥30.0 kg/m^2; n = 294), overweight (OV: 25.0-29.9 kg/m^2; n = 146) and normal weight (NW: 18.5-24.9 kg/m^2; n = 125). Multivariate regression models were used to evaluate the relationship of obesity level to CRF over time controlling for age, race, radiation history, hormonal therapy, cancer stage, exercise level and KPS score. **Results:** At T1, the obese had significantly higher CRF symptoms than normal weight subjects for both the MFSI (OB = 11.4 vs NW = 8.1; p = 0.03) and SI (OB = 3.5 vs NW = 2.9; p = 0.02). Significantly higher SI fatigue scores persisted at T2 for the obese (OB = 4.4 vs NW = 3.8; p = 0.02) with a trend towards significance for the overweight (OV = 4.4 vs NW = 3.8; p = 0.08) group. At T3, obese subjects still had significantly higher SI fatigue scores (OB = 3.8 vs NW = 3.2; p = 0.03). Over the course of the study, obese subjects maintained higher MFSI subscale scores for General, Mental, and Emotional subscales ($p < 0.05$). **Conclusions:** This nationwide multicenter study is one of the first to directly tie obesity to fatigue from pre-chemotherapy through six months post-chemotherapy. Recommendations for weight loss or weight maintenance should be considered to prevent CRF in obese breast cancer patients before and after chemotherapy. Funding: NCI UGCA189961, R25 CA102618

10062 Poster Session (Board #50), Mon, 1:15 PM-4:45 PM

Getting the most out of follow-up: A prospective study using the Measure of Ovarian Symptoms and Treatment concerns (MOST) symptom index to evaluate and track adverse effects (AEs) and detect symptoms of recurrence in patients with ovarian cancer (OC) following first line chemotherapy (1LT). *First Author: Michael Friedlander, Prince of Wales Hospital, Randwick, Australia*

Background: Patients with OC are followed clinically every 3 months (m) after 1LT with the aim of managing symptoms/late AEs and diagnosing recurrence. Studies report that clinicians are unaware of up to half the symptoms patients experience. We developed and validated the MOST in patients with recurrent OC. We hypothesized that patient self-reporting of symptoms could complement clinical follow-up by identifying patients who experience significant late effects and also detect abdominal symptoms of recurrence. **Methods:** Women with OC participating in a prospective study (OPAL) completed MOST every 3m after 1LT for up to 3 years. We analysed MOST subscales representing abdominal, (MOST-Abdo), chemotherapy-related (MOST-Chemo) and psychological (MOST_Psych) symptoms (scales range 0-100, higher scores = greater symptoms). **Results:** 812 patients who received ≥3 cycles and did not progress within 3m of completing 1LT were evaluable. MOST completion rate was 81%. MOST-Chemo revealed high symptom burden just before or < 7 days after the last cycle .Trajectory analyses showed that the symptoms improve significantly/resolve in many patients by 6 months. However, 40% reported persisting moderate symptoms and ~10% had severe symptoms to > 2 years. Patients who scored > 30/100 on MOST-Chemo at the end of chemotherapy were likely to have persistent symptoms and the ~10% who scored > 50/100 reported ongoing severe symptoms to > 2 years. Among ~400 women with recurrence detected during follow-up, the MOST-Abdo symptom scores increased 2-3 months before the clinical diagnosis of progression. **Conclusions:** MOST is a brief patient-reported symptom index that complements clinical surveillance after 1LT. It was well accepted with high compliance rates. It can quantify and track symptoms and AEs experienced post 1LT and can detect the re-emergence of abdominal symptoms associated with recurrence. MOST could help triage the subset of patients likely to experience ongoing moderate-severe symptoms following 1LT for appropriate interventions.

10063 Poster Session (Board #51), Mon, 1:15 PM-4:45 PM

Outcomes of immune-checkpoint inhibitor induced organ toxicities. *First Author: Hamzah Abu Sbeih, Department of Gastroenterology Hepatology and Nutrition, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint inhibitors (ICPIs) are gaining more popularity as treatment for advanced cancers. However, immune-related adverse events (irAE) might limit their use. Immunosuppressants are commonly used to treat irAEs. We aimed to assess the impact of irAEs and their treatment on survival outcomes. **Methods:** We conducted a retrospective review of patients who received ICPIs between 2011 and 2017, who developed irAEs. Descriptive analyses were used to compare different groups. Kaplan-Meier curves and log rank tests were used to estimate overall survival durations. **Results:** A total of 427 patients were included in this analyses. IrAEs were observed in 202 patients; single irAE ($n = 126$), and multiple irAEs ($n = 76$). ICPI-related diarrhea/colitis was confirmed in 117 patients. Immunosuppressant treatment was needed mainly for grade 2 to 4 diarrhea (83.5%) or grade 2 to 3 colitis (62.0%). Ipilimumab treatment duration was shorter than other ICPIs ($P < 0.01$). Ipilimumab based regimens were associated with higher risk of irAEs (OR, 2.33; 95% CI, 1.31 – 4.16). Overall, patients developed irAEs had better overall survival than did patients with no irAEs regardless of immunosuppressant treatment ($P < 0.01$). Patients with mild irAEs who did not need immunosuppressant had better overall survival than did patients without irAEs ($P < 0.01$). Patients with 3 or more irAEs had better overall survival compared to patients with 2 or less irAEs ($P = 0.01$). Overall survival of patients who had irAEs that required immunosuppressant was comparable to patients who had irAE that did not require treatment ($P = 0.73$). Infliximab was associated with shorter duration of steroid use compared to steroid treatment only (2 months [SD, 8] vs. 4 months [SD, 4]). Steroid treatment for more than 30 days was associated with higher rate of infections compared to shorter duration ($P = 0.03$). **Conclusions:** IrAEs are associated with a favorable overall survival, regardless of immunosuppression treatment requirement. IrAEs involving multiple organs appeared to be beneficial for overall survival. Early infliximab use shortens the duration of steroid treatment which decreases the risk of steroid-related adverse events.

10064 Poster Session (Board #52), Mon, 1:15 PM-4:45 PM

Vaginal laser to improve symptomatic vulvovaginal atrophy and sexual function in breast cancer patients: Report from LAAVA pilot study. *First Author: Antonia Pearson, Medical Oncology Department, Royal North Shore Hospital, St Leonards, Australia*

Background: Vulvovaginal atrophy (VVA) is a commonly reported issue among breast cancer patients (pts), and its etiology is multifactorial. The use of systemic and topical estrogens to treat VVA has traditionally been discouraged in hormone positive breast cancer. Laser therapy has been reported to improve symptoms from VVA in women with menopause. We aimed to assess the symptomatic benefit and the impact on sexual function of this treatment in women with early breast cancer (EBC). **Methods:** We performed a single arm investigator initiated pilot study of female EBC pts with symptomatic VVA. 29 pts were recruited between February 2016 and August 2017. 3 pts were not enrolled; 2 had medical conditions that excluded them from treatment, 1 withdrew consent prior to commencing. Baseline demographic data was collected on all pts. A total of 3 vaginal fractional CO2 laser treatments were administered approximately 4 weeks apart for each pt. Questionnaires were completed at baseline, prior to each subsequent treatment and 4 weeks after completion of treatment. Our primary endpoint was symptomatic improvement of VVA (dryness, itch, burning, dysuria and dyspareunia) at 12 weeks on a 10cm visual analog scale (VAS). Our secondary endpoint was improvement in sexual function using the Female Sexual Function Index (FSFI) at 12 weeks. Statistical analysis was performed with a Wilcoxon Signed Rank test. **Results:** 26 pts were enrolled in our study with a median age of 55. All pts were post-menopausal. 25 pts had received anti-estrogen therapy as a part of their breast cancer treatment. All pts received the 3 pre-planned laser treatments, and questionnaire compliance was high (98%). There was significant improvement in VVA symptoms after treatment on a 10cm VAS (table 1) and in sexual function demonstrated on the FSFI ($p = < 0.001$). **Conclusions:** EBC pts had improvement in all 5 domains of VVA symptoms, as well as improvement in sexual function. Further randomized sham-controlled trials are needed to further assess this treatment.

Change in VVA symptoms on 10cm VAS score.

Variable	Mean absolute change	P value
Dryness	4.33	< 0.001
Itch	3.67	< 0.001
Burning	2.93	0.003
Dysuria	3.53	< 0.001
Dyspareunia	3.84	< 0.001

10065 Poster Session (Board #53), Mon, 1:15 PM-4:45 PM

Pregnancies during and following trastuzumab (T) and/or lapatinib (L) in patients (pts) with HER2-positive (HER2+) early breast cancer (EBC): Analysis from the NeoALTTO (BIG 1-06) and ALTTO (BIG 2-06) trials. *First Author: Matteo Lambertini, Institut Jules Bordet, Brussels, Belgium*

Background: Limited data exist on the safety of using targeted agents in pregnant cancer pts. So far, only retrospective studies assessed the prognosis of pts having a pregnancy after prior EBC with no data in HER2+ pts. We aimed to evaluate the outcome of pregnancies occuring during or following T and/or L and the prognostic effect of having a pregnancy in HER2+ EBC pts. **Methods:** NeoALTTO and ALTTO were randomized phase 3 trials in HER2+ EBC pts. In both trials, pregnancy information was prospectively collected. Pregnancy outcomes were compared between pts unintentionally exposed to T and/or L during gestation (exposed group) and those who got pregnant following T and/or L completion (not-exposed group). In the ALTTO trial, disease-free (DFS) and overall survival (OS) of pregnant pts were compared to those of pts ≤40 years without subsequent pregnancy with the Extended Cox Model With Time-Varying Covariates to account for guarantee-time bias. **Results:** Out of 455 and 8,381 pts included in NeoALTTO and ALTTO, 92 pts (7 in NeoALTTO and 85 in ALTTO) had a pregnancy at a median age of 33 years (range 23-40). Pregnancy outcomes are reported in the table No difference in DFS (HR 1.24; 95% CI 0.58-2.6) or OS (HR 0.53; 95% CI 0.13-2.17) was observed between young pts with (n = 85 pts) or without (n = 1,392 pts) a pregnancy. **Conclusions:** Despite fewer live births were described in the exposed group, unintentional exposure to T and/or L during gestation does not seem to affect newborns' outcomes upon treatment discontinuation. Having a pregnancy after HER2+ EBC does not appear to impact on DFS or OS. These data are of high relevance to counsel young EBC pts facing pregnancy-related issues. Clinical trial information: NCT00490139.

	Exposed Group n = 17 pts	Not-exposed Group n = 75 pts
Completed pregnancy	7 (41%)	52 (69%)
Induced abortion	10 (59%)	7 (9%)
Spontaneous abortion	0	10 (13%)
Ongoing/unknown	0	6 (8%)
Live births	7 (41%)	54 (72%)
Congenital anomalies	0	1 (2%)
Oligohydramnios	0	0
Gestational week at delivery (range)	38.5 (34-39)	39 (38-40)
Apgar score (range)	9 (9-9)	9 (9-10)
Newborn weight, g (range)	3,145 (2,880-3,776)	3,440 (3,016-3,710)
Newborn length, cm (range)	50 (49-52.5)	51 (49-52.5)

10066 Poster Session (Board #54), Mon, 1:15 PM-4:45 PM

Meta-analysis of the cardiac events in the adjuvant trastuzumab trials. *First Author: Evandro De Azambuja, Institut Jules Bordet, Brussels, Belgium*

Background: Cardiac dysfunction may occur in patients (pts) receiving adjuvant trastuzumab-based chemotherapy and long follow-up is required to better understand it. This meta-analysis of 3 adjuvant trials investigated the incidence, timing and risk factors for trastuzumab-associated cardiac events. **Methods:** We have conducted an individual patient level data meta-analysis of 3 phase III trials investigating the role of 1 year of trastuzumab (T): HERA, NSBAP B-31, and NCCTG 9831 (Alliance). Definitions of severe CHF (NYHA III or IV) and asymptomatic or mildly symptomatic (NYHA II) cardiac events were considered as per each study, as the precise definitions varied between studies. **Results:** A total of 7445 pts were included in the analysis with a median follow-up in excess of 10 years (119.2-137.2 months): 4017 were in the T arm and 3428 were in the control arm (observation). Nearly all pts (97.5%) in the T arms received anthracycline-based chemotherapy. Table 1 summarizes the incidence of cardiac events in pts treated with 1 year adjuvant T. In total, 452 pts experienced a cardiac event (11.3%). Most of the cardiac events occurred during T use (78.1%). Adjuvant T was completed by 76.2% of pts and 10.0% of pts discontinued T due to a cardiac event. Significant baseline risk factors for cardiac events were LVEF normal but $\leq$60%, hypertension, high BMI ($>$ 25), and age $\geq$60. **Conclusions:** 1-year of T increases the risk of cardiac events, though most are asymptomatic or mildly symptomatic LVEF drops. As cardiac events may lead to interruption in treatment, careful risk-factorr based patient selection, close follow-up and medical intervention (if necessary), are needed. Support: U10CA180868, -180822, UG1-189867, U24-196067; Genentech

Incidence of cardiac events in T treated patients CHF: cardiac heart failure.

	Trastuzumab Combined N = 4017	HERA N = 1682	NSABP B-31 N = 1055	N9831 N = 1280
Any cardiac event	452(11.3%)	92(5.5%)	205(19.4%)	155(12.1%)
Cardiac death	7(0.2%)	3(0.2%)	2(0.2%)	2(0.2%)
Severe CHF (NYHA class III/IV)	94(2.3%)	15(0.9%)	41(3.9%)	38(3.0%)
Asymptomatic or mildly symptomatic (NYHA class II)	351(8.7%)	74(4.4%)	162(15.4%)	115(9.0%)

Note: NSABP B-31 dataset considers an ITT population

10067 Poster Session (Board #55), Mon, 1:15 PM-4:45 PM

Impact of body mass index (BMI) and weight change after treatment in patients (pts) with HER2-positive (HER2+) early breast cancer (EBC): Secondary analysis of the ALTTO BIG 2-06 trial. *First Author: Samuel Martel, Centre Hospitalier Universitaire Sherbrook - Hopital Fleurimont, Sherbrooke, QC, Canada*

Background: Obesity is associated with worse outcomes in hormone receptor-positive (HR+) EBC. However, the association between obesity and prognosis in HER2+ EBC remains unclear. We aimed to determine the impact of BMI at diagnosis and weight change after treatment on the outcomes of HER2+ EBC pts. **Methods:** ALTTO was a phase 3 trial of HER2+ EBC pts. BMI was collected at baseline and at the 2-year visit. WHO BMI categories were used: underweight $<$ 18.5 kg/m^2, normal weight 18.5-24.9 kg/m^2, overweight 25-29.9 kg/m^2, and obese $\geq$30 kg/m^2. A change in weight from baseline of $\geq$5.0% and $\leq$5.0% was categorised as weight gain and weight loss, respectively. The impact of baseline BMI and weight change at the 2-year visit on disease-free survival (DFS), distant DFS (DDFS) and overall survival (OS) were investigated. Multivariate analyses adjusting for baseline pts and tumor characteristics were performed. The impact of weight change was assessed using a landmark analysis. **Results:** A total of 8,381 pts were included: 187 (2.2%), 3,797 (45.3%), 2,690 (32.1%), 1,707 (20.4%) were underweight, normal weight, overweight and obese at baseline, respectively. Compared to normal weight pts, being obese at diagnosis was associated with a significant worse DDFS (adjusted hazard ratio [aHR] 1.25; 95% CI 1.04-1.50) and OS (aHR 1.27; 95% CI 1.01-1.60), and a trend towards worse DFS (aHR 1.14; 95% confidence interval [CI] 0.97-1.32). Weight loss $\geq$5.0% at the 2-year visit was associated with poorer outcomes: DFS (aHR 1.34; 95% CI 1.05-1.71), DDFS (aHR 1.46; 95% CI 1.07-1.98) and OS (aHR 1.83; 95% CI 1.18-2.84). A similar trend, although not significant, was observed for weight gain $\geq$5.0%. Results were affected by hormone receptor status and menopausal status but not by anti-HER2 treatment. Grade 3-4 toxicities, pts with $\geq$1 serious adverse event and treatment discontinuation were more frequent in obese patients. **Conclusions:** In HER2+ EBC pts, obesity at baseline is a poor prognostic factor. Weight changes during treatment and follow-up impacts clinical outcomes: this calls for the need of dietary counselling and physical exercise in the context of survivorship programs. Clinical trial information: NCT00490139.

10068 Poster Session (Board #56), Mon, 1:15 PM-4:45 PM

An individual patient level data pooled analysis of T-DM1 cardiac safety in HER2-positive (HER2+) metastatic breast cancer (MBC) patients. *First Author: Noam Falbel Ponde, Centro Paulista de Oncologia, Sao Paulo, Brazil*

Background: T-DM1 is approved for the treatment of HER2+ MBC and is currently under investigation for use in the early setting. Cardiac dysfunction is a known side effect of trastuzumab, an anti-HER2 antibody that is a component of T-DM1. However, individual studies were not large enough to permit an adequate understanding of cardiac events (CEs) associated with T-DM1 use. We have conducted a pooled analysis of T-DM1 trials in the advanced setting to understand its incidence, clinical presentation as well as to establish possible risk factors. **Methods:** we have conducted an individual patient-level pooled analysis of trials testing T-DM1 in HER2+ MBC patients. CEs were defined either as: (1) congestive heart failure (CHF) of any grade or grade 3/4 LVEF drop (symptomatic CHF); (2) cardiac ischemia, (3) cardiac arrhythmia, (4) grade 1/2 LVEF drop. Logistic regression was used to assess possible risk factors (age, prior heart disease, prior hypertension, prior diabetes, prior anthracycline use, concomitant pertuzumab, among others) for CEs. **Results:** 7 trials with 1961 patients exposed to T-DM1 were obtained. Of these, 1544 received T-DM1 and 417 T-DM1 + Pertuzumab. Median age of patients was 53 years (25-89) and median LVEF at baseline was 63%. 63% of patients had received anthracyclines previously. Symptomatic CHF was reported in 0.7%, cardiac ischemia in 0.1%, cardiac arrhythmia in 0.7% and grade 1/2 LVEF drop in 2%, resulting in a total CE rate of 3.4% (95% CI, 2.6% to 4.3%). No cardiac deaths or cardiac event grade 4 were reported, and only one in five CEs was of grade 3. Multivariate analysis showed patient's age (odds 5% increase per one-year increase, $p < 0.001$) and concomitant pertuzumab use (odds ratio 2.1 {95% CI, 1.2 to 3.5}, p 0.007) as significant risk factors for CEs. Further analysis will be presented at the conference. **Conclusions:** The incidence of CEs in patients receiving T-DM1 was low and most events were not symptomatic. As is the case for trastuzumab, the most common presentation was LVEF drop. Elderly patients receiving T-DM1 should be carefully evaluated for cardiac safety during treatment.

10069 Poster Session (Board #57), Mon, 1:15 PM-4:45 PM

Risk of solid cancer after treatment for testicular germ cell cancer in the platinum era. *First Author: Michael Schaapveld, Department of Psychosocial Oncology and Epidemiology, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Testicular cancer (TC) treatment has been associated with increased risks of subsequent malignant neoplasms (SMNs). It is unknown whether changes in TC treatment over time have affected SMN risk. **Methods:** Solid SMN risk was evaluated in a multicenter cohort, comprising 5,848 one-year survivors treated for TC before age 50 years, between 1976-2007. SMN incidence was compared with cancer incidence in the general population. Cumulative incidences were estimated and treatment-specific risks were assessed using multivariable regression in a case-cohort design. **Results:** After a median follow-up of 14.1 years (interquartile range: 9.3-20.1 years) 350 solid SMNs were observed, translating into a 1.8-fold (95% Confidence Interval (95%CI):1.6-2.0) increased risk compared to the general population. Solid SMN risk was increased both in seminoma (180 SMNs) and non-seminoma (170 SMNs) patients (Standardized Incidence Ratios of 1.5, 95%CI:1.3-1.8 and 2.2, 95%CI:1.9-2.6, respectively). Non-seminoma patients experienced increased risk of SMNs of the thyroid, lung, stomach, pancreas, colon, bladder and of melanoma and soft tissue sarcoma, whereas seminoma patients experienced increased risk of SMNs of the small intestine, pancreas, and urinary bladder. Cumulative solid SMN incidence was 10.3% (95%CI:9.0%-11.6%) at 25 years of follow-up. In multivariable analysis, platinum-based chemotherapy was associated with increased risk of solid SMNs (Hazard ratio (HR) 2.40, 95%CI:1.58-3.62), colorectal SMNs (HR:3.85, 95%CI:1.67-8.92) and non-colorectal gastrointestinal SMNs (HR:5.00, 95%CI:2.28-10.95). With each additional cycle of platinum-containing chemotherapy, the HRs of solid SMNs and gastrointestinal SMNs increased with 22% (95%CI:16-48%) and 53% (95%CI: 34-74%), respectively. The HR of infradiaphragmatic SMNs increased with 6% per Gray of radiation dose administered (95%CI: 5-7%, $P < 0.001$). **Conclusions:** Both radiotherapy and platinum-containing chemotherapy are associated with a dose-depended increased solid SMN risk, specifically with gastrointestinal SMNs.

10070 Poster Session (Board #58), Mon, 1:15 PM-4:45 PM

Independent prognostic value of the EORTC QLQ-C30 summary score on all-cause mortality: Results from the population-based PROFILES registry. *First Author: Olga Husson, Institute of Cancer Research, Sutton, United Kingdom*

Background: Health-related quality of life (HRQoL) has been shown to be a prognostic factor for cancer survival in randomized clinical trials. It is questioned whether this association also holds in the "real world" and which HRQoL scores as measured by the EORTC QLQ-C30 are the best prognosticators. The aims of the present observational, population-based study were to: (1) investigate the association of HRQoL with all-cause mortality; and (2) determine which QLQ-C30 scores (the summary score covering all HRQoL domains, the global QoL or the physical functioning scale) exhibits the strongest association with all-cause mortality. **Methods:** Between 2008 and 2015, cancer patients (colon, rectum, melanoma, basal/squamous cell, endometrial, ovarian, prostate, thyroid, Hodgkin, non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma) were invited to participate in PROFILES ('Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship') disease-specific registry studies (response 69%). In this secondary analysis on a collated patient sample with complete data (n = 6895) multivariate Cox proportional hazard regression models were used to analyze the association between the QLQ-C30 scores and all-cause mortality. **Results:** In the overall regression model including sociodemographic and clinical variables, the QLQ-C30 summary score was associated significantly with all-cause mortality (HR = 0.77; 95%CI = 0.72-0.82; $p < 0.01$). In stratified analyses, significant associations between the summary score and all-cause mortality were found for colon, rectal, prostate cancer, non-Hodgkin lymphoma, chronic lymphocytic leukemia and multiple myeloma only. The summary score had a stronger association with all-cause mortality than the global QoL (HR = 0.82; 95%CI = 0.78-0.85; $p < 0.01$) and the physical functioning scales (HR = 0.81; 95%CI = 0.78-0.84; $p < 0.01$). **Conclusions:** Our results indicate that, in a population-based setting, HRQoL, as assessed by the summary score of the QLQ-C30, has prognostic value for a number of cancer patient populations above and beyond that provided by clinical and sociodemographic variables.

10071 Poster Session (Board #59), Mon, 1:15 PM-4:45 PM

Prevalence and predictors of decreased cardiorespiratory fitness among cancer patients. *First Author: Jesse Pittard Caron, Brigham and Women's Hospital Heart and Vascular Center, Boston, MA*

Background: Exercise limitation is prevalent among cancer (CA) patients (pts). Predictors of decreased cardiorespiratory fitness (CRF) in CA pts require investigation. **Methods:** Single-center retrospective study of 1,632 CA pts (mean age 64 ± 12 years; 58% male, 45% prostate CA; 27% breast CA, 15% Hodgkin lymphoma, 13% head and neck CA) referred for exercise treadmill testing (ETT) a median of 6.8 (3.1, 12.4) years after a CA diagnosis. CRF was determined by peak metabolic equivalents (METs) achieved during ETT. Decreased CRF was defined as failure to achieve > 8 METs. Multivariable logistic regression models assessed associations of CA therapies with decreased CRF. **Results:** 36.6 % of CA pts had decreased CRF. Any chemotherapy, supra-diaphragmatic radiation therapy (RT), and the combination, were independently associated with a significantly higher likelihood of decreased CRF in an age- and sex-adjusted model (Table). These factors remained significant and anthracycline exposure was associated with a 53% increased risk of decreased CRF in the larger multivariable model. **Conclusions: :** Decreased CRF is prevalent among CA pts. Exposure to chemotherapy and/or supra-diaphragmatic RT predispose to decreased CRF in this cancer cohort. Interventions to improve CRF should be considered for select CA pts, especially those treated with chemotherapy and/or supra-diaphragmatic RT.

	Age- and sex-adjusted OR (95% CI), p value	Adjusted* OR (95% CI), p value
Any chemotherapy (n = 478, 29%)	1.75 (1.33, 2.29), p < 0.0001	1.84 (1.35, 2.52), p = 0.0001
Anthracycline chemotherapy (n = 267, 16%)	1.36 (0.96, 1.92), p = 0.08	1.53 (1.04, 2.27), p = 0.032
Supra-diaphragmatic RT (n = 703, 43%)	1.52 (1.16, 1.98), p = 0.001	1.56 (1.14, 2.11), p = 0.005
Combination of any chemotherapy and supra-diaphragmatic RT (n = 386, 24%)	1.92 (1.43, 2.57), p < 0.0001	1.99 (1.42, 2.81), p < 0.0001

*Adjusted for age, sex, low body mass index, obesity, diabetes mellitus, congestive heart failure, ischemic heart disease, hypertension, smoking history, atrioventricular nodal blocking agents, abnormal heart rate recovery, abnormal blood pressure response to exercise, chronotropic incompetence, positive ETT result, and interval from diagnosis to ETT

10072 Poster Session (Board #60), Mon, 1:15 PM-4:45 PM

Cardioprotective effect and safety of dexrazoxane in all breast cancer stages in patients treated with anthracyclines with or without trastuzumab: A systematic review and meta-analysis. *First Author: Ariane Macedo, Federal University of Minas Gerais, Belo Horizonte, Brazil*

Background: Anthracyclines continue to rank among the most effective agents in Breast Cancer (BC) treatment, but its use is limited by a dose-dependent cardiotoxicity. Clinical studies have suggested that dexrazoxane (DZR) could reduce this toxicity, however it is unclear whether the effect is maintained during an adjuvant treatment followed by trastuzumab(TTZ). DZR is frequently used in the metastatic setting, when higher anthracycline cumulative doses are needed, but is often omitted in adjuvancy. We aimed to analyse whether DZR is cardioprotective in all BC stages in patients receiving anthracycline-based chemotherapy followed or not by trastuzumab. **Methods:** We performed a systematic review and meta-analysis. The review was registreded in PROSPERO database. We searched data from 1990 to august 2017 in Cochrane Central Register of Controlled Trials, google scholar, MEDLINE/pubmed, LILACS, web of science, articles references and ASCO proceedings. Studies assessing congestive heart failure or cardiac event (cardiac function alterations without cardiac symptoms or hospitalization for cardiac reasons) as primary endpoints were included. Secondary outcomes were potential adverse effects of DZR on response (complete or partial, overall and progression free survivals). Two reviewers independently performed the studies selection, risk of bias assessment and data extraction. Meta-analysis was done using random effect model for estimation of treatment effect. Heterogeneity was assessed by visual inspection of forest plots and by Q test. **Results:** Nine studies were identified, including 1545 patients. DZR reduced heart failure incidence (RR 0.182, CI95%: 0.080-0.413, $p < 0.0001$) and cardiac events (RR 0.262, CI95%:0.169-0.407, $p < 0.0001$), without impact on response rate or survival. In a subgroup analysis of studies using TTZ after anthracycline, the overall benefit and safety of DZR was maintained. **Conclusions:** DZR delayed and reduced anthracycline induced cardiac toxicity, with or without trastuzumab. These findings may have significant implications for clinical practice

10073 Poster Session (Board #61), Mon, 1:15 PM-4:45 PM

Symptom burden and employment status in breast cancer (BC) survivors. *First Author: Ines Maria Vaz Duarte Luis, Dana-Farber Cancer Institute, Boston, MA*

Background: At time of BC diagnosis, a large proportion of patients (pts) work. However, long term effects of BC and BC treatment are likely to impact employment status in follow up. **Methods:** The ECOG ACRIN protocol E5103 was a phase III trial that randomized BC pts to receive adjuvant doxorubicin, cyclophosphamide, and paclitaxel with either bevacizumab or placebo. Telephone based surveys were administered to all pts enrolled between 01/Jan/10 and 08/Jun/10 as part of a Decision-Making/QOL component. Symptom burden was evaluated using the Memorial symptom assessment scale's (MSAS) global distress index (GDI), psychological and physical scores. Employment status was defined as 1) full time, 2) unemployed, disabled, medical leave 3) other (part time, homemaker, retired and other/unk). Results presented here are part of the 18 months (m) post enrollment follow up. **Results:** Of 519 pts who had not withdrawn at a time point prior to 18 m, pt reported outcomes (PRO) were available from 460 (88.6%). At enrollment (at least 1 m from primary surgery), 38% of pts were working full time and 19% were unemployed, disabled or on medical leave. At 18 m, 42% of pts were working full time, but 13% were unemployed, disabled or on medical leave. Pts who were unemployed, disabled or on medical leave reported significantly worse symptom burden -Table. **Conclusions:** Among pts enrolled in a randomized controlled trial and treated with contemporary adjuvant BC chemotherapy, persistent symptomatology was associated with negative employment outcome. Future strategies are needed to support BC survivors at risk of difficulties in job reintegration. Clinical trial information: NCT00433511.

Employment by MSAS symptom burden* at 18 m.

	N	Median	Min	Max	P**
GDI score					
Overall	460	0.6	0	3.3	
No symptoms	74				
Full time	193	0.5	0	3.1	< 0.01
Unemployed, disabled, medical leave	62	1.4	0	3.3	
Others	205	0.6	0	3.3	
Psychological score					
Overall	460	0.8	0	4.0	
No symptoms	109				
Full time	193	0.7	0	3.7	< 0.01
Unemployed, disabled, medical leave	62	1.7	0	4.0	
Others	205	0.6	0	3.7	
Physical score					
Overall	460	0.4	0	3.1	
No symptoms	87				
Full time	193	0.3	0	3.1	< 0.01
Unemployed, disabled, medical leave	62	0.9	0	2.8	
Others	205	0.4	0	2.1	

*PRO of how pt feels in past 7 days; score range 0-4; higher: worse QOL.
**Wilcoxon rank sum test: full time vs unemployed, disabled, medical leave.

10074 Poster Session (Board #62), Mon, 1:15 PM-4:45 PM

Ultra-low doses of TX-004HR to improve symptoms of vulvar and vaginal atrophy (VVA) while maintaining serum levels of estradiol within the normal postmenopausal range. *First Author: Shari Beth Goldfarb, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: More than 60% of postmenopausal breast cancer (BC) patients have symptoms of dyspareunia and vaginal dryness that often result from endocrine therapy, and are challenging to treat. Local vaginal estrogens are proven safe and effective for VVA treatment, but a major concern of BC patients is the potential risk of systemic absorption and adverse breast effects; and it is contraindicated by the FDA to be used in this population. TX-004HR, an investigational, vaginal, softgel capsule of soluble 17β-estradiol (E2), is being developed to treat menopausal VVA. Serum E2 levels following TX-004HR treatment, which significantly reduced moderate-to-severe dyspareunia and vaginal dryness, were determined and compared with that of the normal postmenopausal range. **Methods:** A 12-wk, randomized, placebo-controlled, phase 3, safety/efficacy study (REJOICE) was conducted in menopausal women with VVA. TX-004HR (4 or 10 μg) was administered daily for 14 d, then twice weekly for 10 wks. Serum E2 levels using validated GC/MS/MS and pharmacokinetics (PK) were determined in 17-19 subjects/group on days 1 and 14 of daily dosing and day 84 of twice-weekly maintenance dosing. **Results:** The day 1, 0-h, mean±SD, serum E2 level was 4.05±2.69 pg/mL (95th percentile 8.49 pg/mL). The mean 24-h average levels on day 1 for the placebo, 4 μg, and 10 μg groups were 4.86±3.22, 3.92±1.46, and 5.76±3.13 pg/mL, respectively. Day 14 mean serum levels were lower than those on day 1; 4.34±2.77, 3.63±1.78, and 4.59±2.27 pg/mL, respectively. No accumulation of E2 was observed on day 14. On day 84 (maintenance phase), serum E2 levels were 4.36, 4.25, and 4.79 pg/mL, respectively. Primary efficacy and safety endpoints had been met for both doses. Changes in E2 levels from baseline to day 14 and day 84 were similar. **Conclusions:** TX-004HR (4 or 10 μg) improved VVA symptomatology, while maintaining serum E2 levels within the normal postmenopausal range. Although not yet studied in BC patients, further study in this population, especially in those taking aromatase inhibitors, is warranted. Clinical trial information: NCT02253173.

10075 Poster Session (Board #63), Mon, 1:15 PM-4:45 PM

Cancer survivorship, financial wellbeing and food insecurity in the U.S. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: Cancer is associated with increased out-of-pocket spending for medical care and limitations in the ability to work, frequently lasting many years after diagnosis. Few studies have addressed other non-medical financial consequences of cancer. This study examines general financial wellbeing and food insecurity for cancer survivors. **Methods:** Using the National Health Interview Survey (2013-2016), we identified cancer survivors (18-64: n = 4340; 65+: n = 6014) and those without a cancer history (18-64: n = 99,958; 65+: n = 27,642). Financial wellbeing measures included worry about standard of living, monthly bills, housing costs, and credit card payments. Financial food insecurity measures included food running out, food not lasting, and eating unbalanced meals. Additionally, skipping meals, eating less, hungry, losing weight, and not eating for an entire day were examined among those who reported any food insecurity. Predicted margins were generated to examine the burden associated with a cancer history, controlling for demographic characteristics, health insurance, income, and comorbidities, stratified by age (non-elderly: 18-64; elderly: 65+). **Results:** In the non-elderly population, cancer survivors consistently reported higher worry about standard of living (45% vs 41%), monthly bills (35% vs 31%), housing costs (28% vs 25%), and credit card payments (14% vs 13%) than those without a cancer history. Moreover, a cancer history was associated with increased food insecurity, i.e. food running out (18% vs 15%), food not lasting (16% vs 13%), and eating unbalanced meals (13% vs 11%). Among those with food insecurity, a cancer history was associated higher likelihood of skipping meals (41% vs 36%), eating less (42% vs 38%), and not eating for an entire day (22% vs 18%, all $p < .05$). In the elderly population, cancer survivors (n = 6014) are comparable to those without a cancer history, with 28% reported any financial wellbeing and 10% reported any food insecurity. **Conclusions:** Non-elderly cancer survivors experience poor financial wellbeing and food insecurity, which go beyond medical financial hardships. Future efforts should assess the relationships between various aspects of adverse financial consequences due to cancer.

10076 Poster Session (Board #64), Mon, 1:15 PM-4:45 PM

Oncology patients referred for cognitive training in a military treatment facility: Demographics, symptom reporting and cognitive functioning for CNS and non CNS cancers. *First Author: Katherine Sullivan, Walter Reed National Military Medical Center, Bethesda, MD*

Background: The Brain Fitness Center (BFC) at Walter Reed National Military Medical Center (WRNMMC) offers computer-based cognitive training, biofeedback, and brain-health classes. Originally designed for service members with traumatic brain injury, the BFC is experiencing an increase in patients with oncology-related cognitive complaints, prompting the need to better understand symptom reporting and objective cognitive functioning in this population. The goal of this analysis is to gain a better understanding of this patient population and compare the presenting symptoms and concerns of cancer patients with and without a history of central nervous system (CNS) involvement. **Methods:** Retrospective review and analysis of six validated symptom self-report questionnaires and objective cognitive functioning assessed by the Automated Neuropsychological Assessment Metrics (ANAM). Participants were 97 Military medical beneficiaries with cancer-related treatments referred to the BFC. Data are derived from an IRB-approved retrospective analysis protocol and were compared with published norms. **Results:** The average age of the study sample at time of referral was 47.3 years (SD 13.3; 49% men, 51% women), with 49% classified as CNS cancer (primary or metastatic disease) and 51% as non CNS cancer. Questionnaire results indicated moderate resilience, low adverse headache impact on daily function, reduced satisfaction with life, mild-to-moderate self-reported functional and neurobehavioral concerns, and subclinical posttraumatic stress symptoms. Average cognitive processing efficiency was poorer than demographically-matched controls (> 1 SD below average) and was inversely associated with self-reported symptom concerns (r -.273 to -.339, $p < .05$). There were no differences between the CNS and non CNS groups on symptom reporting or objective cognitive performance ($p > .05$). **Conclusions:** CNS and non CNS oncology patients produce comparable symptoms and cognitive scores and demonstrate less cognitive efficiency than sex, military service, and age- matched normative groups. Limitations and clinical implications are discussed.

10077 Poster Session (Board #65), Mon, 1:15 PM-4:45 PM

Self-reported functional assessment by patients receiving different prostate cancer strategies: Five-year results from the VICAN large prospective cohort. *First Author: G Raldine Pignot, Institut Paoli-Calmettes, Marseille, France*

Background: Several treatment options are available for prostate cancer (PC) with different functional side effects. The aim of our study was to assess the long-term consequences of the therapeutic strategies on continence, sexual function and quality of life (QOL) for men with a diagnosis of PC from the 5-year VICAN survey. **Methods:** The VICAN survey consisted in a French representative sample of 4174 5-years cancer survivors. Self-reported data were collected through telephone interviews. The questionnaire aimed to document the living conditions and quality-of-life (using the SF-12 questionnaire) of cancer survivors, including treatments' side-effects. **Results:** 447 out of 4174 survivors had PC, median age 71 [57-86] years. Strategies included: radical prostatectomy alone (RP) (42.8%) or with salvage radiotherapy (RP+RT) (7.5%), radiotherapy alone (RT) (17.5%) or in association with hormonal therapy (RT+HT) (11.6%), surveillance (17.4%), and hormonotherapy alone (HT) (3.2%). A total of 51.5% of patients had urinary leakage (sometimes 36.2%, often 12.3%, or very often 3.0%), with a significant impact on physical and mental QOL, and perceived discrimination ($p = 0.049$, $p = 0.020$, and $p = 0.025$, respectively). Patients treated with RP had significantly more urinary leakage than other strategies (59.0% versus 36.6% for RT, and 47.3% for RT+HT, $p = 0.026$). Among 380 pts assessable for sexual function, 56.0% reported dysfunction, with a significant difference to the detriment of RP+RT (74.1% versus 63.5% for RP, 48.6% for RT, 58.2% for RT+HT, 43.4% for HT and 37.8% for surveillance, $p = 0.004$). More significant decrease in the number of sexual intercourse (70.6%) and libido (74.6%) were reported in case of HT ($p = 0.035$), with a significant impact on depressive symptoms, physical and mental QOL ($p = 0.002$, $p < 0.001$, and $p = 0.002$). **Conclusions:** Self-assessed functional outcomes 5 years after PC diagnosis remain poor, specifically for continence after RP and sexual dysfunction after HT, with a significant impact on QOL. Implementation of new long-term management strategies for these patients is required to improve their urinary, sexual function and QOL.

10078 Poster Session (Board #66), Mon, 1:15 PM-4:45 PM

Cumulative burden of severe chronic health conditions (CHC) and health related quality of life (HRQoL) among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort study (SJLIFE). *First Author: Nickhill Bhakta, St. Jude Children's Research Hospital, Memphis, TN*

Background: Childhood cancer survivors have high cumulative burden of severe and life-threatening CHC. The impact of CHC burden on self-reported HRQoL, however, has not been extensively assessed. **Methods:** Participants included 2666 survivors (mean age at study 34 years [range 18-66]) enrolled in the SJLIFE cohort; eligibility: survived ≥10 years and ≥18 years of age. Survivors were clinically assessed for the presence of a severe/life-threatening condition for 78 CHC using the SJLIFE modified CTCAE. HRQoL was assessed with the Short Form 36 and categorized into suboptimal (< -0.5 SD) or optimal (≥ -0.5 SD) based on the physical and mental component summaries (PCS, MCS). A latent class analysis approach was used to generate CHC classes, identify socio-demographic and exposure determinants and estimate associations with HRQoL. **Results:** Unique HRQoL profiles corresponded with the three CHC latent classes identified: optimal PCS and MCS (81% of survivors), suboptimal PCS/optimal MCS (4%) and suboptimal PCS & MCS (15%). Component scores and the prevalence of a subset of CHCs by HRQoL profiles are presented in the Table. Survivors who received ≥30Gy cranial radiation were more likely to have suboptimal PCS/MCS while those who received ≥250mg/m^2 anthracyclines clustered in the suboptimal PCS/optimal MCS class ($p < 0.01$, respectively). **Conclusions:** Despite a high cumulative burden of CHC, most adult survivors of childhood cancer report a HRQoL similar to the general population. Results suggest that most survivors adjust well to the excess disease burden, but also identified profiles of subgroups with suboptimal HRQoL who may benefit from targeted interventions.

	Class 1: Suboptimal PCS and MCS	Class 2: Suboptimal PCS/ optimal MCS	Class 3: Optimal PCS and MCS
HRQoL			
Mean PCS	39*	43*	53
Mean MCS	41*	54	48
% Prevalence CHC**			
Stroke	6	0	1
Myocardial infarction	9	27	1
Heart valve disease	5	24	1
Cardiovascular dysfunction	7	73	2
Arrhythmias	7	27	1
Pulmonary disorder	39	37	2
Chronic renal disease	4	9	1
Hypogonadism	11	23	2
Diabetes	14	14	4
Peripheral neuropathy	20	13	1
Hearing loss	16	23	6
Second neoplasm	19	18	4

*SD < -0.5; **p < 0.01 across 3 classes

10079 Poster Session (Board #67), Mon, 1:15 PM-4:45 PM

Hypogonadism and effects on quality of life in previously treated germ cell tumor survivors: A single-centre, non-randomized, prospective observational study. *First Author: Nabin Khanal, Indiana University School of Medicine, Indianapolis, IN*

Background: Prior studies have shown that around 12% to 16% Germ Cell Tumour (GCT) survivors can have subnormal serum testosterone level as well as up to 15% reported decreased health related Quality of life (QOL). It is important to identify the correlation of hypogonadism with QOL scores in survivors of GCT. **Methods:** This is a single-centre, non-randomized, prospective observational study in GCT survivors 18-50 yrs of age previously treated with Surgery and Chemotherapy or Surgery alone. Total testosterone was measured at baseline, 3, and 6 months. Patients completed a validated QOL questionnaire at baseline, 3, and 6 months. Patients could get supplemental testosterone as standard of care. Mean QOL scores were compared between two treatment groups and within each group between survivors with hypogonadism (serum testosterone level < 300 ng/dL) versus without (> 300 ng/dL). A two-sided independent-groups t test was used to compare means. **Results:** We evaluated 199 GCT survivors. At baseline, the prevalence of hypogonadism was 48.2% overall, 51.45% in Chemo + Surgery group (C) and 44.7 % in surgery alone (CN) (p = 0.39). Overall, there was no statistically significant difference in QOL scores between two groups, except the C group exhibited greater Aging Male Symptoms (AMS) on the AMS scale score than the CN group, at baseline and 6 months. However, compared to patients with testosterone ≥ 300, patients with hypogonadism reported more fatigue (p = .04), poor sleep quality (p = .02) and worse general health (p = .006) at baseline. There was no statistically significant difference in depression (p = .33), or sexual functioning (satisfaction, p = .44; interest, p = .56; ability to have an erection, p = .23). There were no statistical differences in QOL between testosterone groups at 3 months or 6 months; however, sample sizes were small for participants who were measured on the testosterone at 3 months and 6 months. **Conclusions:** GCT survivors treated with chemo exhibited greater Aging Male Symptoms compared to chemo naive group. Hypogonadism was associated with sleep disturbance, worse energy and lower general health QOL scores at baseline.

10080 Poster Session (Board #68), Mon, 1:15 PM-4:45 PM

Unmet need for clinician engagement about financial toxicity after diagnosis of breast cancer. *First Author: Reshma Jagsi, University of Michigan Health System, Ann Arbor, MI*

Background: Little is known about whether growing awareness of the financial toxicity of cancer diagnosis and treatment has led to increased clinician engagement nor the status of current patients' needs. **Methods:** In 2013-15, we surveyed women with early-stage breast cancer, identified through population-based sampling from two SEER regions (Los Angeles and Georgia), and their physicians. We describe responses about experiences with financial toxicity and its management received from 73% of surgeons (n = 370), 61% of medical oncologists (n = 306), 67% of radiation oncologists (n = 169), and 68% of patients (n = 2502). **Results:** Half (50.9%) of responding medical oncologists reported that someone in their practice often or always discusses the financial burden of cancer with patients, as did 15.6% of surgeons and 43.2% of radiation oncologists. Among patients, 17% spent ≥10% of household income on out-of-pocket medical expenses and 7% spent ≥10% of household income on out-of-pocket nonmedical expenses. Debt from treatment was reported by 27.1% of whites, 58.9% of blacks, 33.5% of Latinas, and 28.8% of Asians. Privations were common: 21.5% of whites and 22.5% of Asians had to cut down spending on food, as did 45.2% of blacks and 35.8% of Latinas. Few whites (1.4%) or Asians (1.0%) lost their home, but 4.7% of blacks and 6.0% of Latinas did. Many patients desired to talk to healthcare providers about the financial impact of breast cancer: 15.2% of whites, 31.1% of blacks, 30.3% of Latinas, and 25.4% of Asians. Unmet patient needs for engagement with doctors about financial concerns were common. Of the 945 women who expressed worrying at least somewhat about finances, 679 (72.8%) indicated that cancer doctors and their staff did not help at least somewhat. Of the 523 women who expressed a desire to talk to healthcare providers about the impact of breast cancer on employment or finances, 283 (55.4%) reported that they had not had a relevant discussion. **Conclusions:** Improved clinician assessment and communication regarding financial toxicity are necessary. Even physicians who perceive that they are routinely offering necessary services may fail to meet patient needs. Cure at the cost of financial ruin falls short of physicians' duties.

10081 Poster Session (Board #69), Mon, 1:15 PM-4:45 PM

The hidden burden of anxiety and depression in ovarian cancer: A prospective longitudinal study from diagnosis. *First Author: Penelope M Webb, QIMR Berghofer Medical Research Institute, Brisbane, Australia*

Background: Women with ovarian cancer (OC) report high rates of anxiety (A) and depression (D), but most studies have used a cross-sectional design at a single time-point, not considered prior history and not included women who are symptom-free due to medication. Our goals were to quantify the total burden of A/D among women newly diagnosed with OC; the proportions who experienced symptoms only after their OC diagnosis and those with persistent symptoms; and determine use of appropriate medication/services by those affected. **Methods:** The OPAL (Ovarian Cancer Prognosis & Lifestyle) Study is a prospective study of Australian women diagnosed with OC from 2012-15. At baseline, they were asked if they had ever been diagnosed with A or D and if they took medication for this in the year before their OC diagnosis. At follow-up (3, 6, 9, 12, 24, 36 & 48 months after diagnosis) they complete the Hospital Anxiety and Depression Scale (HADS) and are asked about current medication use. **Results:** Of 893 women with ≥1 follow-up questionnaire, 373 (42%) reported clinical levels of anxiety (HADS > 10, 18%) and/or depression (15%) and/or use of anxiolytic or antidepressant medications (A/D meds) (18%) on at least one occasion during the first 3 years after diagnosis. An additional 166 women (19%) reported subclinical A or D (HADS 8-10). Of those with clinical A/D or taking A/D meds, 159 (42%) reported this at ≥3 time-points, 218 (58%) reported no prior history of A or D and 274 (73%) reported no use of A/D meds in the year prior to diagnosis. When women reported clinical levels of A or D, only 45% reported taking medication (37%) and/or seeing a psychiatrist or psychologist (19%). Among those not already on A/D medication at diagnosis, a prior history and low levels of optimism were the strongest predictors of A/D onset. **Conclusions:** More than 40% of women with OC experienced clinical levels of A or D during treatment or the first 3 years of follow-up. For 42% of those affected this was their first experience of distress and > 50% did not receive appropriate medication or psychological support. The hidden burden of anxiety and depression in this population is much greater than previously reported but is amenable to effective intervention if recognized.

10082 Poster Session (Board #70), Mon, 1:15 PM-4:45 PM

Sustained long-term benefits of a psycho-educational intervention targeting fear of cancer recurrence in people at high risk of developing another melanoma: A randomised controlled trial. *First Author: Mbathio Dieng, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*

Background: People with melanoma want and need effective treatments for managing and living with fear of cancer recurrence (FCR). This study reports the long-term efficacy of a psycho-educational intervention designed to reduce FCR in people at high risk of developing another primary melanoma compared to usual care. **Methods:** Adults previously diagnosed with stage 0, I or II melanoma were randomly allocated to the intervention (n= 80) or control (usual care) arm (n= 84). Of 164 participants, 87% completed the 12-month assessment. Outcomes for 8 participants (5%) who completed the 6-month but not the 12-month assessment were imputed using model-based multiple imputation; thus, 151 participants are reported in the analysis. The intervention comprised a 76-page psycho-educational resource and three individually-tailored, telephone-based sessions with a psychologist, scheduled at specific time-points around participants' dermatological appointments. The intervention effect at 12-months was estimated by intention-to-treat analysis of the mean change in FCR score using a linear mixed model and as a FCR severity sub-score $\geq$13 vs $<$ 13 using logistic regression adjusted for repeated measures. **Results:** The intervention group had significantly lower FCR at 12 months; the between-group mean difference was -1.41 for FCR severity (95% CI -2.6 to -0.2; p= 0.02), and -1.32 for FCR triggers (95% CI -2.6 to -0.02; p= 0.04). The odds ratio for FCR severity $\geq$13 (54% intervention, 63% control) was 0.59 (95% CI 0.30 to 1.14, p= 0.12). There were no differences in secondary outcomes including anxiety, depression, or health-related quality of life. **Conclusions:** This psycho-educational intervention had a sustained effect in reducing fear of cancer recurrence over the longer-term. This novel intervention has no adverse effects and its benefits persist long after the last psychology session, supporting implementation as part of routine clinical care in melanoma. Clinical trial information: ACTRN12613000304730.

10083 Poster Session (Board #71), Mon, 1:15 PM-4:45 PM

PCPs knowledge and self-efficacy for caring for breast and colon cancer survivors. *First Author: Niharika Dixit, University of California San Francisco/ZSFG, San Francisco, CA*

Background: The role of primary care providers (PCPs) in caring for cancer survivors is critical, as care shifts from active cancer treatment to managing late and long-term effects of treatment and health maintenance. Safety net providers often need to provide cancer survivorship care in limited resource settings. This study assessed PCPs' knowledge, attitudes, and self-efficacy related to caring for breast and colon cancer survivors in a public hospital setting. **Methods:** A modified National Cancer Institute Survey of Physician Attitudes Regarding the Care of Cancer Survivors was sent electronically to 220 PCPs in 12 primary care clinics in the San Francisco Health Network affiliated with Zuckerberg San Francisco General Hospital. The response rate was 50% (110/220). **Results:** About half of PCPs strongly/somewhat agreed (vs. strongly/somewhat disagreed) that PCPs have the knowledge needed to provide follow-up care related to breast (49%) and colon cancer (53%). Providers were more likely to report feeling somewhat/very confident (vs. not at all confident) in providing appropriate surveillance testing to detect recurrent colon than breast cancer (73.6% vs. 65.3%). Most providers (92%) correctly reported recommended frequency of mammography, however, frequency of blood tests and other imaging surveillance were not as well recognized for breast or colon cancer. Recognition of long-term side effects of chemotherapy drugs was low (highest = 44% for Adriamycin). Lack of knowledge (76.3%) and unclear delineation of roles between PCP and oncologists (70.7%) were the most commonly reported barriers to providing high quality cancer survivorship care. Only 33% of providers reported receiving any survivorship training on late and long-term effects of treatment. The most preferred model for survivorship care was shared care (40.2%) and least preferred was one in which PCPs have primary responsibility (47.6%). **Conclusions:** PCPs feel they lack the appropriate knowledge, training, and confidence to assume primary responsibility for the care of breast and colon cancer survivors. A shared care model was most preferred, indicating an opportunity to improve survivorship care through effective oncologist-PCP-patient partnerships.

10084 Poster Session (Board #72), Mon, 1:15 PM-4:45 PM

Cannabis use in hematopoietic transplantation survivors. *First Author: Elizabeth Trice Loggers, Seattle Cancer Care Alliance, Seattle, WA*

Background: Approximately 20% of cancer patients report cannabis use (CU) within the last month despite limited data regarding its risks/benefits. CU among hematopoietic transplantation survivors (HTS) is of interest given the high symptom burden, infectious risk and research regarding cannabidiol in graft versus host disease prevention. **Methods:** From January 1 to June 1, 2017, a 15-question module addressing CU was included in a self-administered, annual survey of all adult HTS at Fred Hutchinson Cancer Research Center (Seattle, WA). Analysis included descriptive statistics and logistic regression. **Results:** Responders (n = 697, 32%) were more likely to be older, white and female than non-responders (all $p < 0.001$). Among responders, 329 (47%) considered CU and 124 (18%) reported CU. Reasons for considering CU included: physical symptoms (86%), emotional concerns (50%), recreation (45%) and to treat cancer (22%). While HTS aged 18-39 were 4-fold more likely to consider CU than those $>$ 65 years (odds ratio 4.04, 95% confidence interval 2.25-7.27, $p < 0.0001$), age was not associated with CU. Instead, white race, perception of benefits of CU, CU for cancer treatment, and communication/receipt of information from clinicians, naturopaths or cannabis dispensers or peers was associated with CU (see Table 1). CU was not associated with the legal status of cannabis in the HTS's state/province. **Conclusions:** While most HTS use cannabis to address physical and emotional concerns, nearly a quarter use it with the hope of improving their cancer outcomes. Whereas the perceived benefits of, and communication regarding, cannabis may play a significant role in use, age and legality likely do not.

Factors associated with cannabis use (n = 329).

	OR (95% CI)	*p*-value
Race		
White	1.0	
Other	0.35 (0.12-0.96)	0.04
Transplant relapse*		
Yes	0.27 (0.06-1.12)	0.07
Believe cannabis has benefit*		
Yes	2.18 (1.21-3.95)	0.01
Considered use to treat cancer*		
Yes	2.74 (1.31-5.72)	0.008
Discussed with/received information from:		
Doctor, nurse, or nutritionist*		
Yes	2.92 (1.69-5.05)	0.0001
Naturopath or medicinal/recreational staff person*		
Yes	2.62 (1.35-5.10)	0.005
Family, friend, or other cancer patient*		
Yes	2.54 (1.37-4.72)	0.003

* No = referent (OR = 1.0)

10085 Poster Session (Board #73), Mon, 1:15 PM-4:45 PM

Randomized trial of a text messaging intervention for symptom distress in BCa patients undergoing chemotherapy. *First Author: Kuang-Yi Wen, Fox Chase Cancer Center, Temple University Health System, Philadelphia, PA, Philadelphia, PA*

Background: Chemotherapy is often associated with treatment side-effects that negatively affect HRQOL. The aim of this study was to examine the feasibility and preliminary efficacy of a novel mobile text messaging (TXT) intervention to help breast cancer (BCa) patients coping with chemotherapy. **Methods:** Through an iterative patient-centered formative evaluation process, we developed an automatic bidirectional theory-guided and evidence-informed TXT intervention that sent two daily proactive messages addressing education, symptom management and support with options for patients to request more texts. In a RCT study, 100 BCa patients undergoing chemotherapy were assigned to either the TXT group or a control group that received an ACS chemotherapy booklet. Measures were administered at baseline, 1-month, 2-month, 3-month and 4-month. A satisfaction interview was conducted following the intervention. Acceptability and feasibility were examined. Primary outcomes were symptom distress and HRQOL. Secondary outcomes were depressive symptoms, self-efficacy and doctor-patient communication. **Results:** The majority of the sample was white (70%) with a mean age of 59 years. Both study groups reported significant increase in symptom distress and decline in HQROL from baseline to follow-ups. Symptom distress was found significantly lower and HRQOL was higher in the intervention group at month 1 and month 3 than the control (p-value $\leq$ 0.05). Intervention group reported significant improvement in self-efficacy and doctor-patient communication (p-value $\leq$ 0.05). No difference was found in depressive symptoms between two groups. Regarding acceptability, 70% of eligible participants consented and 90% of the TXT group participants were satisfied with the intervention. Intervention participants texted back to the system a total of 2388 times requesting additional texts with a mean range of 3-58 requests. **Conclusions:** Feasibility, satisfaction, and preliminary efficacy of a TXT intervention to promote better outcomes for BCa patients undergoing chemotherapy were established. Further research is needed to develop additional tailoring and personalization per participants' feedback.

10086 Poster Session (Board #74), Mon, 1:15 PM-4:45 PM

Trust in doctors and non-doctor sources for health and medical information. *First Author: Leo Chen, University of British Columbia, Vancouver, BC, Canada*

Background: Patients today have unprecedented access to health and medical information (HMI) from a diverse range of sources. This access helps inform patients, but it may also misinform and adversely affect patients' trust in doctors (TD). In this study, TD is compared with trust in 8 other sources of HMI. **Methods:** This study examines the Health Information National Trends Survey (HINTS-5) data published July 2017 by the National Cancer Institute. A nationally representative sample was generated from 3,295 Americans, and analyses included the 1873 who sought cancer information. Trust was ranked 1 (not at all) to 4 (a lot). Trust in family (F), news (N), radio (R), internet (I), TV, government (G), charities (C), and religious sources (RS) were independently compared to TD. Logistic regression was used to evaluate associations between demographic characteristics and viewing non-doctor sources as equal or superior to TD (EOSTD) for HMI. **Results:** Post-survey weighting, 75.6% of the sample trusted doctors "a lot", followed by trust in G (32.1%), I (15.4%), and C (8.3%). 60.4% viewed at least one non-doctor source as EOSTD. Earning $75,000 or more was inversely associated with viewing F (OR 0.89, p = 0.009), N (OR 0.91, p = 0.027), T (OR 0.84, p = 0.004), C (OR 0.83, p = 0.003), and R (OR 0.88, p = 0.004) as EOSTD for HMI compared to earning < $20,000. Compared to not completing high school, some college (OR 0.82, p = 0.029), college (OR 0.80, p = 0.011), or postgraduate education (OR 0.80, p = 0.011) reduced OR for viewing TV as EOSTD. Compared to being White, being Non-Hispanic increased viewing I as EOSTD, while being Black (OR 1.14, p = 0.007) or Non-Hispanic (OR 1.27, p = 0.034) increased viewing TV as EOSTD. Being female was associated with viewing F as EOSTD (OR 1.04, p = 0.040). **Conclusions:** Doctors are the most trusted HMI source, but most respondents viewed at least one non-doctor source as EOSTD. Patients should be reminded that alternative sources are not equivalent to doctors for HMI.

10087 Poster Session (Board #75), Mon, 1:15 PM-4:45 PM

Gender differences and trends in suicide risk among cancer survivors. *First Author: Nosayaba Osazuwa-Peters, Saint Louis University School of Medicine, St. Louis, MO*

Background: Cancer survivors have higher risks of dying from suicide compared with noncancer patients as well as the general United States population. This risk may differ based on gender and may be increasing due to the concomitant increase in the number of cancer survivors in the United States. This study aimed at describing the differences and identifying suicide risk trends based on gender. **Methods:** We queried the Surveillance, Epidemiology and End Results 18 database from 2000-2014 for all cancer deaths confirmed as suicide. Mortality rates from suicide was estimated for the 20 most common cancers in the United States, including lung, pancreatic, and head and neck cancers, three sites with leading suicide rates. Multivariate Poisson regression estimated mortality rate ratios (RRs) and 95% confidence intervals (CIs), stratified by sex (when applicable), and adjusting for site, race, marital status, age, year and stage of diagnosis. **Results:** There were 4,769 suicides observed among 4,427,272 cancer survivors from 2000-2014, yielding an incidence rate of 23.6 suicides per 100,000 person-years. Of these, 84.1% were suicides among male cancer survivors. Males cancer survivors were almost six times more likely to die from suicide compared with females (aRR = 5.62, 95% CI:5.17, 6.11). For males, increasing age (ref: 20-39 years) was associated with increasing risk of suicide: 40-59 years (aRR = 1.50, 95% CI: 1.22, 1.84), 60-69 years (aRR = 1.85, 95% CI: 1.50, 2.28), 70+ years (aRR = 2.52, 95% CI: 2.04, 3.11). It was the reverse in female survivors, where 60-69 (aRR = 0.71, 95% CI 0.61, 0.82) and 70+ year olds (aRR = 0.49, 95% CI 0.42, 0.57) were less likely than 20-39 years to commit suicide. Finally, compared with 2000-2004, female survivors diagnosed in 2010-2014 were 32% (aRR = 1.32, 95% CI: 1.19, 1.47) more likely to commit suicide, whereas male survivors were only 12% (aRR = 1.12, 95% CI 1.02, 1.23) more likely to commit suicide in the same period. **Conclusions:** There are significant male vs. female differences in suicide risks among cancer survivors, and there may have been an increased risk of suicide among women of reproductive age, and in the last decade. Survivors of cancer need surveillance to optimize survivorship and decrease suicide risks.

10089 Poster Session (Board #77), Mon, 1:15 PM-4:45 PM

Exercise counseling in integrative oncology: Patient characteristics and effects on self-reported symptoms. *First Author: Gabriel Lopez, University of Texas, MD Anderson Cancer Center, Houston, TX*

Background: Physical activity and exercise have shown benefits for cancer prevention and contribute to improved treatment related outcomes. We reviewed the characteristics of cancer patients referred for physical therapist-led exercise counseling at a comprehensive cancer center and its effects on self-reported symptoms. **Methods:** Patients presenting for an exercise counseling consultation and follow up encounter at an Integrative Medicine Center outpatient clinic from Feb 2016 to May 2017 completed the Edmonton Symptom Assessment Scale (ESAS; 0-10 scale, 10 most severe) pre/post-encounter; a PROMIS 10 global health assessment was also completed within 30 days of each encounter. Exercise counseling was provided by a physical therapist. ESAS individual items and subscales of Physical Distress (PHS), Psychological Distress (PSS), and Global Distress (GDS) were analyzed. We used paired t-tests with a p-value correction (i.e., p < .001) to examine symptoms before and after each encounter. **Results:** Data were available for 367 participants; 68 (18.5%) had at least one follow up encounter at 56.1 days (mean). Most were female (77.7%), caucasian (66.2%) with breast (43%), gastrointestinal (15.8%), or gynecologic (6.8%) cancer. Highest and most frequently reported (%) symptom scores at baseline included poor sleep (63.2%; 3.55), fatigue (59.9%; 3.19), and poor well-being (62.4%; 3.17). Pre/post change for one encounter was statistically and clinically significant for the ESAS GDS subscale (-3.36, SD 6.54, p < 0.001). ESAS change (n = 40) between baseline and first follow up within 60 days was statistically and clinically significant for improvement in fatigue (-1.35, p = 0.006), GDS (-4.55, p = 0.008), and PHS (-3.15, p = 0.016). PROMIS10 scores (n = 321) at baseline included global health 31.34. For the follow up group (n = 67), significant improvements were observed for mental health (p = 0.015) and global health (p = 0.024), not physical health (p = 0.07). **Conclusions:** Patients presenting for an exercise consultation had a moderate symptom burden with global health scores lower than the population mean, with improvements observed in global distress, physical distress, and fatigue after one encounter.

10090 Poster Session (Board #78), Mon, 1:15 PM-4:45 PM

Randomized controlled trial of percutaneous transesophageal gastrotubing for symptom palliation in patients with malignant gastrointestinal obstruction. *First Author: Miyuki Sone, National Cancer Center Hospital, Tokyo, Japan*

Background: Malignant gastrointestinal obstruction occurs in approximately 10-16% of end-stage cancer patients. Nasogastric tubing (NGT) is a standard palliative treatment; however, NGT causes nasopharyngeal discomfort, pain, skin ulcer, and difficulties in the appearance care such as shaving or makeup. Percutaneous transesophageal gastrotubing (PTEG) was developed as an image-guided, minimally invasive tube placement directly accessing to the cervical esophagus under local anesthesia. As the previous phase II study of PTEG (JIVROSG-0205) demonstrated high technical success (100%) and clinical efficacy (91%), we hypothesized that patients receiving PTEG would have higher quality of life (QOL) than NGT. The aim of this multicenter, open-label, randomized controlled trial (JIVROSG-0805) was to evaluate the efficacy of PTEG. **Methods:** Patients with symptomatic malignant gastrointestinal obstruction were randomly assigned (1:1) to receive PTEG or NGT. The primary endpoint was symptomatic scores of four elements (nasopharyngeal discomfort, satisfaction with appearance, restriction of daily life, and sleep disturbance) evaluated with area under the curve (AUC) during 2 weeks after the treatments. Secondary endpoints included change in global health-related QOL (EQ-5D, SF-8) and incidence of adverse events evaluated with CTCAE v.3.0. **Results:** From October 2009 to January 2015, 40 patients were enrolled (PTEG: 20; NGT: 20). Symptomatic scores were evaluable in 39 patients (PTEG: 19; NGT: 20) and the safety was evaluable in all patients. The AUC of the symptomatic scores of the PTEG group (mean: 149.6; 90% CI: 125.2, 173.9) was significantly higher than that of NGT group (mean: 44.9; 90% CI: 21.2, 68.7) ($p<$ 0.0001). Differences in EQ-5D (mean: 3.5; 90% CI: 1.6, 5.3; $p<$ 0.036) and SF-8 (mean: 220.7; 90% CI: 113.3, 328.1; $p<$ 0.0020) between two groups were statistically significant. There was no procedure-related complication in both groups. **Conclusions:** This analysis demonstrated the statistical superiority of the PTEG compared to the NGT. PTEG was effective in reduction of the distressing symptoms caused by NGT. Clinical trial information: UMIN000003565.

10091 Poster Session (Board #79), Mon, 1:15 PM-4:45 PM

PG2 injection, a novel botanical drug approved for improving cancer-related fatigue among advanced cancer patients under standard palliative care: A double blind, multi-center, randomized phase IV study. *First Author: Cheng-Hsu Wang, Chang Gung Memorial Hospital, Keelung, Taiwan*

Background: Cancer-related fatigue (CRF) is one of the most frequent and debilitating symptoms in 60% to 90% of patients with advanced cancer. The fatigue experienced by cancer patients can not only deteriorate patient quality of life, but also affect treatment efficacy and survival rate. PG2 injection developed by PhytoHealth Co., Taiwan with Astragulus Polysaccharides as API is the only drug approved by Taiwan Food and Drug Administration (TFDA) for relieving CRF in patients with advanced cancer. To further explore the effect of PG2 injection at lower dose, we recruited more patients in the current study and observe the effect of PG2 injection in 2 doses. **Methods:** Patients with advanced cancer receiving standard palliative care (SPC) with moderate to severe CRF (Score of the Brief Fatigue Inventory-Taiwan (BFI-T)≥4) were enrolled. Patients were randomized at a 1:1 ratio into two arms of PG2 injection treatment: 500mg dose or 250mg dose (both were prepared in 500ml saline and injected 3 times per week for 4 weeks) for two cycles. Fatigue improvement response rates (FIRR) were analyzed at the end of the first cycle to determine the efficacy of the two PG2 doses. Improvement of BFI-T score for more than 10% is considered as effective for relieving CRF. **Results:** Three hundred and ten patients were enrolled in this study. Two hundred and fourteen patients were included in the ITT population, including 111 subjects in high dose group and 103 subjects in low dose group. Results showed that improvement in fatigue scores by at least 10%, 20%, 30%, and 40% was observed in 65.07%, 46.60%, 34.95%, and 26.61% of subjects receiving 250 mg PG2 injection after one treatment cycle when compared to the baseline; in 500 mg group, fatigue score improvement by at least 10%, 20%, 30%, and 40% was observed in 65.77%, 51.35%, 34.23%, and 18.92% of subjects after one PG2 treatment cycle when compared to the baseline. **Conclusions:** This study demonstrates that more than 60% of subjects showed at least 10% improvement in fatigue score when compared to baseline after both 250mg and500mg PG2 treatments. Clinical trial information: NCT01720550. Clinical trial information: NCT01720550.

10092 Poster Session (Board #80), Mon, 1:15 PM-4:45 PM

Prophylactic treatment for acneiform rash caused by EGFR inhibitors: Prospective randomized double-blind trial comparing daily topical chloramphenicol 3% plus prednisolone 0.5% vs chloramphenicol 3% vs aqua cream. *First Author: Salomon M. Stemmer, Davidoff Cancer Center, Rabin Medical Center-Beilinson Hospital, Petah Tikva, Israel*

Background: Epidermal growth factor receptor inhibitors (EGFR-I), which are indicated for various tumor types, are associated with acneiform rash on the face/torso in approximately 90% of patients. This rash adversely impact patients' quality-of-life and may result in dose reductions/delays and treatment discontinuation. **Methods:** This randomized double blind trial investigated chloramphenicol 3% + prednisolone 0.5% (Threolone) vs chloramphenicol 3% vs aqua cream as prophylactic treatment for acneiform rash caused by EGFR-I. Adult cancer patients treated with EGFR-I (cetuximab, panitumumab, erlotinib, or gefitinib) were randomized to treatment with the 3 above mentioned options and were instructed to administer the assigned topical treatment to their face daily for 3 weeks and every 2 days for another week. The severity of the rash was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as well as the number of facial lesions. Severe rash was defined as grade≥3 by the CTCAE criteria or ≥10 facial lesions. The rash was assessed on Days 0, 14, and 28. **Results:** Overall, 69 patients were randomized (21 chloramphenicol 3% + prednisolone 0.5%, 23 chloramphenicol 3%, and 25 aqua cream). The arms were similar with respect to demographics and tumor types. Number of facial lesions and CTCAE grade were highly correlated (r = 0.9). According to the number of facial lesions, chloramphenicol + prednisolone but not chloramphenicol alone was significantly more effective than aqua cream (Table). **Conclusions:** Topical chloramphenicol 3% + prednisolone 0.5% may be an effective prophylactic treatment for EGFR-I-associated acneiform rash. Clinical trial information: NCT01256437.

Proportion of patients with protocol specified severe acneiform rash.

		Day 14		Day 28		Day 14 or 28	
Study arm	N	Severity by CTCAE, %	Severity by NOL, %	Severity by CTCAE, %	Severity by NOL, %	Severity by CTCAE, %	Severity by NOL, %
Chloramphenicol 3% + prednisolone 0.5%	21	0	14[a]	0	6[a]	0	19[a]
Chloramphenicol 3%	23	5	40	5	16	5	39
Aqua cream	25	20	48	5	43	20	52

[a] $P < 0.05$ vs aqua cream treatment. All other 2-way comparisons were non-significant. NOL: number of lesions

10093 Poster Session (Board #81), Mon, 1:15 PM-4:45 PM

Adapalene gel 0.1% vs. placebo as prophylaxis for anti-EGFR-induced acne-like rash: A randomized left-right comparative evaluation (APPEARANCE). *First Author: Motoko Tachihara, Divisions of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan*

Background: Anti-EGFR drugs frequently cause acne-like rash. Adapalene (ADP), a topical retinoid used as first-line therapy for acne, is efficacious against acne-like rash induced by anti-EGFR drugs. To evaluate the prophylactic efficacy of ADP, we conducted a randomized, placebo (PLC)-controlled, evaluator-blinded, left-right comparative trial. **Methods:** Non-small cell lung, colorectal, or head and neck cancer patients scheduled to receive EGFR monoclonal antibodies (MABs) or tyrosine kinase inhibitors (TKIs) were randomly assigned to once daily ADP application on one side of the face, with PLC on the other side. All patients had topical moisturizer co-applied to both sides of the face, and received oral minocycline. The primary endpoint was the difference in total facial lesion count of acne-like rash at 4 weeks. A sample size of 26 has 80% power to detect a mean of paired differences of 15 with an estimated standard deviation of differences of 25 and a significance level of 0.05. Secondary endpoints included global skin assessment and ≥ grade 2 acne-like rash (MASCC scale) at 4 weeks. Two blinded dermatologists independently evaluated the endpoints from photographs. **Results:** From Feb 2016 to May 2017, 36 patients were enrolled, but 10 discontinued mainly because of poor adherence. Of the remaining 26 evaluable patients, 13 each received EGFR MABs or TKIs. Although the total lesion count did not differ with ADP treatment compared with PLC at baseline (0.6 vs 0.9), ADP treatment was unexpectedly associated with greater lesion count than PLC, although the difference was not statistically significant (12.6 vs 9.8, p = 0.1127). All 4 patients with a difference > 10 in lesion count between face sides had a greater lesion count on the ADP-treated side. No significant differences were observed in global skin assessment or incidence of ≥ grade 2 acne-like rash between ADP- and PLC-treated sides. The most common adverse event other than acne-like rash was dry skin, but the incidence did not differ between ADP- and PLC-treated sides (57% vs. 54%). **Conclusions:** Based on our findings, ADP is not recommended for the prevention of acne-like rash induced by anti-EGFR drugs. Clinical trial information: 000016692.

10094 Poster Session (Board #82), Mon, 1:15 PM-4:45 PM

Patient reported outcomes (PRO) results for prophylactic effect of dexamethasone on regorafenib-related fatigue and/or malaise: a randomized, placebo-controlled, double-blind clinical study in patients with unresectable metastatic colorectal cancer: KSCC1402/HGCSG1402. *First Author: Mototsugu Shimokawa, Clinical Research Institute, National Kyushu Cancer Center, Fukuoka, Japan*

Background: KSCC1402/HGCSG1402 is a phase II, randomized, double-blind, placebo (PLC)-controlled study evaluating the prophylactic effects of oral dexamethasone (DEX) on regorafenib-related fatigue and malaise for patient (pts) with metastatic colorectal cancer. The primary endpoint was incidence of fatigue or malaise (CTCAE ver. 4, all grades) during the protocol period. Here we report intervention related PROs. **Methods:** PROs were assessed at baseline, on every once a week thereafter until 4 weeks, using the Brief Fatigue Inventory (BFI), the European Quality of Life 5 Dimensions-3 Level (EQ-5D-3L), Functional Assessment of Cancer Therapy-General (FACT-G) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C). QOL scores were compared using a mixed-effects models for repeated measures (MMRM), adjusting for baseline score and the stratified randomization (the presence/absence of fatigue and/or malaise and sex). **Results:** Between October 2014 and December 2015, 74 pts were enrolled and randomized (DEX group: 37, PLC group: 37). BFI score, EQ-5D-3L score, FACT-G total score and FACT-C total score were improved at each point in DEX group. Least-squares mean difference from PLC group for baseline-to-week 4 changes were -0.68 (95% confidence interval (CI), -1.56 to 0.20; p = 0.1289), 0.02 (95%CI, -0.04 to 0.09; p = 0.4930), 3.9 (95%CI, -0.8 to 8.5; p = 0.0996) and 5.3 (95%CI, -0.6 to 11.2; p = 0.0775), respectively. **Conclusions:** Among pts who remained on treatment and for whom PROs data were available, dexamethasone had a clinical meaningful improvement at each of the post-baseline timepoints for FACT-G and FACT-C in comparison with those who received PLC, although the relatively small sample size. Clinical trial information: NCT02288078.

10095 Poster Session (Board #83), Mon, 1:15 PM-4:45 PM

Cryocompression for enhanced limb hypothermia in preventing paclitaxel-induced peripheral neuropathy. *First Author: Raghav Sundar, National University Health System, Singapore, Singapore*

Background: Severe peripheral neuropathy is a common dose-limiting toxicity of paclitaxel chemotherapy, with no effective treatment. We have previously described the role of continuous-flow hypothermia in reducing neurotoxicity caused by paclitaxel. We hypothesized that cryocompression (addition of pressure to hypothermia) may enhance depth of cooling and improve efficacy. **Methods:** A proof-of-concept study was conducted in cancer patients receiving taxane chemotherapy. Each subject underwent four-limb cryocompression with each chemotherapy infusion (3 hours) for a maximum of 12 cycles. Cryocompression was administered at 16°C and cyclic pressure (5-15 mmHg). Skin surface temperature and tolerance scores were recorded. Neuropathy was assessed using nerve conduction studies (NCS) conducted before (NCS_{pre}), after completion (NCS_{post}) and 3-months post chemotherapy (NCS_{3m}). **Results:** In total, thirteen patients underwent 142 cycles of cryocompression concomitant with chemotherapy. Mean skin temperature reduction of 3.8 ± 1.7°C was achieved and was well tolerated. Only 1 out of 13 patients required an intra-cycle temperature increase, with no early termination of cryocompression in any subject. NCS analysis showed significant preservation of motor amplitudes at NCS_{3m} compared to baseline (common peroneal nerve below fibula head stimulation: 12.7 ± 25.6 %; $p = 0.013$; tibial nerve abductor hallucis stimulation: 8.8 ± 22.9%; $p = 0.005$). Sensory nerve amplitudes showed a reduction at NCS_{post} compared to baseline but continued to be preserved at NCS_{3m} (% change from baseline: (NCS_{post}) -28.1 ± 21.9 %; (NCS_{3m}) -26.7 ± 19.0 %). Crycompression did not significantly affect taxane-induced changes in nerve velocities. **Conclusions:** Cryocompression is well tolerated and results in preservation of neuron function, as measured by gold-standard NCS. When compared to our previously reported continuous-flow hypothermia (21°C) cohort, cryocompression permitted delivery of lower temperatures with similar tolerability, potentially leading to improved efficacy in neurotoxicity amelioration. Larger studies investigating cryocompression are ongoing. Clinical trial information: NCT03299582.

10096 Poster Session (Board #84), Mon, 1:15 PM-4:45 PM

Effects of mindfulness meditation on quality of life in adults with advanced cancer and family caregivers: A randomized pilot. *First Author: Shelley A. Johns, Indiana University School of Medicine, Indianapolis, IN*

Background: Patients with advanced cancer often avoid emotionally sensitive discussions with family caregivers (FCGs) about their end-of-life (EOL) treatment preferences. Avoidance of these advance care planning (ACP) discussions inhibits EOL preparations and may reduce quality of life (QoL) for both patients and FCGs. Most ACP interventions fail to address emotional barriers that hinder timely ACP. Mindfulness training facilitates emotional regulation and adaptive coping, and was tested in this randomized pilot. **Methods:** Eligible patients had a: (1) locally-advanced solid malignancy; (2) life expectancy < 12 months as rated by their oncologist; (3) score of ≥ 7 on cancer-related cognitive avoidance (Mini-MAC); and (4) FCG willing to enroll. Patient-FCG dyads (n = 55) were randomly assigned to a 6-session mindfulness meditation class with communication training or usual care. Primary endpoints were feasibility, retention, QoL, and ACP confidence (patients only). Outcomes were assessed at baseline and 6- and 10-weeks using intent-to-treat analysis. **Results:** Of 133 patients who screened eligible, 41% enrolled. Dyadic retention was 84% through 10 weeks. Most patients (85%) had stage IV cancer, with breast (29%) and GI (27%) cancers being most prevalent. The majority of patients and FCGs were female (60-62%), white (94-95%), and college educated (63-64%). Mindfulness patients reported a large and significant improvement in existential QoL (d = 0.82, p = 0.009) at 6 weeks compared to controls; however, the magnitude of improvement was not sustained at 10 weeks (d = 0.24, p = 0.43). Mindfulness FCGs reported a significant *within-group* improvement in QoL at 10 weeks (d = 0.45, p = 0.03); however, *between-group* comparisons were not significant at any time point. A non-significant improvement in ACP confidence favoring mindfulness patients over controls at 6 weeks became significant at 10 weeks (d = 0.67, p = 0.03). **Conclusions:** Within limits of a small pilot, results suggest that mindfulness training is feasible and potentially beneficial for improving QoL and ACP confidence in dyads coping with advanced cancer. A full-scale efficacy trial with a more diverse sample is planned. Clinical trial information: NCT03257007.

10097 Poster Session (Board #85), Mon, 1:15 PM-4:45 PM

REZOLVE (ANZGOG-1101): A phase 2 trial of intraperitoneal (IP) bevacizumab (bev) for recurrent ascites in advanced, chemotherapy-resistant, epithelial ovarian cancer (CR-EOC). *First Author: Katrin Marie Sjoquist, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*

Background: We sought to determine the safety and activity of IP bev for recurrent malignant ascites requiring repeated paracenteses, a major problem for women with CR-EOC. **Methods:** Eligible women had CR-EOC and symptomatic, malignant ascites that recurred within 28 days of their last paracentesis (P-1). Participants had IP bev 5mg/kg instilled at the end of their first therapeutic paracentesis on study (P0). Additional doses of IP bev were allowed at each subsequent paracentesis (P1, P2 etc) if the interval from the last dose was 42 days or more. The primary objective was to determine the proportion alive and free of repeat paracentesis at 42 days. Safety and quality of life were secondary outcomes. Serial samples of blood and ascites were collected for translational studies. The hypothesis was that IP bev would be worthy of further study if the proportion alive and free of repeat paracentesis at 42 days was 54% or more, but not if it was 20% or less. **Results:** We recruited 24 participants with a median age of 67 years (range 38 – 86), median of 4.5 lines of prior systemic treatment (range 1 – 12), and ECOG performance status of 0-1 in 9, and 2-3 in 15. The numbers of doses of IP bev administered were 1 in 13 participants, 2 in 5, 3 in 2, 4 in 1, and 5 in 1. The proportion free of paracentesis at 42 days using competing risk analysis was 77% (95% CI 58 to 92). Median time from P0 to P1 or death (puncture-free survival) was 48 days (range 8 to 248 days). Median Paracentesis free interval (P0 to P1 or death) was 4.29 (95% CI 2.4 to 5.8) times higher following first dose of IP bevacizumab compared with the time between paracenteses prior to study entry (P-1 to P0). Grade 3-4 AEs (number of participants, regardless of attribution) included abdominal pain (4), distension (4), small bowel obstruction (3), nausea (2), fatigue (2), and grade 3 bowel perforation (1). **Conclusions:** IP bev was safe, active, and warrants further study as a palliative intervention for recurrent ascites in CR-EOC. Clinical trial information: 12611000801910.

10098 Poster Session (Board #86), Mon, 1:15 PM-4:45 PM

Celiac plexus radiosurgery: A new palliative modality for upper gastrointestinal malignancies—Final results of a proof-of-concept clinical trial. *First Author: Yaacov Richard Lawrence, Sheba Medical Center, Ramat Gan, Israel*

Background: Many patients with upper-abdominal malignancies suffer from severe lower back pain radiating to the epigastrium, caused by infiltration of the celiac plexus. The celiac plexus is a network of nociceptive nerves, located along the aorta. Contemporary approaches (opioids, celiac plexus chemical neurolysis, systemic chemotherapy) are often inadequate. The celiac plexus has not previously been targeted using radiation. We hypothesized that ablative radiation targeted to the celiac plexus would alleviate pain. **Methods:** We conducted a single arm prospective clinical trial. Eligible patients had celiac-pain $> 4/10$ on Numerical Rating Scale (NRS), ECOG ≤ 3, no previous abdominal RT, and were evaluable if they completed treatment per protocol with at least one post-treatment visit. The celiac plexus was irradiated from D12 to L2. Radiation was given as either five fractions of 9 Gy or a single-fraction 25 Gy. The primary endpoint was NRS pain 3 weeks post-treatment. Secondary endpoints were toxicity, pain at 6w, analgesic use, and pain interference with daily activities as evaluated by 'Brief Pain Inventory' before and after radiation. **Results:** 21 patients were evaluable: 2 received fractionated treatment, 19 received 25Gy single fraction. The median age of the study population was 63 yr with a median ECOG of 1, 86% had pancreatic cancer. Patients were a median of 8 months out from diagnosis, and had received a median of one systemic treatment. Toxicity was limited to grade 1-2. All patients reported decreased celiac pain: median baseline pain was 6/10 (IQR 5-7.7), was reduced to 2.3/10 (IQR 0.9-3.9) ($p < 0.0005$) at 3w, and to 1.8/10 (IQR 0-3.2) ($p < 0.0005$) at 6w post-treatment. Seven patients reported their celiac pain had been eliminated entirely. Median morphine consumption decreased (NS). Improvement was seen in multiple quality of life measures, includ. total wellbeing (p = 0.0001), daily activity (p = 0.005) and sleep quality (p = 0.002). **Conclusions:** Celiac plexus radiosurgery alleviates pain, and improves quality of life among patients with advanced upper-GI cancer. An international multi-center phase II trial is accruing. Clinical trial information: NCT02356406.

10099 Poster Session (Board #87), Mon, 1:15 PM-4:45 PM

Relationships between immune cell profiles and frailty in patients with breast cancer from pre- to post- chemotherapy: A University of Rochester NCI community oncology research program prospective, longitudinal study. *First Author: Nikesha Gilmore, University of Rochester Medical Center, Rochester, NY*

Background: Frailty is an important factor for oncologists in determining risk of chemotherapy toxicity, especially for older adults. While inflammation has been associated with survival, its relationship with developing frailty is not understood. In this secondary analysis we sought to determine whether changes in immune cell profiles are predictive of frailty after chemotherapy. **Methods:** Patients (pts) had stage I-IIIc breast cancer (n = 583, mean age 53; range 22-81) scheduled to receive adjuvant/neoadjuvant chemotherapy. Frailty was assessed by a modified Fried score (0-4) using self-reported measures of weakness, exhaustion, physical activity and walking speed. Absolute counts of immune cell types as well as neutrophil:lymphocyte ratio (NLR) and lymphocyte:monocyte ratio (LMR) were calculated at pre-chemotherapy (PrC; $\leq$7 days of first cycle) and post-chemotherapy (PoC; $\leq$ 1 month of last cycle). Separate linear regressions were used to evaluate the associations between PrC cell counts and ratios with PoC frailty, controlling for relevant covariates and baseline frailty. Additional analyses examined the associations of changes in cell counts and ratios with changes in frailty (PoC minus PrC). **Results:** Chemotherapy significantly increased pts mean frailty score (PrC = 1.28, PoC = 2.0; $p < 0.001$). Higher PrC LMR was significantly associated with higher PoC frailty ($\beta = 0.20$; $p = 0.035$). Lower PrC NLR was marginally associated with higher PoC frailty ($\beta = -0.158$; $p = 0.078$). In both models higher baseline frailty and older age were significantly predictive of PoC frailty. From PrC to PoC, greater lymphocyte decrease ($\beta = -0.27$; $p = 0.036$) and NLR increase ($\beta = 0.18$; $p = 0.015$) were predictive of increased frailty change score. LMR decrease ($\beta = -0.17$; $p = 0.058$) was also marginally associated with increased frailty score. **Conclusions:** Baseline LMR and lymphocyte decline were both predictive of PoC frailty. Immune cell counts may help clinicians identify pts at risk of frailty PoC. Future research is needed to further elucidate inflammation-related mechanisms of frailty in cancer patients.

10100 Poster Session (Board #88), Mon, 1:15 PM-4:45 PM

Effect of pre-treatment sleep disturbance on radiation therapy (RT)-induced pain in 676 women with breast cancer. *First Author: Anita Roselyn Peoples, University of Rochester Medical Center, Rochester, NY*

Background: Pain is a debilitating side effect that remains poorly controlled in ~50% of cancer patients. Data from the general population has shown a strong bi-directional relationship between sleep disturbance and pain; however, little is known about this relationship in cancer patients. The present secondary analyses examine the effect of pre-RT moderate-severe cancer-related sleep disturbance (CRSD) on subsequent RT-induced pain. **Methods:** Analyses were performed on 676 female breast cancer patients (mean age 58) scheduled to receive RT from a previously completed multicenter, phase II RCT examining the efficacy of oral curcumin on radiation dermatitis. The trial was conducted at 21 community oncology practices throughout the U.S. affiliated with the URCC NCORP Research Base. CRSD and total pain as well as the subdomains: sensory pain (SP), affective pain (AP), and perceived pain intensity (PPI) were assessed at pre-RT (baseline) and post-RT by the modified MD Anderson Symptom Inventory and the short-form McGill Pain Questionnaire, respectively. Patients were dichotomized into 2 groups: those with moderate-severe CRSD at baseline (N = 101) vs. those with mild or no CRSD (control; N = 575). **Results:** Spearman rank correlations showed that changes in CRSD from baseline to post-RT were significantly correlated with concurrent changes in total pain, SP, AP, and PPI ($r = 0.21$–0.38; all p's < 0.001). Generalized linear estimating equations, after controlling for baseline pain and other covariates (baseline fatigue and distress, age, sleep medications, anti-anxiety/depression medications, prescription pain medications, and depression or anxiety disorder), showed that patients with moderate-severe CRSD at baseline had significantly higher mean values of post-RT total pain (by 39%; $p = 0.033$), SP (by 41%; $p = 0.046$), and AP (by 55%; $p = 0.035$) than the control group, but not for PPI ($p = 0.066$). **Conclusions:** These findings suggest that moderate-severe disturbed sleep prior to RT is an important predictor of pain at post-RT in breast cancer patients. Further research is needed to confirm these findings. *NCI UG1CA189961, NCATS TL1 TR002000.* Clinical trial information: NCT01246973.

10101 Poster Session (Board #89), Mon, 1:15 PM-4:45 PM

Risk stratification using patient-reported outcomes (PROs) in patients (pts) with advanced cancer. *First Author: Shiven B. Patel, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Performance status is often used to stratify cancer pts for treatment and to guide supportive care resources. This retrospective study was conducted to evaluate whether PROs have prognostic value, independent of physician assessment of functional status. **Methods:** Pts treated at Huntsman Cancer Institute were assessed using the NCI PROMIS-Ca bank from May 2016. Physical function, fatigue, depression, anxiety, and pain scores were collected via iPad in pts with metastatic NSCLC, CRC, and breast cancer. A single PRO score at the time of metastatic disease for each pt was merged with outcome data using the Flatiron Health database, processed with technology-enabled abstraction and supplemented with third-party death information. Associations between PROs, PROs and overall (OS), and PROs and hospital-free survival (HFS) were assessed. **Results:** The five PRO domains were interrelated with moderate-strong correlation coefficients (0.40-0.79). Physical function score was worse for NSCLC than both CRC ($p < 0.001$) and breast cancer ($p < 0.001$), while both anxiety and depression were worse for NSCLC than CRC ($p = 0.003$ and $p = 0.042$, respectively). All individual PRO domains and a summary score were strongly associated with outcomes. Physical function and fatigue provided the greatest discrimination. The correlation of PROs with 12-month survival (table) and HFS were statistically significant. **Conclusions:** PRO scores, independent of physician interpretation, are prognostic for OS and HFS. These findings have substantial implications for patient care, treatment planning, clinical research, and financial modeling.

Kaplan-Meier estimates of 12 month survival by tertile by PRO.

	Probability of Survival to 12 months			
	Low Tertile	Middle Tertile	High Tertile	Log-rank P-Value
Physical Function	0.57 (0.46-0.71)	0.70 (0.61-0.81)	0.83 (0.73-0.94)	< 0.001
Pain Interference	0.72 (0.61-0.85)	0.81 (0.72-0.90)	0.54 (0.42-0.68)	< 0.001
Fatigue	0.82 (0.72-0.94)	0.69 (0.60-0.79)	0.57 (0.45-0.72)	< 0.001
Anxiety	0.73 (0.63-0.86)	0.73 (0.64-0.83)	0.67 (0.56-0.79)	0.014
Depression	0.81 (0.71-0.91)	0.70 (0.60-0.81)	0.62 (0.51-0.75)	0.002
Composite	0.77 (0.66-0.90)	0.75 (0.66-0.86)	0.59 (0.48-0.72)	< 0.001

10102 Poster Session (Board #90), Mon, 1:15 PM-4:45 PM

A multi-center, randomized, double-blinded, placebo-controlled trial of additive effect of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids: JORTC- PAL08 (DIRECT study). *First Author: Eriko Satomi, Department of Palliative Medicine,National Cancer Center Hospital, Tokyo, Japan*

Background: Management of cancer patients experiencing neuropathic pain (NP) refractory to opioids remains an important challenge. Gabapentinoids are one of the most widely used therapies for NP. However, duloxetine is also used for NP. We have evaluated the efficacy of addition of duloxetine for neuropathic cancer pain refractory to opioids and gabapentinoids. **Methods:** Multicenter, randomized, double-blind, placebo-controlled trial. Patients with any cancer NP, currently being administered opioids, non-responsive or intolerant to gabapentinoids were eligible. Patients with chemotherapy-induced peripheral neuropathies were excluded. Patients were administrated 20 mg to 40 mg of duloxetine or placebo for 10 days. The primary endpoint was the average pain intensity (Brief Pain Inventory (BPI) item 5) at Day 10, the main analysis was *t* test (significance level one side 5%), Complete Case (CC) analysis was performed to handle missing primary data and Baseline Observation Carried Forward (BOCF) analysis was performed for sensitivity analysis. **Results:** 70 patients were registered at 12 sites in Japan. BPI item 5 at Day 10 was i) average of Group D (Duloxetine) 4.03 [90% CI 3.33, 4.74], Group P (Placebo) 4.88 [4.37, 5.38] ($p = .053$) (CC analysis); ii) Group D 4.06 [3.37, 4.74], Group P 4.91 [4.41, 5.41] ($p = .048$) (BOCF analysis). Point estimate of the difference of average values between the two groups was -0.84 [-1.71, 0.02] (CC analysis) and -0.85 [-1.69, -0.01] (BOCF analysis). Compared to Day 0, the improvement rate of 50% or more at Day 10 was 32.4% in Group D and 3.0% in Group P ($p = .002$). **Conclusions:** The minimum important difference (MID) with clinical significance in cancer pain is said to be 1 point in 11 stages of the Numerical Rating Scales (NRS), and our results were close to the MID (-0.84; CC analysis). Moreover, sensitivity analysis and secondary analysis show significant improvement in Group D. Overall, duloxetine is clinically effective for NP. Clinical trial information: UMIN000017647.

10103 Poster Session (Board #91), Mon, 1:15 PM-4:45 PM

Evaluation of a mobile application to prepare and engage cancer patients prior to a palliative care (PC) visit: Results of a randomized, controlled trial. *First Author: Arif Kamal, Duke Cancer Institute, Durham, NC*

Background: Despite the growth in guidelines and evidence supporting routine PC for patients with advanced cancer, up to 40% of patients referred and given an appointment never show up. This high "no show" rate stems from patients harboring misconceptions about PC (e.g. confusing with hospice care) and not knowing its value. No tool to educate patients on the value of PC and prepare them for an upcoming visit has been tested. **Methods:** We conducted a randomized, controlled trial of PCforMe, a web-based mobile education and engagement tool, from December 2016 through February 2018. Patients were randomly assigned prior to a new PC clinic appointment to either PCforMe or an active control on a tablet device. The active control included three popular websites about PC developed by major specialty societies. We collected demographics and assessed system usability scores, patient preparedness (PEPPI), change in knowledge about PC, and change in no-show rate. **Results:** 78 patients were enrolled. Mean age was 61 (range 20-83) with 56% with less than a Bachelors education. The mean usability score was 77, putting PCforMe usability in the 90th percentile of mobile health tools. Scores on the single-item "I know what questions to ask" improved significantly ($p < 0.002$) after using PCforMe. Similar improvements were not seen in the control arms. Scores on the knowledge survey improved more in the intervention arm ($p < 0.05$). No show rates for new visits during the course of the trial decreased by 35%. **Conclusions:** Even among an elderly population with advanced cancer, a novel, mobile tool to prepare and engage cancer patients prior to a PC appointment is highly usable. The tool led to greater sense of readiness and familiarity with PC and reductions in the no-show rate to palliative care clinic. Larger, multi-site trials are needed to further test this novel tool.

10104 Poster Session (Board #92), Mon, 1:15 PM-4:45 PM

Racial disparities in palliative and hospice care beliefs of lung cancer patients. *First Author: Aditya Varnam Shreenivas, Icahn School of Medicine at Mount Sinai, Newyork, NY*

Background: Minority patients with lung cancer often have higher rates of morbidity and mortality. Recent data shows that early integration of palliative care with standard oncologic care for advanced lung cancer patients is associated with better quality of life and potential survival. Little is known about racial disparities in palliative and hospice care beliefs and the influence of these factors on the utilization of palliative care and hospice. **Methods:** We performed a prospective cohort study of patients diagnosed with advanced lung cancer (stage III and IV). At baseline (within 3 months of diagnosis), patients completed a validated survey assessing palliative and hospice beliefs as well as care preferences. Multivariate methods were used to compare differences in these beliefs among minority (Black and Hispanic) and non-minority patients. Responses to questions on beliefs were scored on a scale of 1-5, with 1 standing for strongly agree and 5 for strongly disagree. Using ANOVA, mean score differences between minorities and non-minorities were assessed. **Results:** We enrolled 97 of 160 eligible patients (61%). To date, baseline surveys have been completed on 61 patients. Of those, 38 (62.3%) were minorities and 23 (37.7%) were non-minorities. There were no significant differences in baseline demographics. In terms of palliative care beliefs, minorities reported feeling more hopeful ($p = .008$) and more secure ($p = .03$) with palliative care referral. Minorities were more likely to believe that they cannot afford hospice ($p = .002$), that hospice is not as good as the hospital for cancer care ($p = .02$), were less likely to believe that hospice care can be provided at home ($p = .04$) or that hospice can help with physical, psychological , social and spiritual needs ($p = .04$). Additionally, more minorities compared to non-minorities preferred palliative care to hospice ($p = 0.007$). **Conclusions:** Minority patients with advanced lung cancer are more likely to prefer palliative care than hospice and hold false beliefs about hospice. Having adequate palliative and hospice care for minorities is necessary to ensure health equity among patients with lung cancer. Future studies will be performed to see how these beliefs effect the use of these services.

10105 Poster Session (Board #93), Mon, 1:15 PM-4:45 PM

Patterns and determinants of pain and emotional distress in older adults with cancer: A population based study. *First Author: Amy J. Davidoff, Yale School of Public Health, New Haven, CT*

Background: There is increasing concern about the adequacy of symptom management among older adults with cancer. We examined patterns and predictors of pain and emotional distress after a cancer diagnosis. **Methods:** Using the linked SEER-Medicare Health Outcomes Survey database, we selected participants from 2007-2012, within 5 years of cancer diagnosis. We used survey responses describing activity limits due to pain and emotional distress within the past 30 days to construct study outcomes. We undertook bivariate analyses and estimated multivariable logistic regression to determine the association of pain and emotional distress with cancer type, stage at diagnosis, years since diagnosis, demographics, socioeconomic status (educational attainment and area poverty rates) and chronic conditions. **Results:** Among 9481 respondents, prostate (31%) and breast (19%) cancers were most prevalent. Activity limits due to pain were reported by 22%, with highest rates among adults with lung cancer (37%), stage 4 diagnosis (34%), depression (53%) and heart failure (44%), minorities, and patients with lower socioeconomic status. The odds of reporting pain were increased for lung (ref = breast; adjusted odds ratio (aOR):1.5; 95% confidence interval (CI) 1.2-1.9); stage 2-4 (stage 4 aOR: 1.75; CI 1.36-2.25); and chronic conditions; and were decreased for prostate (aOR: .70; CI .54-.92) or colorectal cancers and higher socioeconomic status. Limitations due to emotional distress were reported by 14%, with the highest rates among patients with lung (27%), stage 4 (24%), prior depression (50%), Crohn's disease (33%), heart failure (30%), and lower socioeconomic status. The odds of emotional distress were higher with increasing age (80+ years, aOR: 2.1; CI 1.7-2.6), Hispanic ethnicity, prior depression (aOR: 7.9; CI 6.7-9.1), stroke, COPD, stage 3-4 diagnosis, and reduced for prostate cancer or lymphoma, initial surgery, and year 2 post diagnosis (ref=year 5). **Conclusions:** Despite an increased focus on symptom management, pain and emotional distress remain prevalent among older adults with cancer. Efforts to identify and target unmet supportive care needs are necessary to further improve quality of life.

10106 Poster Session (Board #94), Mon, 1:15 PM-4:45 PM

Impact of oncologist outpatient productivity on prevalence of goals of care discussions. *First Author: Sofya Pintova, Mount Sinai Medical Center, Brooklyn, NY*

Background: Oncologists report that time required to conduct goals of care (GoC) discussions impede its practice, yet, little data is available to support this widely held belief. We studied the impact of oncologists' productivity on their ability to have meaningful GoC discussions. **Methods:** At community, academic, municipal and rural hospitals, we recruited & randomized solid tumor oncologists & their newly diagnosed advanced cancer patients with < 2 year prognosis to participate in a RCT, testing a coaching model of communication skills training. Patients were surveyed after the post-imaging visit where GoC discussion was expected. We measured quality of GoC discussions by patients' rating how well their physician talked about goals. We measured productivity by work revenue value units (wRVUs) per hour for each day the oncologist saw the study patient post-imaging. Analyses were done with Kruskal-Wallis and Wilcoxon tests. **Results:** We enrolled 22 oncologists and 221 productivity days were assessed. The highest median productivity was observed in the Community hospital. In all four sites participating in this study, no significant difference in productivity was observed between visit days where quality GoC discussion took place vs no quality GoC discussion occurred. A multivariate analysis controlling for intervention group, hospital, patient and oncologist characteristics, found no relationship between productivity and conduct of high quality GoC discussion. **Conclusions:** The prevalence of high quality GoC discussion reported by advanced cancer patients was high among the four institutions in this study. Despite concerns about time constraints, productivity was similar regardless of whether or not a quality GoC discussion took place . Clinical trial information: NCT02374255.

Hospital N = 221	Prevalence of High Quality GoC Discussion	Productivity Median	Productivity Quality GoC Discussion Occurred (+)	Productivity No Quality GoC Discussion Occurred (-)	p value
Community	77%	4.3 (1.7-9.9)	4.3 (1.7-9.9)	3.8 (2.7-6.0)	0.69
Academic	80%	3.6 (0.4-7.5)	3.6 (0.9-6.4)	3.8 (2.3-7.5)	0.45
Municipal	70%	3.0 (0.7-6.1)	2.9 (0.7-6.1)	3.1 (3.0-3.2)	0.62
Rural	62%	2.9 (1.4-6.0)	3.0 (1.7-6.0)	2.9 (1.4-4.1)	0.48
	$p = 0.1$	$p < 0.001$			

10107 Poster Session (Board #95), Mon, 1:15 PM-4:45 PM

Length of time to conduct goals of care visits. *First Author: Sofya Pintova, Mount Sinai Medical Center, Brooklyn, NY*

Background: Oncologists report that time to conduct a goals of care (GoC) discussion is a barrier. We studied the relationship of GoC discussion and visit times at different type hospitals. **Methods:** At community, academic, municipal and rural hospitals, we recruited & randomized solid tumor oncologists & their newly diagnosed advanced cancer patients with < 2 year prognosis to participate in a RCT, testing a coaching model of communication skills training. Patients were surveyed after post-imaging visits. These visits were audiotaped and median encounter time recorded. We define GoC discussions as patient report that their doctor talked about preferences for cancer treatment and clarified things most important to them given their illness. Analyses were done with Kruskal-Wallis and Wilcoxon tests. **Results:** For 22 randomized oncologists in the study, 137 post-imaging encounters were audiotaped. The median face-face time oncologists spent during a GoC encounter with an advanced cancer patient was 15 minutes. Encounter times when GoC discussions were expected varied between the four sites, ranging from 9.5 minutes to 18 minutes, p = 0.05. The encounters where no GoC discussions occurred were longer, taking 16.5 minutes vs 13 minutes, p = 0.05. Visits that took place after progression of disease took longer, 18 minutes vs 13 minutes, p = 0.006. **Conclusions:** Visit times vary by hospital type and average 15 minutes. With disease progression, visit time is longer. Despite physician perceptions, GoC discussions do not lengthen visits. Clinical trial information: NCT02374255.

Hospital (N)	Encounter Time* Minutes (range)	Encounter Time GoC Discussion Occurred (+) Minutes (range)	Encounter Time No GoC Discussion Occurred (-) Minutes (range)	p value	Encounter Time Progression of Disease Minutes (range)	Encounter Time No Progression of Disease Minutes (Range)	p value
Overall (137)	15 (4-40)	13 (4-40)	16.5 (4-40)	0.05	18 (12-22)	13 (10-19)	0.006
Community (10)	9.5 (4-38)	9.5 (4-38)	NA	-	18 (9-38)	9 (5-12)	0.14
Academic (98)	15 (4-40)	13 (4-40)	15 (4-33)	0.18	17 (12-20)	13 (10-20)	0.16
Municipal (15)	12 (6-40)	10 (6-35)	14.5 (7-40)	0.42	24 (19-28)	10 (7-17)	0.09
Rural (14)	18 (10-34)	18 (10-34)	18 (10-34)	0.75	22 (22-34)	17 (12-23)	0.12

*p = 0.05

10108 Poster Session (Board #96), Mon, 1:15 PM-4:45 PM

Community-based palliative care utilization in elderly pancreatic cancer patients. *First Author: Zhanni Lu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Community-based Palliative Care (CBPC) has shown to stabilize symptoms, alleviate psychological and spiritual burdens, satisfy care preferences, and improve quality of life among care recipients. We evaluated CBPC utilization and predictors in pancreatic cancer patients ≥66 years. **Methods:** Palliative Care (PC) encounters among pancreatic cancer patients were identified by ICD-9-CM codes using SEER-Medicare data from 2007 to 2013, and patients were followed until 2014. PC encounters outside hospital settings were classified as CBPC. We tested time trends of CBPC utilization and time to PC referral after cancer diagnosis. Multivariable random intercept logistic models were used to determine the predictors of CBPC utilization at the patient and Health Service Area (HSA) levels. **Results:** 16,106 patients were included, of whom 27.8% used palliative care; of those, 1,530 (9.5%) used CBPC, and 2,956 (18.3%) used Hospital-based Palliative Care (HBPC). CBPC utilization increased from 8.2% in 2007 to 9.4% in 2013 (p = .014). Median (IQR) PC referral time after cancer diagnosis decreased from 5 (2, 11) mo. in 2007 to 2 (1, 5) mo. in 2013 (p = .001). Being female (OR 1.27 [1.12, 1.45]; p < .001), a diagnosis of advanced cancer stage (III/IV: OR 1.29 [1.002, 1.67]; p = .049), cancer treatment participation (OR 2.24 [1.92, 2.60]; p < .001), or residing in an urban area (OR 1.57 [1.03, 2.39]; p = .035) were positively associated with CBPC utilization. Those living in the poorest communities (OR 0.62[0.47, 0.81]; p = .001) and southern SEER Registries (Georgia, Kentucky and Louisiana) (OR 0.15 [0.09, 0.24]; p < .001) were less likely to use CBPC. HSAs with high density of HBPC programs (an indicator of regional health care resources) were positively associated with CBPC usage (OR 1.50 [1.03, 2.20]; p = .035). **Conclusions:** CBPC usage increased and referral time decreased over 6 years. Patient-level factors, geographic area characteristics, and regional health care resources were associated with likelihood of receiving CBPC.

10109 Poster Session (Board #97), Mon, 1:15 PM-4:45 PM

Patterns of palliative care utilization in stage IV non-small cell lung cancer in the National Cancer Database. *First Author: Urshila Durani, Mayo Clinic, Rochester, MN*

Background: Early integration of Palliative Care (PC) improves survival in stage IV non-small cell lung cancer (NSCLC). Here we explore patterns in PC utilization in this group. **Methods:** We queried years 2004-2014 of the National Cancer Database for adults with stage IV NSCLC. Patients receiving pain management +/- other palliative procedures were PC utilizers. In addition to descriptive statistics, multivariable logistic regression models with interaction analyses identified predictors of PC utilization. **Results:** Of 341,993 patients, 3.2% received PC at initial treatment. PC utilization increased significantly from 2004-2006 to 2013-2014 (2.3% vs 4.2%, p < 0.01). Whites had higher PC utilization (3.3%) than blacks (2.6%) and Hispanics (2.3%, p < 0.01 for both). Significant predictors of PC on multivariable regression are listed in the Table. Interaction analyses found that Hispanics and Asians had a slower increase (p < 0.01) in PC utilization over time compared to Whites or Blacks. An additional 13.8% and 5.3% received palliative radiation or chemotherapy, respectively. 0.9% received palliative surgery, and 1.4% received some combination of the 3 modalities. **Conclusions:** PC utilization in stage IV NSCLC is markedly low and plagued by racial and socio-economic disparities despite guidelines advocating early PC integration.

Multivariable regression of PC utilization in Stage IV NSCLC.

Parameter	Odds Ratio (95% CI)
Race/Ethnicity	
White	REF
Black	0.8 (0.7-0.8) **
Hispanic	0.7 (0.6-0.8) **
Asian	1.0 (0.9-1.2)
Age (per 10 years)	0.9 (0.9-1.0) *
Year	
2004-2006	REF
2007-2008	1.3 (1.2-1.3) **
2009-2010	1.4 (1.3-1.5) **
2011-2012	1.7 (1.6-1.8) **
2013-2014	1.8 (1.7-1.9) **
Male	1.5 (1.2-2.0) **
Primary Payer	
Private	REF
Medicaid	1.8 (1.1-3.1) *
Medicare	0.6 (0.4-0.9) **
Uninsured	0.9 (0.5-1.8)
Median Income Quartile of Zip code	
1	REF
2	0.9 (0.8-0.9) **
3	0.8 (0.7-0.8) **
4	0.7 (0.7-0.8) **
% No High School Degree	
> = 21%	REF
13-20%	1.5 (1.0-2.1) *
7.0-12.9%	2.2 (1.6-3.2) **
< 7%	1.3 (0.8-1.9)
Academic vs Community Facility	1.2 (1.1-1.3) **
Charlson/Deyo score	
0	REF
1	1.4 (1.4-1.5) **
2+	1.5 (1.4-1.6) **

* P < .05 ** P < .01
Grade, Histology, Primary site, Distance to facility, Region, and Rural status not shown

10110 Poster Session (Board #98), Mon, 1:15 PM-4:45 PM

Comparisons of palliative care utilization in metastatic cancer patients between multi-payer non-universal health care and single-payer universal health care systems. *First Author: Raymond Nienchen Kuo, National Taiwan University, Taipei City, Taiwan*

Background: Previous studies reported that private insurance was associated with receiving recommended care and better outcomes. However, it is unclear whether insurance type is associated with the utilization of palliative care among metastatic cancer patients who survived for less than 6 months following diagnosis. This study compares the utilization of palliative care among patients in the U.S. and patients in Taiwan. **Methods:** Analysis was conducted using data for the period 2010 – 2013 obtained from the U.S. National Cancer Database and Taiwan Cancer Registry. This study include patients newly diagnosed with metastatic (M1) breast, colorectal, lung, and prostate cancers and who died within six months after diagnosis. Logistic regression models were used to compare the odds of receiving palliative care under different health insurance schemes. **Results:** This study included 70,084 U.S. patients (49,374 lung, 13,591 colorectal, 4,837 breast, 2,285 prostate) and 8,882 Taiwanese patients (6,131 lung, 2,188 colorectal, 255 breast, 308 prostate). Among these cases, 18,458 patients in the U.S. (26.3%) and 5,338 patients in Taiwan (60.1%) received palliative care before dying. In the U.S., breast, colorectal, and lung cancer patients covered by private health insurance were more likely to utilize palliative care (17.6% - 31.1%), than were patients covered by public health insurance (16.0% - 28.7%). Multivariate logistic regression analysis revealed that after controlling for demographic factors, disease severity and treatment type, there were no differences in the administration of palliative care among patients covered by private health insurance and those covered by public health insurance. **Conclusions:** This study revealed that there were no differences in the administration of palliative care among patients covered by private health insurance and those covered by public health insurance. Nonetheless, Taiwanese patients were more likely to undergo palliative care than were patients in the U.S. This implies that the lower cost and more comprehensive benefit scheme may improve access to palliative care.

10111 Poster Session (Board #99), Mon, 1:15 PM-4:45 PM

Patient-reported outcomes in light of supportive medications in treatment-naïve lung cancer patients. *First Author: Johnny Hoang, Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, TX*

Background: Symptom burden of cancer patients is high and can be assessed using patient-reported outcomes (PROs). However, the impact of supportive medications on PROs has not been systematically assessed. We describe the supportive medications used by treatment-naïve lung cancer patients at hospital admission and assess the association between their use and PROs. **Methods:** Patients with a diagnosis of non-small cell or small cell lung cancer who had not received any form of cancer therapy at the initial visit and completed the MD Anderson Symptom Inventory (MDASI) survey within 45 days of diagnosis were included. Baseline patient and tumor characteristics and a complete medication list (categorized based on USP v7.0) were abstracted using the EPIC system. Symptoms were compared using Mann-Whitney U test in patients taking a supportive care medication. **Results:** Lung cancer patients (N = 459) with median age of 66 years (range: 23-90) were included in this study. About half (46%) of patients took any analgesics with 27% of patients taking opioid-containing regimen. One-third (31%) of patients with moderate to severe pain (5 or above on a 0 -10 scale) were not on any analgesics. Compared to patients not taking any analgesics, those on the opioid-containing regimen had significantly worse median pain scores (6 vs. 0), but not those on non-opioid analgesics (1 vs. 0). This was despite higher proportion of patients with moderate to severe pain taking opioid-containing regimen compared to those with mild pain (52% vs. 16%) . Patients on opioid-containing pain regimen also reported worse drowsiness, fatigue, disturbed sleep, shortness of breath, lack of appetite, general activity, mood, work, relations with others, walking, and enjoyment of life. Patients taking antidepressants did not significantly differ in any individual MDASI symptoms associated with depression compared to those not on the therapy. **Conclusions:** Treatment-naïve lung cancer patients presenting at MD Anderson had poorly managed pain and associated functional symptoms and interference. Since patients' functional status may result in suboptimal cancer therapy, our results suggest a need for better pain and symptom management in these patients.

10112 Poster Session (Board #100), Mon, 1:15 PM-4:45 PM

The impact of pain in recurrent ovarian cancer patients: An individual participant data meta-analysis of the North-Eastern German Society of Gynecological Oncology (NOGGO) of 1226 patients. *First Author: Hannah Woopen, Department of Gynecology, European Competence Center for Ovarian Cancer, Charité, University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: Pain has a major impact on quality of life in ovarian cancer (OC) patients. The influence of pain on survival is unclear in OC. Aim of this study was to analyze the impact of pain on quality of life and survival in recurrent OC patients. **Methods:** Raw data including the QLQ-C30 questionnaire from three phase II/III trials ("Topotecan phase III", "Hector" and "TRIAS") conducted by the North-Eastern German Society of Gynecological Oncology (NOGGO) were synthesized and analyzed using logistic and cox regression analyses. **Results:** Out of 1226 patients there were data on pain available for 952 patients. More than one third of patients (36.6%) experienced moderate to severe pain, defined as pain $\geq$ 50 in the QLQ-C30 symptom scale, which was independent from the administered chemotherapy. 31% were taking non-opioid pain medication and 16% opioids. Median age at randomization was 61 years (range 25-84). Most patients (84.7%) were diagnosed in advanced stages. Pain was independent from age, FIGO stage, grading, amount of recurrences and chemotherapy free interval. ECOG was significantly worse in patients with pain ($p < 0.001$). These patients experienced more frequently fatigue, nausea/vomiting, sleeping disorders, abdominal symptoms such as loss of appetite, diarrhea and constipation (all $p < 0.001$). Quality of life was significantly diminished ($p < 0.001$). Pain was also an independent marker for overall survival (OS). Median OS was 18.2 months in patients with pain compared to 22.0 months in patients without pain ($p = 0.013$, HR 1.25, 95% confidence interval 1.05-1.48). OS was shorter in patients with pain and without pain medication compared to those on sufficient pain medication, whereas OS was mostly decreased in patients having pain despite pain medication (18.5, 19.6 and 15.0 months respectively; $p = 0.026$). There was no difference regarding progression free survival and prior treatment discontinuation. **Conclusions:** Effective pain management is crucial for both quality of life and overall survival in patients with recurrent ovarian cancer. Patients shall therefore receive best supportive care as early as possible.

10113 Poster Session (Board #101), Mon, 1:15 PM-4:45 PM

Prospsective phase II pilot study to evaluate the use of intravenous iron in the treatment of anemia in cancer patients. *First Author: Youjin Kim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South)*

Background: Iron deficiency anemia (IDA) are common complications in cancer patients. Evidence on intravenous (IV) iron for treatment of chemotherapy-induced anemia (CIA) is emerging. Herein, we evaluated the efficacy of IV iron for improvement of anemia in cancer patients. **Methods:** This prospective single arm phase II study aims at evaluation of efficacy of IV iron without additional ESA for correction of CIA. Patients received Ferinject® (ferric carboxymaltose) 1000mg injection on the first day of chemotherapy . Thereafter, hemoglobin (Hb) response defined by increase of Hb $\geq$ 1.0g/dL was assessed at visit 1, visit 2 and visit 3. To identify biochemical parameter predictive for Hb response, TSAT, sTFR, hepcidin, EPO, IL-6, CRP were also assessed at each visit. **Results:** Between Oct 2010 and Jul 2017, a total of 104 patients were enrolled, and 92 patients were available for for injection. Hemoglobin response was observed in 36, 53 and 61 patients at visit 1 (39.1%), visit 2 (57.6%) and visit 3 (66.3%), respectively. When excluding 19 patients (20.6%) with absolute IDA defined by ferritin $<$ 30ng/mL or TSAT $<$ 20%, Hb response rate was 83.5% (61/73). Of 73 patients without absolute IDA, there were i) 56 patients whose serum ferritin were between 30- 500 ng/ml , ii) 6 patients whose serum ferritin were between 500-800 ng/ml and TSAT $<$ 50 % , and iii) 10 patients whose ferritin levels were $>$ 800ng/mL or TSAT $\geq$ 50% . In patients groups of i), ii) and iii), Hb response was observed in 60.7% (34/56), 50% (6/6), and 50%(5/10), respectively. Regarding anemia related biochemical parameters, responders had significantly lower levels of hepcidin (13.5 vs. 35.2 ng/mL, $p = 0.007$), CRP (0.7 vs. 2.5mg/mL, $p = 0.044$) and ferritin (249.2 vs. 575.3 ng/mL, $p = 0.048$). When comparing Hb response by baseline hepcidin level, there were significantly more responders in the low hepcidin (58/61, 95.1%) compared to the high hepcidin group (3/61, 4.9%) at the cut-off value of 34.1 ng/mL ($p = 0.002$). **Conclusions:** IV iron supplementation alone showed promising result in improving anemia in cancer patients. Hepcidin may predict response to IV iron in cancer and chemotherapy induced anemia, and is superior to TSAT or ferritin for this purpose. Clinical trial information: NCT02599012.

10114 Poster Session (Board #102), Mon, 1:15 PM-4:45 PM

Does cytotoxic chemotherapy (CT) have a role in palliative treatment of hepatocellular carcinoma (HCC)? *First Author: Guilherme Nader Marta, Instituto do Câncer do Estado de São Paulo - ICESP, Sao Paulo, Brazil*

Background: Palliative treatment of patients (pts) with HCC after progression to sorafenib represents a clinical challenge due to the usual concomitance with hepatic failure. Although new drugs have recently demonstrated survival benefit in phase III trials after sorafenib therapy, these agents are not widely available and their use is limited by the stringent inclusion criteria of the clinical trials. CT is broadly used as a palliative treatment in this clinical setting, although there is no proof of its efficacy. We analyzed a cohort of HCC pts treated with CT with the aim of evaluating the efficacy and safety of this approach. **Methods:** A cohort of pts with advanced HCC treated with CT after progression to sorafenib was retrospectively evaluated. Survival (PCS) was calculated from the first day of CT to death or last data record. PCS was estimated using Kaplan-Meier and curves were compared by log-rank test. **Results:** We analyzed 240 HCC pts treated with sorafenib from Oct-2007 to Jan-2017. At sorafenib discontinuation, best supportive care was the only treatment for 79.2%, while 18.3% received cytotoxic CT and 2.5% were enrolled in clinical trials. For pts treated with CT, median age 60 years (19-74), 75.6% male, 42.2% had HCV, 71.1% Child-Pugh (CP) A, 95.6% had extrahepatic spread, and 55.6% received doxorubicin-based CT. The median PCS was 8.0 months (3.9-12.1) and 53.3% had progressive disease as best response. Survival benefit from CT could not be predicted by CP A ($p = 0.66$), ECOG PS 0-1 ($p = 0.09$), CT regimens used ($p = 0.97$) or α-fetoprotein ($p = 0.29$). Grade 3 or 4 toxicities occurred in 37.7% of pts and the most common grade 3 or 4 adverse events (AE) were nausea/vomiting (20%), mielotoxicity (18%) and fatigue (11%). CT was most commonly discontinued due to unacceptable AE (44.4%) and disease progression (37.8%). **Conclusions:** Palliative treatment of HCC pts with CT after sorafenib failure is associated with high rates of toxicity and low efficacy. These data suggest that CT seems to have very limited activity in a group of pts with a very poor prognosis without a clear survival benefit and should only be recommended in very selected cases.

10115 Poster Session (Board #103), Mon, 1:15 PM-4:45 PM

Incorporating geriatric patient reported outcomes into novel screening tool of distress and supportive care concerns. *First Author: Christine B. Weldon, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: The Institute of Medicine (IOM) 2013 Report recommends that supportive oncology care start at cancer diagnosis; the Commission on Cancer (CoC) Standard 3.2 requires distress screening and indicated action. The Supportive Oncology Collaborative, collaborative of 100+ clinicians funded by The Coleman Foundation, developed a patient-centric screening tool (CSOC-ST) adapted from ASCO Distress, NCCN Distress Problem List, IOM report and CoC standards, and other validated sub-tools (Weldon, ASCO-Q 2017). The Collaborative then revised the CSOC-ST tool to align with geriatric guidelines. **Methods:** Literature and guidelines review of geriatric screening, added items to CSOC-ST, and piloted at 4 sites. Descriptive statistics and Fisher's exact test used. **Results:** 473 patients screened with added geriatric relevant items to CSOC-ST: self-care concerns (PROMIS Instrumental Support), living alone (ASCO Distress 2014), and memory / cognition (PROMIS item bank). Treatment/care concern items were revised to identify interest in health care power of attorney and advance directives. Geriatric related items endorsed by patients, see Table. PHQ4, Anxiety and Depression, average score 2.4 (mild $>$ 3). Higher scores on the PHQ-4 were significantly associated with each of the following: self-care concerns, memory/cognition concerns and specific treatment/care concerns ($p <$ .0001). **Conclusions:** Pilot results and comparison to geriatric guidelines identified important items to support geriatric patient reported outcomes screening. After pilot, added 3 items for falls/frailty. Eight sites implementing this CSOC-ST.

Screening Item	Frequency n = 473
I want help letting my family, friends and team know my medical wishes if unable to do so myself [health care power of attorney]	38%
I want help discussing, with my family and friends, my treatment options and what is important to me [advance directives]	36%
I have difficulty concentrating, difficulty remembering things, and/or difficulty finding the words I want to say	35%
Are you concerned about having someone available to help: if you cannot get out of bed, you feel sick and cannot do daily chores, and/or you cannot run errands?	31%
I live alone	26%

10116 Poster Session (Board #104), Mon, 1:15 PM-4:45 PM

Barriers to palliative care (PC) utilization in hematopoietic stem cell transplantation (HCT). *First Author: Areej El-Jawahri, Massachusetts General Hospital, Boston, MA*

Background: Despite the benefits of PC for patients undergoing HCT, transplant recipients rarely utilize PC. We assessed transplant physicians' attitudes about PC and perceived barriers to PC utilization. **Methods:** We conducted a cross-sectional survey of transplant physicians recruited from the American Society of Blood and Marrow Transplantation. We examined physicians' attitudes about PC and their perceived barriers to PC utilization. As noted in prior literature, we used a composite score of physicians' attitudes about PC (mean = 16.9, SD = 3.37) and a linear mixed model to explore predictors of attitudes about PC. **Results:** 277/1005 (28%) completed the survey. The majority (76%) stated that they trust PC clinicians to care for their patients, but 40% felt that PC clinicians do not have enough understanding to counsel their HCT patients. Nearly half (46%) perceived the service name 'palliative care' as a barrier for them to refer patients; 51% thought it was synonymous with hospice and end-of-life (EOL) care; and 67% endorsed that it decreased hope in patients and families. Only 8% perceived 'supportive care' as a barrier to refer patients, 7% thought it was synonymous with hospice and EOL care, and 11% endorsed that it decreases hope in patients and families. Physicians endorsed the following barriers to PC utilization 1) patients' and families' discomfort with discussing EOL care issues (80% and 83% respectively); 2) lack of knowledge about PC by transplant physicians (60%); and 3) cultural factors influencing EOL care (84%). Female sex (β = 0.85, P = 0.024), having less than 10 years of clinical practice (β = 1.39, $P < 0.01$), and perceived quality of PC (β = 0.60, $P < 0.001$) were associated with a more positive attitude towards PC. Physicians' perception of unmet PC needs in HCT was not associated with their attitude towards PC. Higher sense of ownership over patients' PC issues (β = -0.36, $P < 0.001$) was associated with a more negative attitude towards PC. **Conclusions:** The majority of transplant physicians trust PC, but have substantial concerns about PC clinicians' knowledge about HCT and patients' perception of the term 'palliative care'. Interventions are needed to promote collaboration and enhance integration of PC in HCT.

10117 Poster Session (Board #105), Mon, 1:15 PM-4:45 PM

Quality of life(QoL) outcomes including neuropathy associated scale (FACT-T) from a phase II, multicenter, randomized trial of eribulin plus gemcitabine(EG) versus paclitaxel plus gemcitabine(PG) as first-line chemotherapy for human epidermal growth factor receptor 2 (HER2)- negative metastatic breast cancer (MBC): Korean Cancer Study Group trial (KCSG BR13-11). *First Author: Ji-Yeon Kim, Samsung Medical Center, Seoul, Republic of Korea*

Background: A phase II, multicenter, randomized clinical trial of EG and PG as first-line chemotherapy for patients with HER2-negative MBC showed that EG was less neurotoxic, but conferred a survival outcome similar to that of PG. In this study, we analyzed FACT-T questionnaires from patients participating in this clinical trial to determine their health-related Quality of life (HR QoL). **Methods:** Patients were randomly assigned to either EG or PG chemotherapy arm in a 1:1 ratio. QoL was assessed using the Korean version of the FACT-T questionnaire. After baseline assessment, HRQoL was assessed every 2 cycles for 12 cycles and every 3 cycles after 13 cycles of chemotherapy. The linear mixed model was used to evaluate the difference in HRQoL between the two treatments. **Results:** Of 118 patients, 117 patients except 1 patient in PG arm responded to the FACT-T questionnaires at baseline. Baseline FACT-T subscale QoL scores and overall QoL scores were not different between the EG and PG arms. During treatment, overall QoL scores and other FACT-T subscale scores did not differ between EG and PG arm. In terms of taxane-associated HRQoL, PG arm much increased taxane subscale scores after 2 cycles of chemotherapy compared to EG arm until the 13^{th} cycle of treatment (all ps < 0.05, except 11^{th} cycle [$p = 0.164$]). Of taxane subscale scores, neuropathy specific subset scores were presented as similar pattern to taxane subscale scores. After 13 cycles of treatment, both groups had similarly intense symptoms. Therefore, although taxane subscale score and neuropathy specific subset score were higher in the PG arm compared to the EG arm, there was no statistical significance ($p = 0.086$ and $p = 0.062$, respectively). **Conclusions:** EG delayed and decreased chemotherapy induced adverse events including neuropathy compared to PG. Therefore, eribulin would be a reasonable substitute for paclitaxel as first line treatment in MBC, especially concerning neurotoxicity. Clinical trial information: NCT02263495.

10118 Poster Session (Board #106), Mon, 1:15 PM-4:45 PM

Efficacy of omega-3 (ω3) supplementation versus omega-6 (ω6) supplementation for reducing pain among breast cancer survivors: A URCC NCORP RCT. *First Author: Luke Joseph Peppone, University of Rochester Medical Center, Rochester, NY*

Background: Pain is a highly prevalent side effect of breast cancer therapy. High pain levels can reduce treatment adherence and increase discontinuation rates for hormonal therapies (HT) while reducing quality of life. We conducted a multi-site, blinded phase II RCT examining the efficacy of ω3 fatty acid (fish oil) supplementation versus ω6 fatty acid (soybean oil) supplementation for improving pain through the URCC NCORP. **Methods:** Breast cancer survivors between 4-36 months post-adjuvant therapy were randomized into 3 arms: 1) High-dose ω3 (ω3; 6 g/day), 2) Low-dose ω3/ω6 (ω3/ω6; ω3: 3 g/day and ω6: 3 g/day) and 3) High-dose ω6 (ω6; 6 g/day) for 6 weeks. Pain was assessed via the Brief Pain Inventory (BPI) at pre- and post-intervention. Serial blood was collected for serum fatty acid and inflammatory biomarker analysis. ANCOVAs, controlling for baseline pain and type of HT (AI, tamoxifen, or none), were used to calculate mean change from baseline to post-intervention for this secondary data analysis. **Results:** 108 female breast cancer survivors were accrued (93% white, mean age = 60). Biochemical blood analyses confirmed high compliance in all arms with minimal contamination. Mean baseline Worst Pain levels did not differ between groups (ω3 = 4.9, ω3/ω6 = 5.6, ω6 = 4.7; p = 0.43). The mean Worst Pain score decreased by 0.8 points for ω3, by 0.8 points for ω3/ω6, and by 1.7 points for ω6 (ω3 vs ω6 p-value = 0.18). The mean change in Current Pain score was more pronounced (Change score: ω6 = −1.8 vs ω3/ω6 = −0.8 vs ω3 = −0.5; ω3 vs ω6 p = 0.05) and indicated a dose-response. Similar changes were found for Average Pain and Least Pain but the differences were not significant. The ω6 group had a significant reduction in the inflammatory biomarker IL-6 compared to the ω3 group (IL-6 change: ω3 = +0.17 vs ω6 = −0.30; $p < 0.01$). **Conclusions:** ω6 supplementation reduced pain levels compared to ω3 supplementation in breast cancer survivors. ω6 also significantly reduced IL-6 levels compared to ω3, indicating a potential mechanism of action. Further research is needed on the effects of ω6 fatty acids in cancer patient. Funding: NCI R03CA175599 & UG1CA189961. Nordic Naturals Inc. supplied all study agents. Clinical trial information: NCT02352779.

10119 Poster Session (Board #107), Mon, 1:15 PM-4:45 PM

Longitudinal patient-reported symptom severity and symptom interference with activity-related and mood-related functioning and survival in patients with advanced cancer on early-phase clinical trials of immunotherapeutic or targeted agents. *First Author: Goldy George, Department of Symptom Research, Department of Investigational Cancer Therapeutics (Phase I Program), The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We examined longitudinal changes in symptom severity and symptom interference with activity-related (WAW: work, general activity, walking) and mood-related (REM: relations with others, enjoyment of life, mood) functioning and their association with overall survival in patients with advanced cancer in early-phase clinical trials of immunotherapeutic and targeted agents. We also examined effects of therapeutic class. **Methods:** Patients completed the MD Anderson Symptom Inventory (MDASI) at baseline (within 1 day before start of an early-phase clinical trial), and twice-weekly assessments thereafter for 60 days. Linear mixed models and Cox proportional hazards modeling with time-dependent covariates were used. **Results:** 579 MDASI questionnaires were completed by 40 patients (mean age 57y, 50% male) on trials of targeted agents (50%) or immune mono/combination therapy (50%). At least 1 severe symptom ($\geq$7 on 0-10 scale) was reported by 55% of patients and the most frequent severe symptoms were pain (28% of patients), fatigue (25%), disturbed sleep (25%), distress (18%), dry mouth (18%), drowsiness (15%), and lack of appetite (15%). Skin rash ($P < 0.00$) and symptom interference with WAW ($P < 0.001$) and REM ($P = 0.024$) worsened from baseline to Day 60. From baseline to last completed MDASI, worsening by $\geq$2 points (0-10 scale) was seen in 28% of patients for WAW and 15% of patients for REM; improvement by $\geq$ 2 points was seen in 8% of patients for WAW and 5% of patients for REM. Targeted therapy was associated with worse fatigue ($P = 0.039$), drowsiness ($P < 0.001$), disturbed sleep ($P = 0.014$) and lack of appetite ($P < 0.001$); immune therapy was associated with worse REM ($P = 0.042$). Worsening of composite symptoms, WAW, or REM was associated with lower overall survival ($P < 0.001$ for each). **Conclusions:** Symptom burden trajectories varied by class of therapeutic agent. Longitudinal symptomatic assessments during early-phase clinical trials can provide a fuller view of patients' symptomatic experience and facilitate needed supportive care.

10120 Poster Session (Board #108), Mon, 1:15 PM-4:45 PM

Determinants of quality of life and survival in ambulatory oncology patients receiving chemotherapy. *First Author: Derek Gerard Power, Mercy University Hospital, Cork, Ireland*

Background: Identifying prognostic variables that may improve outcome in patients (pts) with cancer is a cornerstone of research. Recently, there has been interest in the prognostic value of nutritional status in pts with cancer. **Methods:** A prospective cohort study of ambulatory adult oncology pts undergoing chemotherapy between 2012-16 was conducted. A survey was devised, incorporating lifestyle, clinical, nutritional, biochemical [CRP, albumin] and quality of life (QoL) data. Nutritional status was evaluated using the cancer cachexia (CC) consensus definition and body composition was assessed using computed tomography. Skeletal muscle index (SMI) and mean muscle attenuation (MA) were obtained. Random forest algorithms were used to identify predictors of QoL and survival. Partial dependence plots were used to assess the direction and association of these predictors with outcome. **Results:** 1015 pts with solid tumors participated, 56% male, median age of 64 years [IQR 55-71]. Colorectal cancer was the most prevalent (27%). The majority (54%) of pts had stage IV disease. Overweight and obesity (BMI > 25 kg/m^2) was highly prevalent (57%), despite high rates of cachexia (42%), sarcopenia (39%) and low MA (45%). Percentage weight loss was the biggest predictor of global QoL. Weight stable pts had the highest global QoL scores after adjustment for other variables. Significant prognostic variables for survival were cancer site and stage, followed by systemic inflammation, anorexia, weight loss and mean MA, collectively considered hallmarks of CC. Highest predicted 1 and 3 year survival rates were observed in pts with a low CRP, high albumin ($>$ 38 g/L), without anorexia, who remained weight stable with a high mean MA ($>$ 36 HU). **Conclusions:** Malnutrition and abnormal body composition features are common in pts receiving chemotherapy but are often masked by adiposity. WL adversely impacts QoL. Nutritional parameters were more reliable prognostic indicators than many clinical variables, such as performance status, age and smoking status. Identifying significant prognostic variables provides conceptual guidance for the development of evidence based prediction models and tools. Further investigation is warranted.

10121 Poster Session (Board #109), Mon, 1:15 PM-4:45 PM

Intensive 4-weeks' mindfulness therapy in the treatment of chronic pain in patients with cancer: Pilot study. *First Author: Anna Kieszkowska-Grudny, Minds of Hope, Warsaw, Poland*

Background: Cancer pain can occur at any stage of disease and occurs on average in 51% of patients (pts) with cancer. Badly managed pain in cancer patients causes suffering and a significant reduction in the quality of life. Chronic pain (ChP) pts expect quick improvement in pain reduction. This pilot study was designed to check whether shortened and modified version of mindfulness training and therapy (MFNT) can help in ChP decrease in cancer patients' group. **Methods:** 83 (63%F) oncological pts with ChP (21-90y,M = 52,4y; SD = 18,7y) took part in this longitudinal study. Patients were invited to 4-weeks MFNT (1session/w), which was 2times shortened than standard Mindfulness Based Stress Reduction Therapy. Each session (90 min) included 30min of psychoeducation and 60min of practice. In addition, pts participated in 4h MFN day (only practice) and practiced MFN 30min every day. Participants based on questionnaires rated the pain intensity 4x (each session), psychological functioning and quality of life (QoL) 2x (before and after 4w). **Results:** There was a significant change in the intensity of pain symptoms recorded in the morning ($F(3, 81) = 7,86; p < 0,001, \eta^2 = 0,23$), evening ($F(3, 81) = 10,72; p < 0,001; \eta 2 = 0,28$)and average during the day ($F(2,82) = 24,02; p < 0,001; \eta 2 = 0,37$). Additionally, pts observed depression ($t(83) = 9,95$; $p < 0,001$)and anxiety ($t(83) = 9,88$; $p < 0,001$) reduction, as well as improvement in QoL ($t(83) = 9,24$; $p < 0,001$). Pts assessed a whole participation in MFNT at 7,9 (scale0-10) and at 9 as a recommendations for other ChP pts. **Conclusions:** Intensive 4w MFNT seems to be an interesting supportive treatment option in ChP reduction, but also an effective alternative for 8w MBSR. It could be a way for better pain management, depression and anxiety symptoms decreasing and QoL increasing among cancer pts. In addition, MFNT meets the needs of patients in terms of length of therapy.

10122 Poster Session (Board #110), Mon, 1:15 PM-4:45 PM

The association of serum ghrelin, GIP, insulin, and leptin levels with sleep quality and cancer-related fatigue in cancer survivors. *First Author: Po-Ju Lin, University of Rochester Medical Center, Rochester, NY*

Background: Sleep disruption leads to metabolic alterations such as increased appetite and reduced insulin sensitivity. Sleep disruption often co-occurs and is likely associated with cancer-related fatigue (CRF) in cancer survivors. Whether metabolic alterations are also associated with CRF is unknown. This preliminary data analysis assessed the association of serum metabolic markers, ghrelin, gastric inhibitory polypeptide (GIP), insulin, and leptin, with sleep quality and CRF in cancer survivors. **Methods:** Serum samples collected from 36 cancer survivors in an ongoing multi-center RCT examining the efficacy of yoga, health education, and cognitive behavioral therapy in reducing insomnia were analyzed at baseline and post 4-week intervention. They were selected based on changes in CRF, evaluated by Multidimensional Fatigue Symptom Inventory (MFSI), with 12 survivors in each of improved, no-change, and worse fatigue groups. Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI). Serum ghrelin, GIP, insulin, and leptin were assessed by a Luminex Multiplex Immunoassay. Spearman's rank correlation was used to examine the association of metabolic markers with sleep and CRF. **Results:** Changes in PSQI were significantly correlated with changes in MFSI ($r = 0.44$, $p < 0.01$), indicating that higher sleep quality is associated with less CRF. Baseline ($r = 0.35$, $p = 0.04$) and changes in serum ghrelin ($r = -0.32$, $p = 0.06$) were correlated with changes in MFSI, suggesting that increased serum ghrelin level is associated with improvements in CRF. Baseline serum GIP ($r = 0.36$, $p = 0.03$) and leptin ($r = 0.34$, $p = 0.04$) were significantly correlated with MFSI at post-intervention, suggesting that lower baseline serum GIP and leptin levels are associated with improvements in CRF. A trend toward significant correlation was found between baseline serum insulin and changes in MFSI ($r = 0.30$, $p = 0.08$) and between changes in serum leptin and changes in PSQI ($r = -0.30$, $p = 0.08$). **Conclusions:** These exploratory findings suggest potential associations of metabolic markers with CRF in cancer survivors. More studies are needed to further establish the association of energy metabolism and CRF. Clinical trial information: NCT02613364.

10123 Poster Session (Board #111), Mon, 1:15 PM-4:45 PM

Incidence of dermatological toxicities and fatigue in patients with cancer treated with regorafenib: A systematic review and meta- analysis of randomized controlled trials. *First Author: Miguel Quirch, TTUHSC, Lubbock, TX*

Background: Fatigue and skin toxicities notably contributed to the quality of life of cancer patients undergoing chemotherapy. Regorafenib, an oral small molecule multi kinase inhibitor, targets signaling pathways implicated in tumor angiogenesis, oncogenesis and the tumor microenvironment and are utilized in many solid tumors. We performed a systematic review and meta-analysis of randomized controlled trials (RCT) to determine the risk of fatigue and dermatological toxicities among patients with cancer treated with regorafenib. **Methods:** We conducted a comprehensive literature search using MEDLINE, EMBASE databases and meeting abstracts from inception through August 2017. Phase 3 RCTs that mention hand foot syndrome (HFS), rash, fatigue and anorexia as adverse effects were incorporated in the analysis. Mantel-Haenszel method was used to calculate the estimated pooled risk ratio (RR) with 95% confidence interval (CI). Random effects model was applied. **Results:** A total of 1723 patients with hepatocellular, colorectal cancer and gastrointestinal stromal tumors from four phase 3 RCTs were eligible for analysis. Studies compared regorafenib versus placebo. All grade-HFS incidence was 603 (34.9%) in regorafenib arm vs 44 (2.55%) in control arm with a RR of 6.683 (95% CI: 4.392–10.169, $P < 0.0001$). High-grade HFS was reported in 178 (10.33%) in regorafenib group vs 2 (0.12%) in control group with a RR of 29.246 (95% CI: 9.381–91.176, $P < 0.0001$). The relative risks of all-grade rash was 6.435 (95% CI: 3.713–11.154, $P < 0.0001$); high-grade rash: 9.166 (95% CI: 1.753–47.927, $P = 0.009$); all- grade fatigue: 1.624 (95% CI: 1.376–1.917, $P < 0.0001$); high-grade fatigue: 2.209 (95% CI: 1.329 – 3.672, $P = 0.002$); all-grade anorexia: 2.425 (95% CI: 1.678–3.503, $P < 0.0001$); and high-grade anorexia: 1.704 (95% CI: 0.507–5.720, $P = 0.389$). **Conclusions:** Patients on regorafenib experienced a significant increase in all-grades of HFS with a relative risk of 29 for grade 3 and 4 HFS. They also contributed to significant toxicity of all-grade and high-grade rash and fatigue as well as all-grade anorexia.

10124 Poster Session (Board #112), Mon, 1:15 PM-4:45 PM

Opioid use in rural breast cancer patients. *First Author: Emilio Paul Araujo-Mino, Kymera Independent Physicians, Roswell, NM*

Background: The Epidemic opioid overuse spans different communities and cancer patients frequently develop pain from their disease, cancer therapy or sequela for which opioids are commonly used. Breast Cancer is a common malignancy seen across different practices. **Methods:** This is a retrospective study evaluating BC patients Stages I-III from January 2013 until January 2018 in three rural community cancer practices in Southeast New Mexico who had been prescribed opioids during their cancer diagnosis and treatment. Exclusions were development of Stage IV, other concurrent malignancies, remote history of cancer for which use opioid data was missing. Chi-square and logistic regression were performed to identify correlation and predictors of long term opioid use respectively. **Results:** A total of 664 patients were identified; among these 150 (23%) were prescribed an opioid at some point. 54 were excluded according to prespecified criteria. The rate of opioid use was 72% (69/96) at 3 months, 62 % at 6 months (60/96) and 52% (50/96) at 12 months. 72% of user at 3 months (50/69) were also using opioids at 12 months from initial prescription x2 40.8 p=<0.001. Also 83% (50/60) of opioid use at 6 months were opioid user at 12 months x2 62.6 p=<0.001. Patient with smoking history, type of initial opioid (tramadol), opioid prescribed by surgeon, history of mental health and residence in smaller rural communities were more likely to continue using long term opioid, however it was not statistically significant. **Conclusions:** Curable breast cancer patients with increased short-term use of opioids at 3 months are significantly associated with continued long-term use at one year. Several factors in the rural community may need to be further evaluated in larger studies.

TPS10125 Poster Session (Board #113a), Mon, 1:15 PM-4:45 PM

iMETx (Individualized Metabolic Rx): Pilot study of an environmental intervention to increase energy expenditure among breast cancer survivors. *First Author: Tarah Jean Ballinger, Indiana University, Indianapolis, IN*

Background: Physical activity (PA) is associated with improved quality of life and outcomes in breast cancer survivors. However, many are inactive at diagnosis and activity levels worsen following treatment. PA interventions in breast cancer survivors have suffered from low acceptability and sustainability. The motives, capability, and environment affecting each individual vary, and an effective PA intervention will need to account for these differences. Designed to address this need, this study pilots an individualized, dynamic intervention (iMETx) to increase energy expenditure in breast cancer survivors. **Methods:** Patients with history of stage 0-III breast cancer who have completed primary treatment are recruited from Indiana University Simon Cancer Center. Those with comorbidities precluding use of a stationary bicycle are excluded. Energetic capacity (power generation) is assessed at baseline using a stationary bicycle protocol designed to be accurate over a range of physical capabilities and feasible in a clinic setting. Patients wear a GPS/accelerometer activity monitor for 3 weeks to collect baseline energy expenditure. During the subsequent 12 week intervention, patients receive tailored "prescriptions" every 1-3 days from the iMETx web application. Prescriptions are based on individual power ability and environment, and are dynamic, adjusted to achieve pre-determined energy endpoints. Following the intervention, power generation is re-assessed. Patients are monitored for 12 additional weeks to estimate sustainability. Each assessment point also includes DEXA to determine body composition, serum for markers of inflammation and metabolism, and questionnaires assessing quality of life and psychosocial factors. Throughout the study, patients interact with the web application to provide continuous feedback and actively engage in the research process. Feasibility will be assessed by compliance with study procedures, and preliminary effect of the intervention will be determined by changes in energetic capacity, energy expenditure, body composition, and quality of life. Sixteen patients have accrued out of a planned 60. Clinical trial information: NCT03158519.

TPS10126 Poster Session (Board #113b), Mon, 1:15 PM-4:45 PM

Circuit aerobic and resistance exercise to target metabolic dysregulation in breast and prostate cancer survivors: The CARE trial study design. *First Author: Christina Marie Dieli-Conwright, University of Southern California, Los Angeles, CA*

Background: Breast and prostate cancer survivors are at an increased risk of developing comorbidities such as metabolic syndrome (MSY), diabetes, and cardiovascular disease exacerbated by cancer treatments. MSY is a cluster of risk factors including visceral adiposity, insulin resistance, hyperglycemia, hyperinsulinemia, low serum high-density lipoprotein cholesterol, and hypertension. Exercise is an effective strategy to target MSY and therefore, we designed a novel exercise intervention referred to as circuit aerobic and resistance exercise (CARE). Our primary objective is to determine whether a 16-week CARE intervention improves components of MSY among breast and prostate cancer survivors with the primary endpoint of MSY cumulative score. **Methods:** We are currently recruiting sedentary, overweight/obese (BMI > 25 kg/m^2) women and men diagnosed with Stage I-III breast cancer or prostate cancer, respectively, from the USC Norris Comprehensive Cancer Center and Los Angeles County Hospital. Participants are randomized to either the CARE or Attention Control group. The CARE group participates in supervised exercise sessions 3 times per week for 16 weeks. CARE is a systematically progressed program of aerobic and resistance exercise performed in a circuit that begins at a low intensity and gradually increases to high intensity over the duration. The Attention Control group performs a home-based stretching program 3 days per week. At baseline (month 0), post-intervention (month 4), and follow-up (month 8), all participants are tested for MSY components. Statistical analyses for each outcome will involve mixed effects linear regression models. The sample size (25/arm within each cohort) reflects the need to obtain unbiased estimates of differences with reasonable precision. We will recruit an additional 90 patients (at present time n = 10) over the next 3 years. It is expected that this intervention will improve components of MSY in breast and prostate cancer survivors when compared to the Attention Control group, thus defining intervention and biomarker variables for more definitive trials. Clinical trial information: NCT03284346.

TPS10127 Poster Session (Board #114a), Mon, 1:15 PM-4:45 PM

Early nutrition support therapy to improve the nutrition status of head and neck cancer patients accepted concurrent chemoradiotherapy (NSTIP): Interim analysis from a prospective randomized controlled clinical study. *First Author: Peng Zhang, Sichuan Cancer Hospital, Chengdu, Sichuan, China*

Background: We given nutrition support treatment according to the changes by nutrition status in head and neck cancer patients at the process of definitive concurrent chemoradiotherapy(CCRT). Analyze the relationship between nutrition support therapy and CCRT side effects, quality of life score, treatment effect, prognosis and other indicators. **Methods:** 100 patients with head and neck cancer undergoing definitive chemoradiotherapy were enrolled. They were randomly divided into a nutritional intervention group (n= 50) and a conventional diet group (n= 50). The nutritional intervention group treated with prophylactic enteral nutrition powder formula (645.43 kcal/day; 2701.3 kJ/day) feeding before the initiation of CCRT. All patients were subjected to a standardised follow-up programme which included prospective evaluation of psychological status and HRQoL, prior to, during and after CCRT. The psychological status of those two groups were evaluated by Patient Health Questionnaire 9(PHQ-9), Generalised Anxiety Disorder Assessment 7(GAD-7) and Distress Thermometer. The primary endpoint was the nutritional indicators including body weight, white blood cells, lymphocyte, albumin etc. The secondary endpoints were the psychological status.This study is ongoing; data for this interim analysis were collected at December 30, 2017. This trial is registered with www.chictr.org.cn, number. Clinical trial information: ChiCTR-IIR-17011243.

TPS10128 Poster Session (Board #114b), Mon, 1:15 PM-4:45 PM

Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). *First Author: Antony Mersiades, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia*

Background: Up to half of patients receiving chemotherapy of moderate or high emetic risk experience CINV despite optimal anti-emetic prophylaxis. Limited evidence suggests cannabinoid medicine in the form of tetrahydrocannabinol (THC) may reduce CINV, and addition of cannabidiol (CBD) may improve efficacy and tolerance. The aim of this multi-centre, randomised, placebo-controlled, phase II/III trial is to determine efficacy and cost-effectiveness of the addition of an oral cannabinoid-rich THC/CBD cannabis extract for control of CINV. **Methods:** Target population is adult patients experiencing CINV during moderate and highly emetogenic chemotherapy regimens despite appropriate anti-emetic therapy, who are scheduled to receive at least 2 more consecutive cycles (A, B and, where applicable, C). Treatment consists of oral THC 2.5mg/CBD 2.5mg (Tilray TN-TC11M) capsules or placebo TDS days -1 to 5, in addition to guideline-consistent anti-emetics, including rescue medications. Patients will start with 1 tablet PO TDS and can dose-titrate to a maximum of 4 tables PO TDS based on nausea control and side-effects. In the pilot trial (N = 80), subjects are randomised for cycle A, cross-over for cycle B, and nominate preferred treatment for cycle C (if applicable). The planned definitive trial (N = 250) will randomise subjects to investigational product or placebo for cycles A, B and C in a parallel design. The primary end-point is the proportion of patients gaining a complete response (no emesis and no use of rescue medications) (0 – 120h), with additional end-points of (i) complete response, (ii) no emesis, (iii) no significant nausea and (iv) no use of rescue medication during the a) acute, b) delayed, and c) overall phases of cycle A, B and C, (iv) adverse events, (v) quality of life, and (vi) cost-effectiveness. As of 12/02/2018, 41 of 80 patients have been recruited to the pilot study, with expected recruitment completion in 2nd quarter 2018. Funding: NSW Department of Health. Acknowledgements: Trial participants, investigators and research staff. Drug supply by Tilray. ACTRN: 12616001036404 Clinical trial information: 12616001036404.

TPS10129 Poster Session (Board #115a), Mon, 1:15 PM-4:45 PM

Effect of nutritional support with highly purified, whey proteins for malnutrition and sarcopenia in patients affected with stage II-III colorectal or breast cancer: A blind, placebo controlled, randomized clinical trial. *First Author: Federica Mazzuca, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy*

Background: Malnutrition and sarcopenia may arise in both colorectal and breast cancer since the first visit. Previous studies demonstrate that malnourished cancer patients have a decreased quality of life and experience more chemotherapy-toxicity. Protein supplementations could prevent loss of lean body mass that goes along with malnutrition and sarcopenia. Therefore, the role of whey proteins takes a great deal of interest. We propose a randomized study, placebo-controlled, aimed at evaluating the activity and safe of a highly purified, whey protein nutritional support (PROLYOTIN) in cancer patients undergoing adjuvant chemotherapy (EudraCT n. 2018-000122-64). **Methods:** Patients with histological diagnosis of stage II/III according to AJCC system, breast or colorectal cancer, referred for adjuvant chemotherapy, with no metabolic disease, will be eligible. Obtained written informed consent, all patients will be blind-randomized with 1:1 ratio in two arms: A (PROLYOTIN) vs. B (placebo). Patients will be assessed before starting chemotherapy (T0), after 3 (T1) and 6 months (T2), with respect to a physico-nutritional examination, skeletal muscle mass calculation by CT scan and Body Impedance Assessment. Mini Nutritional Assessment, Malnutrition Universal Screening Tools and Quality of life by EORTC QLQ C-30 will be also done. At the same time frames (T0, T1, T2) detailed medical records, tumor characteristics, dietary practices and laboratory values (blood count, serum proteins, cholesterol, triglycerides, amylases, lipases, ESR, CRP, glucose, tumor markers, cortisol, insulin, vitamin D, LDH and CK) will be collected by a specialist team of medical oncologists and dieticians. The patient-adherence to protocol will be also monthly evaluated. Primary objective is to evaluate the nutritional status at baseline, T1 and T2 and the difference between the PROLYOTIN and placebo arms. Secondary, correlations between nutrtional status and clinicopathological parameters, and the quality of life will be analyzed. A total of 220 patients will be enrolled (95% CI, β 10%). Clinical trial information: 2018-000122-64.

TPS10131 Poster Session (Board #116a), Mon, 1:15 PM-4:45 PM

A randomized phase II study of the nutritional and exercise treatment for the elderly patients with advanced non-small cell lung or pancreatic cancer: The NEXTAC-TWO study. *First Author: Satoru Miura, Niigata Cancer Center Hospital, Niigata, Japan*

Background: Most advanced cancer patients experience fatigue, anorexia, and declining physical function due to cancer cachexia and /or aging, for which effective treatment has not been established. We performed a phase I study, called NEXTAC-ONE, and demonstrated the feasibility of multi-modal interventions, namely, nutritional support and physical exercise in elderly cancer patients. We conducted the next-step multi-center, randomized phase II study to evaluate the efficacy of previously investigated multi-modal interventions in elderly cancer patients. **Methods:** Patients with chemonaïve advanced non-small cell lung cancer or pancreatic cancer, age $>=$ 70 years, PS $<=$ 2, with adequate organ function and without disability by the modified Katz index, will be eligible. Totally, 130 participants will be recruited from 15 Japanese institutions and will be randomized into either the intervention group or a control group. Interventions and assessment will be performed 4 times every 4$\pm$2 weeks from the date of randomization. Interventions will consist of nutritional counseling, nutritional supplements (rich in branched-chain amino acids), and a home-based exercise program. The exercise program will include low-intensity daily muscle training and life-style education to promote physical activity. The primary endpoint is disability-free survival. It is defined as the period from the date of randomization to the date of developing disability or death due to any cause. This trial also plans to evaluate improvement in nutritional status, physical condition, quality of life, activities of daily living, overall survival, and safety as secondary endpoints. Enrollment began in August 2017. Eighteen of the planned 130 participants have been enrolled at the time of this submission. Study results will demonstrate efficacy of multi-modal interventions for elderly cancer patients and application for maintenance of physical and nutritional condition of patients with cancer cachexia. This work is supported by a grant-in-aid from the Japan Agency for Medical Research and Development. Clinical trial information: UMIN000028801.

TPS10132 Poster Session (Board #116b), Mon, 1:15 PM-4:45 PM

A randomized phase II clinical trial of a fasting-mimic diet prior to chemotherapy to evaluate the impact on toxicity and efficacy. *First Author: Tanya B. Dorff, City of Hope, Duarte, CA*

Background: Chemotherapy toxicity impacts dose intensity as well as temporarily deteriorating quality of life; some toxicity can be permanent, such as neuropathy. We previously demonstrated that fasting induces Differential Stress Resistance and hypothesized that fasting may protect normal host cells from chemotherapy toxicity, while potentially sensitizing cancer cells to chemotherapy. A low calorie, low protein fasting-mimicking diet (FMD) may be more acceptable than pure fasting. We are studying whether FMD will reduce chemotherapy toxicity and/or enhance efficacy. Changes in glucose and insulin-like growth factor 1 (IGF1) may mediate or be biomarkers for the protective effects of fasting and will be studied in the trial population. **Methods:** Randomized phase II in 2 parallel cohorts (Prostate, n = 60, Breast n = 60). Treatment: Arm A = restricted diet consumed 3 days prior to and 24 hours after chemotherapy for 4 cycles. Arm B = regular diet. Eligibility: breast cancer with AC or TC in neoadjuvant setting, prostate cancer treated with Docetaxel, up-front or for mCRPC. BMI > 18.5. Exclusion: Diabetes Mellitus. Endpoints: Primary: Grade 2+ non-hematologic symptomatic toxicities experienced during 4 courses; additionally, radiographic (RECIST) response and PSA changes. Secondary: toxicity (all grade 2-4 events, dose reductions/delays) and efficacy (pathologic response for breast cancer, PSA/RECIST response for prostate cancer). Biomarker: plasma insulin, glucose, IGF1 and IGF binding protein (IGFBP) at baseline, and each cycle. Statistics: Proportion of patients with grade 2-4 symptomatic toxicities will be compared between treatment arms using stratified Mantel-Haenszel test; p-value ≤ 0.20 indicates the diet intervention is promising. With 60 patients in each cohort there is 88% power; initial analyses will evaluate breast/prostate cancer separately, yielding standard error no more than +/- 0.18 for estimates of the difference in the proportions of patients who experience a specific toxicity (or the composite). Quality of life will be assessed with SWOG questionnaire on day 1 of each chemotherapy cycle. Progress: 70 of 120 planned subjects have been accrued. Clinical trial information: NCT01802346.

10500 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

COG AALL0434: A randomized trial testing nelarabine in newly diagnosed t-cell malignancy. *First Author: Kimberly P. Dunsmore, Carilion Children's, Roanoke, VA*

Background: Nelarabine (Nel) is a T-cell specific agent, FDA approved for patients who have failed at least two chemotherapy regimens. COG AALL0434 evaluated its safety and efficacy when incorporated into COG augmented BFM (ABFM) chemotherapy in newly diagnosed T-ALL and T-LL patients. **Methods:** AALL0434 enrolled 1,895 patients (2007-2014) and included a 2 x 2 pseudo-factorial randomization using the ABFM regimen. Patients were randomized to receive escalating dose methotrexate without leucovorin rescue + pegaspargase (CMTX) or High Dose MTX (HDMTX) + leucovorin rescue. Intermediate and high-risk patients with T-ALL and T-LL were randomized to receive or not receive six 5-day courses of (Nel) 650 mg/m^2/day. The intermediate and high risk T-ALL patients received prophylactic (1200 cGy) or therapeutic (1800 cGy for CNS3) cranial irradiation. T-ALL patients with induction failure were non-randomly assigned to HDMTX+Nel. **Results:** For all randomized T-ALL patients, the 4-year disease-free survival (DFS) and overall survival (OS) rates were 84.3 +/- 1.1% and 90.2 +/- 0.9%. The 4-year DFS rate for T-ALL patients randomized to Nel (N = 323) vs no Nel (N = 336) was 88.9 +/- 2.2% vs 83.3 +/- 2.5%, (p = 0.0332). Among T-ALL patients randomized to CMTX the 4-year DFS for Nel (N = 147) vs no Nel (N = 151) was 92.2 +/- 2.8% vs 89.8 +/- 3.0%, p = 0.3825. For those randomized to HDMTX, 4-year DFS was 86.2 +/- 3.2% with Nel (N = 176) vs 78.0 +/- 3.7% without Nel (N = 185), p = 0.024. Differences between DFS in a 4-arm comparison were highly significant (P = 0.002), with no significant interactions between MTX and nelarabine randomizations (p = 0.41). T-ALL induction failure patients (N = 43) assigned to HDMTX/Nel had a 4-year DFS of 54.8 +/- 8.9%. Nelarabine did not show an advantage for high risk T-LL patients, with 4-year DFS 85.0 +/- 5.6% vs 89.0 +/- 4.7% for Nel (N = 60) vs no Nel (N = 58), p = 0.2788. Overall toxicity and neurotoxicity were acceptable and not significantly different between all four arms. **Conclusions:** COG AALL0434 is the largest trial ever conducted for newly diagnosed T-ALL and T-LL, and showed outstanding overall outcomes. Nelarabine improves DFS for children and young adults with T-ALL and should become a new standard of care for this population. Clinical trial information: NCT00408005.

10501 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Effect of dexrazoxane on left ventricular function and treatment outcomes in patients with acute myeloid leukemia: A Children's Oncology Group report. *First Author: Kelly D. Getz, The Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Overall survival (OS) for pediatric acute myeloid leukemia (AML) has improved to > 65% due in part to the use of anthracycline (ATC)-containing chemotherapy regimens. ATC is also associated with increased cardiotoxicity risk. Cardioprotective agents such as dexrazoxane (DEX) may reduce cardiac injury during treatment. While data on the benefit of DEX are promising, studies in pediatric AML patients are limited. Given the very high ATC exposure in pediatric AML therapy, evaluating the utility of DEX in this population is critical. **Methods:** On Children's Oncology Group trial AAML1031, DEX was administered at the discretion of treating physicians. DEX exposure was documented at each treatment course, and ejection fraction (EF) and shortening fraction (SF) values were recorded after each course and in follow up. Absolute change in EF from baseline (ΔEF) was computed for each course. Early LVSD was defined as any EF < 50% or SF < 24% from the start of frontline therapy through the follow-up at one-year off-protocol. ΔEF at each course, occurrence of LVSD, and 3-year OS and disease free survival (DFS) were compared for DEX exposed and unexposed. **Results:** 1014 patients were included; 96 were DEX-exposed at each ATC course received and 918 were never exposed. Distributions of sex, age, race, initial white blood cell count, risk group, and treatment arm were similar for DEX exposed and unexposed. DEX exposed patients had smaller declines in EF than unexposed patients across courses (range of course-specific median ΔEF: 0 to -4.0 versus 0 to -6.4; all $p < 0.05$) and an overall lower risk for early LVSD (6.3% vs 19.2%, RR = 0.33, 95% CI: 0.15-0.72, p = 0.005). The effect of DEX on LVSD risk was particularly pronounced for female patients (RR = 0.16, 95% CI 0.05 – 0.65). DEX exposed patients had non-significantly higher 3-year OS (71.9% vs 63.0%, p = 0.093) and EFS (54.4% vs 44.2%, p = 0.070) compared to those unexposed. **Conclusions:** DEX is associated with smaller reductions in EF throughout pediatric AML therapy and a lower risk for early LVSD. Small numbers may have limited our ability to detect differences in OS and EFS. Longer follow-up is required to elucidate the sustained benefit of DEX.

10502 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Improved survival among children and adolescent and young adults with acute lymphoblastic leukemia (ALL) treated at specialized cancer centers in California. *First Author: Elysia Marie Alvarez, University of California, Davis School of Medicine, Sacramento, CA*

Background: We previously demonstrated that adolescent and young adult (AYA) patients who received induction treatment at specialized cancer centers (SCC; versus community hospitals) had lower early mortality within 60 days of diagnosis. However, the effect of location of treatment on long term survival has not yet been evaluated at the population-level. **Methods:** Using the California Cancer Registry linked to a statewide hospitalization database, we identified children (0-18 years) and AYAs (19-39 years) with first primary ALL who received inpatient treatment, 1991-2014 (n = 7,724). Patients were classified as receiving all or part/none of their treatment at a SCC (Children's Oncology Group or National Cancer Institute-designated cancer center) within 3 years of diagnosis. Propensity scores were created for treatment at an SCC in each age-group. Inverse probability of treatment-weighted, multivariable Cox regression models estimated the magnitude of associations between location of treatment, sociodemographic and clinical factors with leukemia-specific survival. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CI). **Results:** Overall, 21.3% of children and 42.6% of AYAs died over the study period (median follow-up time: 11.6 years). Seventy-eight percent (n = 4511) of children and 19% of AYAs (n = 356) received all their treatment at SCCs. In multivariable models, receiving all treatment at a SCC (vs part/no care) was associated with better leukemia-specific survival (HR 0.86, CI 0.75-0.99) in children and AYAs (HR 0.83, CI 0.72-0.97). In both age groups, worse survival was associated with older age, Hispanic and African American race/ethnicity (vs non-Hispanic white), public insurance (vs private) and comorbidities. **Conclusions:** Our results demonstrate that treatment at a SCC through end of therapy is associated with better leukemia-specific survival in children and AYAs. In contrast to AYAs, the majority of children receive care at a SCC, but both age groups benefit from care at a SCC. This highlights the need for these patients to be referred to and treated at SCCs.

10503 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). *First Author: Andrea M. Gross, National Institutes of Health, Bethesda, MD*

Background: PN in NF1 can cause substantial morbidity, and there are no approved medical therapies. In a phase I trial of selumetinib, 17/24 (71%) patients (pts) had a partial response (PR)(Dombi, et al. *N Engl J Med 2016*; 375:2550-2560). This open-label phase II study (NCT01362803) determines the PR rate of PN treated with selumetinib and changes in PN related morbidities. **Methods:** Patients 2-18 years old with NF1, inoperable PN and ≥ 1 PN related morbidity received selumetinib at the recommended phase II dose (25 mg/m^2 PO BID) with continuous dosing (1 cycle = 28 days). Response was evaluated with volumetric MRI analysis (PR = target PN volume decrease ≥20%) and PN related morbidities (pain, disfigurement, functional morbidities) assessed with standardized evaluations after every 4 cycles. **Results:** Fifty children (30 male, median age 10.2 years, range 3.5, 17.4) enrolled. Disfigurement (n=44), motor dysfunction (n=33) and pain (n=28) were the most frequent PN related morbidities. As of November 5, 2017: median cycle number 19.5 (range 0, 29) with 38 pts remaining on treatment; median change in PN volume from baseline -27.7% (range -50.6%, 2.2%); best response PR (36 pts, 72%), stable disease (12 pts, 24%); 2 subjects (4%) had no re-staging. Of the 36 total PR, 32 were confirmed on ≥ two consecutive restaging scans and 22 continue to have a PR ≥ 1 year after it was first achieved. Between baseline and end of year 1 evaluations, parent and child-reported pain intensity and pain interference scores significantly improved ($p < 0.01$), as did strength (0-5 scale) and range of motion (degrees) of affected muscle groups/joints ($p < 0.01$). The most frequent toxicities were nausea/vomiting, diarrhea, asymptomatic creatine kinase increase, acneiform rash and paronychia. Selumetinib dose was reduced in 12 pts, of which 5 were removed from treatment. **Conclusions:** The response rate from this study (72%) confirms our previously observed response rate (71%). Most responses were sustained ≥6 months. Improvements in PN related pain and motor impairment demonstrate that selumetinib can provide clinical benefit. Data validation and further analyses are ongoing. Clinical trial information: NCT01362803.

10504 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Trametinib in pediatric patients with neurofibromatosis type 1 (NF-1)–associated plexiform neurofibroma: A phase I/IIa study. *First Author: Geoffrey Brian McCowage, The Children's Hospital at Westmead, Westmead, Australia*

Background: NF-1 loss-of-function alterations are associated with development of plexiform neurofibromas (PNs). NF-1–associated PNs can arise early in life in different locations, with variable and significant morbidity. Many patients (pts) progress following surgery, and currently there are no approved systemic therapies. The MEK inhibitor trametinib is being evaluated in pediatric pts across a spectrum of tumor types in a dose-escalation cohort of a phase I/IIa study (NCT02124772) to determine a recommended dose; disease-expansion cohorts include pts with NF-1 PN. Here we present an interim analysis of safety and clinical benefit of trametinib in pediatric pts with NF-1–associated PN. **Methods:** Pts aged 1 mo to < 18 y with medically significant, unresectable NF-1–associated PN were treated with trametinib 0.025 to 0.040 mg/kg/d. The primary objective was safety, and secondary objectives included tumor response assessed by independent review (IR) using published MRI volumetric criteria. **Results:** Twenty-six pts received trametinib (0.025 mg/kg/d, n = 21; 0.032 mg/kg/d, n = 1; 0.040 mg/kg/d, n = 4). Presented here are results from the disease-expansion cohort (n = 10). Median duration of exposure was 408 d (range, 360-429 d), and 8 pts (80%) had treatment ongoing at the data cutoff (September 2017). Median age was 5.5 y (range, 1-16 y), and prior therapies included surgery (n = 5), biologics (n = 1), and targeted therapy (n = 1). Treatment-related AEs (TRAEs) were reported in 9 of 10 pts (90%), and 1 pt discontinued due to a TRAE. The most frequent TRAEs were paronychia (50%) and rash (40%). No deaths occurred on treatment. Analysis of the full NF-1 PN cohort (n = 26) is ongoing; across this cohort, 12 of 26 pts (46%) had a PR (≥ 20% volume reduction) by IR, and 10 of the 12 responses (83%) were ongoing. **Conclusions:** Trametinib demonstrated a manageable safety profile in pediatric pts with NF-1–associated PN. Using volumetric criteria for response determination, the objective responses observed with trametinib support continued investigation in this pt population. Clinical trial information: NCT02124772.

10505 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Dabrafenib in pediatric patients with *BRAF* V600–positive high-grade glioma (HGG). *First Author: Darren R Hargrave, Great Ormond Street Hospital for Children, London, United Kingdom*

Background: The *BRAF* V600 mutation constitutively activates the MAPK/ERK pathway and is an oncogenic driver in many tumor types, including pediatric brain cancers. There are limited effective therapies for patients (pts) with HGG, ≈ 5% of whom have *BRAF* V600 alterations. The kinase inhibitor dabrafenib (which targets *BRAF* V600) demonstrated tolerability in pediatric pts across tumor types in a dose-escalation (ESC) cohort of a phase I/IIa study (Kieran et al, ASCO 2015; NCT01677741). Here we report preliminary analyses in this study of safety and clinical benefit with dabrafenib in pts with HGG across the ESC and disease-expansion (EXP) cohorts. **Methods:** Pts aged 1 to < 18 y with *BRAF* V600–positive HGG who had refractory or progressive disease after receiving ≥ 1 standard therapy were treated with dabrafenib (2 equal daily doses) either in the ESC cohort or with the recommended dose of 5.25 mg/kg/d (pts < 12 y) or 4.5 mg/kg/d (pts ≥ 12 y) in the EXP cohort. Measurable disease was not required. Primary objectives were safety and tolerability, and secondary objectives included tumor response and pharmacokinetics. Tumor response was reported by independent review (IR) and investigator assessment (INV) using RANO criteria. Exploratory analyses included independent histopathological review and tumor biology analysis (eg, mutation, methylation status). **Results:** Pts (n = 31) were treated with dabrafenib across the ESC (n = 8) and EXP (n = 23) cohorts. Median age was 14 y (range, 3 - < 18 y). Across both cohorts (n = 31), the most frequent AEs (any causality) were fatigue (48%), vomiting (42%), and headache (39%). Grade 3/4 AEs occurred in 12/31 pts (39%). No on-treatment deaths occurred. Median duration of exposure was 22 wk (range, 4-225 wk), and 10/31 pts (32%) had treatment ongoing. ORR by IR was 45% (14/31, with 3 CRs), and ORR by INV was 32% (10/31, with 4 CRs). By IR, median duration of response was 7.7 mo (95% CI, 3.0 mo-not estimable) and 13/19 pts with measurable lesions (68%) achieved a maximum tumor reduction of ≥ 50%. Tumor mutational and methylation analyses are ongoing. **Conclusions:** Dabrafenib was well tolerated in pediatric pts with *BRAF* V600–positive HGG, and a number of durable objective responses demonstrate the potential for clinical benefit. Clinical trial information: NCT01677741.

10506 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Efficacy and safety results from a phase I/IIa study of dabrafenib in pediatric patients with *BRAF* V600–mutant relapsed refractory low-grade glioma. *First Author: Mark W. Kieran, Harvard Medical School, Boston Children's Hospital, Dana-Farber Cancer Institute, Boston, MA*

Background: The primary treatment for many pediatric patients (pts) with low-grade glioma (LGG) remains surgical resection with curative intent. However, pts whose tumors cannot be completely resected or recur may require additional treatment, eg, radiotherapy or chemotherapy. Pediatric pts with *BRAF* V600–mutant LGG may benefit from treatment with the BRAF inhibitor dabrafenib. We report 2-y follow-up data from a 2-part phase I/IIa study investigating dabrafenib in pediatric *BRAF* V600–mutant LGG (NCT01677741). **Methods:** Part 1 determined the recommended phase 2 dose (RP2D); the Part 2 disease expansion evaluated efficacy and safety of dabrafenib in 4 pediatric tumor–specific cohorts, including LGG. Efficacy for LGG was determined by investigator and independent (IND) review per Response Assessment in Neuro-Oncology [RANO] criteria. Adverse events (AEs) were assessed per NCI-CTCAE version 4.0 criteria. **Results:** Thirty-two pediatric pts with relapsed, refractory, or progressive *BRAF* V600–mutant LGG were enrolled (Dec 2013 to Jul 2015). Fifteen pts were treated in Part 1 (n = 7 at RP2D) and 17 in Part 2. RP2D is 4.5 mg/kg/d for pts ≥ 12 y of age and 5.25 mg/kg/d for pts < 12 y of age, each divided into 2 equal doses per day. Common histologies included pilocytic astrocytoma (n = 13; 41%), ganglioglioma (n = 7; 22%), and pleomorphic xanthoastrocytoma (n = 3; 9%). At interim analysis (Sep 2017), median duration of exposure was 25 mo (range, 0.1-42.6 mo), with 15 ongoing. Most frequent reason for discontinuation was elective, following ≥ 1 yr of treatment. Across all dose levels, the confirmed overall response rate (ORR, complete response [CR] + partial response [PR]) per IND review was 44% (95% CI, 26.4%-62.3%), including 1 CR and 13 PR. Eleven pts had stable disease, and 2 had progressive disease as best response. Median PFS by IND review was 35 mo (95% CI, 12.9 mo-NE). Common AEs of all grades, regardless of causality, included pyrexia (72%), vomiting (53%), and headache (47%). **Conclusions:** Dabrafenib demonstrated clinical activity with tolerability in pediatric pts with relapsed, refractory, or progressive *BRAF* V600E mutation–positive LGG and supports its further clinical evaluation. Clinical trial information: NCT01677741.

10507 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

The randomised induction for high-risk neuroblastoma comparing COJEC and N5-MSKCC regimens: Early results from the HR-NBL1.5/SIOPEN trial. *First Author: Alberto Garaventa, Istituto Giannina Gaslini, Genova, Italy*

Background: From 2013-2017 the HRNBL1.5/SIOPEN trial tested the hypothesis that the N5-MSKCC induction regimen *(Kushner, JCO 2004)* increases metastatic complete response (mCR) or event-free survival (EFS) compared to Rapid COJEC *(Ladenstein, JCO 2010).* **Methods:** Eligible patients had stage 4 or 4s with MYCN amplification (MNA) aged < 21 years, or without MNA aged 12-18 months with segmental chromosome alterations, and > 18 months with any genomic profile. Patients were stratified for national groups and metastatic sites. Further treatments included addition of 2 TVD *(Amoroso, Cancer Res Treat 2018)* if < mCR, primary tumour resection, BuMel megatherapy, primary site irradiation, ch14.18/CHO antibody ± IL2 plus 13-cis-RA. Primary endpoints were to increase mCR rate to 45% with N5 MSKC (33% for Rapid COJEC) and by 12.5% the 2-year EFS to 52.5%. **Results:** 630 patients were randomised (313 for Rapid COJEC, 317 for N5). 56% were female. 99% had stage 4. Median age: 3.2 years (0.2-20.4) with 16 infants and 56 aged 12-18 mos. Median follow-up: 1.7 years. No primary endpoint differences were observed: 2-year EFS was 53% ±4 for Rapid COJEC *vs* 51%±4 for N5-MSKCC. mCR rate after induction was 33% for Rapid COJEC *vs* 37% for N5-MSKCC. No difference was detected also in secondary endpoints: overall survival was 72%±3 for Rapid COJEC *vs* 69%±3 for N5-MSKCC. 2-year relapse-unrelated mortality was 8%±2 with Rapid COJEC *vs* 6%±2 with N5-MSKCC. Cumulative incidence of relapse/progression was 39%±3 for Rapid COJEC *vs* 43%±4 for N5-MSKCC. A comparison of CTC Grade 3-4 toxicities showed significant differences favouring Rapid COJEC over N5-MSKCC: non-haematological 47% *vs* 68% (*P*= .000), compromise of general conditions 12% *vs* 19% *(P*= .055); neutropenia 94% *vs* 98% (*P*= .020); low platelet count 91% *vs* 96% (*P*= .031); infections 24% *vs* 35% (*P*= .005); stomatitis 3% *vs* 26% (*P*= .000); nausea/vomiting 7% *vs* 16% (*P*= .001); diarrhoea 3% vs 7% (*P*= .033); hypertension 10% vs 6% (*P*= .050); central neurotoxicity 0% *vs* 1% (*P*= .049). **Conclusions:** As Rapid COJEC was less toxic and no differences in primary and secondary outcomes were observed it was maintained as standard induction for future SIOPEN studies. Clinical trial information: NCT01704716.

10508 Oral Abstract Session, Sat, 3:00 PM-6:00 PM

Phase II trial of irinotecan/temozolomide/dinutuximab/granulocyte macrophage colony stimulating factor (I/T/DIN/GMCSF) in children with relapsed/refractory neuroblastoma (NBL): A report from the Children's Oncology Group (COG). *First Author: Rajen Mody, University of Michigan, Ann Arbor, MI*

Background: COG ANBL1221 was a randomized Phase II selection design trial for patients (pts) with relapsed/refractory NBL. Randomization was stopped early when I/T/DIN/GMCSF was shown be the optimal combination for further study. In the small cohort assigned to I/T/DIN/GMCSF, the objective response rate was 53%. An expanded cohort was evaluated to more accurately assess response rate and better define the toxicity profile of this combination. **Methods:** Pts were eligible at first relapse/progression or first designation of refractory disease. Cycles were administered every 21 days. Objective responses were confirmed centrally. Toxicities were graded according to CTCAE v4.0. **Results:** 53 eligible pts were assigned to I/T/DIN/GMCSF; 17 during the randomized portion, 36 during study expansion. Median age was 5.1 years (range 1.3-15.9), 39 pts (74%) had measurable disease. Fourteen (26%) had *MYCN* amplified tumors, 20 (38%) had previously undergone high-dose chemotherapy with stem cell rescue, and 14 (26%) had received prior anti-GD2 antibody. 22 (42%) had relapsed disease and 31 (58%) had refractory/progressive disease (PD). Subjects received 378 total cycles (median 6). Of 53 pts assigned to I/T/DIN/GMCSF, 21 experienced objective responses [40%; 95% CI (26, 53)]; 10 PR, 11 CR. Seven had PD, 23 had stable disease. Two did not receive protocol therapy and did not undergo disease evaluations, but were included in the intention-to-treat analysis. Among responders, 4 (19%) had *MYCN* amplified tumors and 9 (43%) had previously received an anti-GD2 antibody. Of the 51 evaluable for toxicity, 13 (25%) had Grade 3 pain, 8 (16%) had Grade 3 diarrhea, and 4 (8%) had Grade 3 vomiting. Neutropenia (^{3}Grade 3) was observed in 14 (27%), Grade 3 thrombocytopenia in 5 (10%), and Grade 3 fever/infection in 11 (22%). **Conclusions:** I/T/DIN/GM-CSF showed significant anti-tumor activity in pts with relapsed/refractory NBL. This combination was well-tolerated in a cohort of $>$ 50 pts. Studies of biomarkers that may identify pts most likely to respond to this chemo-immunotherapeutic regimen are in progress. Clinical trial information: NCT01767194.

10509 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Subsequent malignant neoplasms (SMNs) among non-irradiated survivors of childhood cancer treated with chemotherapy in the Childhood Cancer Survivor Study. *First Author: Lucie Marie Turcotte, University of Minnesota, Minneapolis, MN*

Background: In recent treatment eras radiotherapy (RT) use decreased while chemotherapy (CT) increased. RT is an established risk factor for SMNs. Limited data exist on how CT increases risk for SMNs $>$ 5 years after childhood cancer. **Methods:** SMNs were evaluated in 5-year survivors diagnosed $<$ 21 years of age between 1970-99, treated with CT and not RT (N = 7447, 138,008 person-years follow-up). 30-year cumulative incidence and 95% confidence intervals (CI) and standardized incidence ratios (SIRs) for SMNs were estimated. SIRs were estimated for chemotherapy exposures [alkylator: 0, 1-3999, 4000-7999, $\geq$8000 mg/m^2; platinum: 0, 1-400, 401-750, $>$ 750 mg/m^2; anthracycline: 0, 1-100, 101-300, $>$ 300 mg/m^2; epipodophyllotoxin: 0, 1-1000, 1001-4000, $>$ 4000 mg/m2]. **Results:** There were 154 SMNs among 139 survivors. Cumulative incidence for SMNs at 30 years was 4.5% (95% CI 3.4-5.6) and risk for SMN was 3-fold greater than the general population. Survivors of leukemia, lymphoma, and sarcomas had increased risk for SMNs (Table), whereas, survivors of Wilms tumor, neuroblastoma and CNS cancer did not. Exposure to moderate- to high-dose alkylator ($\geq$4000 mg/m^2) or platinum ($>$ 400 mg/m^2) or high-dose anthracycline ($>$ 300 mg/m^2) or epiodophyllotoxin ($>$ 4000 mg/m^2) therapy had SIRs of $\geq$4.0. A combination of alkylators and platinum, one of the two being high-dose and the other being moderate or high-dose, had a SIR of 13.0 (95% CI 6.5-23.2). **Conclusions:** Non-RT exposed survivors are at increased risk for SMN and should be counseled regarding the potential for genetic predisposition and the need for increased surveillance for early detection of subsequent cancers.

SIRs (95% CI) for SMNs by childhood cancer diagnosis.

		SMN				
Primary Cancer	All SMNs (n = 154)	Leukemia/ Lymphoma (n = 21)	Breast (n = 34)	Soft tissue sarcoma (n = 14)	Thyroid (n = 20)	Melanoma (n = 15)
All diagnoses	3.1 (2.6-3.6)	2.9 (2.4-3.4)	6.3 (4.4-8.9)	4.1 (2.2-6.8)	3.5 (2.2-5.5)	3.4 (2.1-5.3)
Leukemia/lymphoma (n = 4309)	2.7 (2.2-3.4)	2.1 (1.2-3.4)	6.3 (3.7-10.1)	1.5 (0.3-4.3)	2.6 (1.2-5.0)	4.1 (2.3-6.9)
Sarcoma (n = 1484)	3.8 (3.0-4.9)	2.5 (1.0-5.1)	7.1 (4.1-11.3)	10.0 (4.8-18.4)	5.6 (2.6-10.7)	3.2 (1.2-7.0)

10510 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Risk-adapted therapy for pediatric Hodgkin lymphoma (HL) results in lower risk of late effects: a report from the Childhood Cancer Survivor Study (CCSS). *First Author: Kevin C. Oeffinger, Duke University, Durham, NC*

Background: The goal of multi-modal, risk-adapted therapy for HL is to increase cure rates while decreasing risk for late effects; this is particularly important for children due to their vulnerability to cytotoxic therapy and life expectancy. **Methods:** Severe, disabling, life-threatening and fatal chronic conditions (CTCAE v4.03 grades 3-5) were determined for 2,996 5-yr HL survivors from CCSS diagnosed age $<$ 21 from 1970-1999. Cox models evaluated hazard ratios (HR) and 95% confidence intervals (CI), comparing risks of grade 3-5 chronic conditions by age 40 among treatment regimens with historical total lymphoid irradiation (TLI) as the referent group. **Results:** HL survivors were a mean age of 35.6 years (range, 12-58). The cumulative incidence of any grade 3-5 condition by age 40 was 43.6% (95% CI 41.1-46.1). Risk-adapted therapy using hybrid chemotherapy with or without radiotherapy (RT) was associated with a substantial reduction in risk for serious late effects (Table). While omitting radiation was associated with a 3-fold reduction in risk of late effects, HL survivors with a history of recurrence and/or a hematopoietic transplant (HCT) had an overall risk similar to those treated with TLI. **Conclusions:** Risk-adapted therapy has resulted in a reduction in serious long-term outcomes. While omitting radiotherapy is associated with a further reduction in risk, this consideration must be balanced with the risk of recurrence and the serious morbidity associated with salvage therapy.

HR (95% CI) for selected treatment groups, adjusted for sex, age at HL, and other treatment regimens, for a grade 3-5 condition, subsequent malignant neoplasm (SMN), cardiopulmonary disease (CPD), or endocrinopathy (Endo).

		CTCAE Grade 3-5 Chronic Condition			
Treatment Group	N	Any	SMN	CPD	Endo
TLI ≥ 35 Gy (referent)	570	1.0	1.0	1.0	1.0
Recurrence or HCT	296	1.2 (0.9-1.5)	0.6 (0.4-0.9)	2.2 (1.6-3.1)	0.9 (0.6-1.4)
Chest RT^q 15.0 - 34.9 Gy + hybrid* chemo	383	0.7 (0.5-0.9)	0.7 (0.5-1.1)	0.7 (0.4-1.1)	0.8 (0.6-1.2)
Hybrid chemo without RT	216	0.3 (0.2-0.4)	0.4 (0.2-0.8)	0.3 (0.1-0.8)	0.2 (0.1-0.5)

^{q}with / without abdominal RT; *hybrid chemotherapy including an anthracycline plus an alkylator

10511 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Mortality following breast cancer in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *First Author: Chaya S. Moskowitz, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Female childhood cancer survivors have a high risk of subsequent breast cancer (BC). Little is known about mortality following BC in this population. **Methods:** Risk of all-cause and BC-specific mortality were estimated in 274 5-year survivors of childhood cancer diagnosed with invasive (71% ER+) or in situ BC. Median age at first BC diagnosis was 38 years (range 20-58); median follow-up after BC was 8 years (range 0-26), 195 (71%) were treated with chest radiation (RT) for their primary cancer. Hazard ratios (HRs) were estimated from cause-specific proportional hazards frailty models comparing mortality with a population-based control group with BC selected in a 1:5 ratio from SEER matched on sex, race, stage, age and calendar year of BC diagnosis (69% ER+). Cumulative incidence was estimated accounting for competing risks. **Results:** 92 childhood cancer survivors died, 49 from BC. Risk of death from any cause after a BC diagnosis was higher among childhood cancer survivors compared to controls (HR = 2.2, 95% CI 1.7-3.0) and remained elevated after adjusting for BC treatment with RT (HR = 2.2, 95% CI 1.7-3.1), chemotherapy (HR = 2.3, 95% CI 1.8-3.2) or both (HR = 2.4, 95% CI 1.7-3.2). Risk of death after diagnosis with early stage BC was elevated compared to controls (Stage 0, 1 & 2, n = 200, HR = 2.6, 95% CI 1.9-3.7) but BC-specific mortality was not significantly higher among survivors (HR = 1.4, 95% CI 0.9-2.0). Ten-year cumulative incidence of all-cause mortality was 33% (95% CI 27-40%) among survivors and 16% among controls (95% CI 14-18%); for BC-specific mortality it was 20% (95% CI 15-25%) and 13% (95% CI 11-16%) and for deaths from other causes was 13% (95% CI 9-19%) and 3% (95% CI 2-4%), respectively. Other causes of deaths among childhood cancer survivors with BC included other subsequent neoplasms (44%) and cardiovascular disease (26%). **Conclusions:** Mortality after BC is high in childhood cancer survivors compared to women with BC in the general population, even in the setting of early stage disease. Future research should determine if this increased mortality reflects co-morbidity, limited therapeutic options and/or missed opportunities for risk-reducing interventions at the time of BC diagnosis.

10512 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Association of exercise with late mortality in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor study. *First Author: Jessica Scott, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Adult survivors of childhood cancer are at excess risk for late mortality compared to the general population. Whether exercise attenuates this risk is not known. **Methods:** We examined the association between self-reported vigorous exercise [metabolic equivalent-hrs/week (MET-h/wk)] and cause-specific late mortality among 15,450 adult survivors participating in the Childhood Cancer Survivor Study using multivariable piecewise exponential regression analysis to estimate rate ratios (RR). Longitudinal change in vigorous exercise was evaluated among a subset of 5689 survivors. **Results:** During a median follow-up of 10 years (interquartile range: 15 years), 1063 deaths (811 health-related, 120 recurrence/progression of primary cancer, 132 external/unknown causes) were documented. At 15 years the cumulative incidence of all-cause mortality was 11.7% (95% CI, 10.57-12.80) for 0 MET-h/wk, 8.6% (95% CI, 7.42-9.72) for 3 to 6 MET-h/wk, 7.4% (95% CI, 6.23-8.57) for 9-12 MET-h/wk, and 8.0% (95% CI, 6.50-9.45) for 15-21 MET-h/wk ($P < 0.001$). There was a significant inverse association across quartiles of exercise and all-cause mortality after adjusting for chronic health conditions and treatment exposures (P_{trend}= 0.023). Among a subset of 5689 survivors, increased exercise (+7.9 ± 4.4 MET-h/wk) over an 8-year period was associated with a 40% reduction in all-cause mortality rate compared with maintenance of low exercise (RR = 0.60; 95% CI, 0.44 to 0.82, p = 0.01). **Conclusions:** Vigorous exercise in early adulthood and increased exercise over eight years is associated with lower risk of late mortality in adult survivors of childhood cancer.

10513 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Impact of exercise on psychological burden in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Emily S. Tonorezos, Adult Long Term Follow-Up Program, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: Adult survivors of childhood cancer are at risk for adverse psychological outcomes. Whether exercise can attenuate this risk is unknown. **Methods:** Using a longitudinal design, 6199 CCSS participants (median [range] age 34 years [22-54] and median [range] age at diagnosis 10 years [0-21]) completed a baseline questionnaire assessing vigorous exercise, medical and psychological conditions. Psychological outcomes were evaluated in a subsequent questionnaire a median of 7.8 years later (range 0.1-10). Primary outcome was overall psychological burden, defined as: symptom level above the 90th percentile of population norms on the Brief Symptom Inventory-18 for depression, anxiety, or somatization ; cancer-related pain; cognitive impairment; or poor quality of life. Log-binomial regression estimated associations between exercise [total metabolic equivalent-hrs·wk^{-1} (MET-hrs·wk^{-1})] and these outcomes adjusting for cancer diagnosis/treatment, demographics, and baseline medical/psychological illness. **Results:** The prevalence of overall psychological burden at follow-up was 71.3%. The prevalence of depression was 11.4%, anxiety 7.4%, and somatization 13.9%. Among those not engaged in vigorous exercise, the prevalence of overall psychological burden was 75.9%, compared to 68.6% in those who exercised ≥3 MET-hrs·wk^{-1} ($p < 0.001$). Compared to 0 MET-hrs·wk^{-1} of vigorous exercise, the adjusted prevalence ratio (PR) for overall psychological burden was 0.98 (95% CI, 0.95-1.01) for 3-6 MET-hrs·wk^{-1}, 0.93 (95% CI, 0.90-0.96) for 9-12 MET-hrs·wk^{-1}, and 0.94 (95% CI, 0.90-0.98) for 15-21 MET-hrs·wk^{-1}. Compared to not reporting vigorous exercise, 9 to 12 MET-hrs·wk^{-1} was associated with an adjusted PR of 0.76 (95% CI, 0.62-0.93; p = 0.004) for depression and 0.79 (95% CI, 0.66-0.94; p = 0.003) for somatization. Vigorous exercise was associated with higher cognitive function in domains of task completion, organization, and working memory (p's < 0.05) but was not associated with cancer pain or quality of life. **Conclusions:** Vigorous exercise is associated with lower psychological burden and less cognitive impairment in long-term survivors of childhood cancer.

10514 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Patient-level predictors of lack of healthcare provider recommendation for human papillomavirus (HPV) vaccination as reported by childhood cancer survivors and their families. *First Author: Jocelyn M York, University of Alabama at Birmingham, Birmingham, AL*

Background: Childhood cancer survivors are at increased risk for HPV-related morbidities, yet HPV vaccine initiation rates in survivors are low. Lack of healthcare provider recommendation for HPV vaccination is strongly associated with vaccine non-initiation (OR = 10.8, 95%CI, 6.5-18.0; *J Clin Oncol*, 2017; 35:3582-90). We aimed to examine patient-level predictors of lack of provider recommendation for HPV vaccination as reported by childhood cancer survivors and their families (hereafter referred to as NO RECOMMENDATION). **Methods:** Cancer survivors age 9-26y and 1-5y post-treatment completed a cross-sectional survey (parent-completed for survivors age 9-17y). NO RECOMMENDATION was evaluated as the outcome of interest in a multivariate logistic regression model that included relevant patient-level sociodemographic, clinical, and vaccine-related variables. **Results:** Participants included 955 survivors; 54% were male, 66% were non-Hispanic white, 59% had leukemia/lymphoma. Survivor age at survey (Mean±SD) was 16.3±4.7y; time off therapy was 32.8±14.7 months; 72% of participants reported NO RECOMMENDATION. Patient-level predictors associated with increased odds of NO RECOMMENDATION included perceived lack of insurance coverage for vaccine (OR = 3.7, $p < .0001$), male sex (OR = 3.2, $p < .0001$), black race (OR = 2.4, p = .003), and endorsement of barriers to vaccination (e.g., time, cost; OR = 1.8, p = .003). Predictors associated with decreased odds of NO RECOMMENDATION included older age (13-17y: OR = 0.3, $p < .0001$; 18-26y: OR = 0.3, $p < .0001$; referent group: 9-12y), non-Christian religion (OR = 0.4, p = .02), parent-child communication regarding HPV vaccine (OR = 0.6, p = .0001), and endorsement of social influences (e.g., opinions of friends/family) as important in HPV vaccine decision-making (OR = 0.8, p = .03). **Conclusions:** Nearly 3 in 4 childhood cancer survivors reported not receiving a healthcare provider recommendation for HPV vaccination. Interventions targeted to increase vaccine uptake should focus on factors influencing the provision of provider recommendation for HPV vaccination to all young cancer survivors.

10515 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Targeted resequencing of pediatric rhabdomyosarcoma: report from the Children's Oncology Group, the Children's Cancer and Leukaemia Group, The Institute of Cancer Research UK, and the National Cancer Institute. *First Author: John Frederick Shern, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD*

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of childhood. Despite aggressive therapy, the 5-year survival rate for patients with metastatic or recurrent disease remains poor. Genomic studies by our group and others have identified 39 genes as known or potential somatic driver mutations in RMS. We therefore performed a large-scale validation study through an international consortium to more accurately determine the incidence of driver mutations and their association with clinical outcome. **Methods:** Formalin fixed paraffin embedded material was collected from patients enrolled on Children's Oncology Group trials and UK patients enrolled on MMT trials. Pathology was reviewed centrally and extracted DNA subjected to targeted capture sequencing. Mutations, indels, deletions, gene amplifications and genome-wide copy number variation was called using analysis pipelines developed at the NCI. **Results:** DNA from six hundred and thirty-one patients was suitable for analyses. A median of 2 variant calls were found per tumor. Mutation of a RAS isoform was found in 29% of all fusion negative cases, mutation of a RAS pathway member was seen in greater than 50% of cases, and 24% had no putative driver mutation identified. *BCOR* (15%), *NF1* (11%) and *TP53* (12%) mutations were found at a higher incidence than previously reported. Interestingly, mutations in *HRAS* were notable in the infant population whereas those in *NRAS* were enriched in adolescents. Among infants < 1 year, 71% of cases harbored a mutation in *HRAS* or *KRAS*. In contrast, mutation of *MYOD1* was associated with an older age and parameningeal primary site. Finally, 29% of the evaluated tumors harbored multiple driver mutations consistent with subclonal variation and tumor heterogeneity in fusion negative RMS. Detailed analyses of the association of mutations with anatomical location, histology and outcome are currently underway. **Conclusions:** This is the largest genomic characterization of clinically annotated patients with RMS tumors to date and adds to the understanding of the biology of this disease.

10516 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

A prospective study of pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN0321. *First Author: James I. Geller, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: Although renal cell carcinoma (RCC) is the second most common pediatric kidney cancer, no previous prospective clinical trials have been conducted. AREN0321 tested the hypothesis that RCC with localized completely resected disease, including those with lymph node involvement, has a favorable prognosis without adjuvant medical therapy. **Methods:** From 2006 to 2012, patients up to age 30 years with centrally reviewed pathology confirmation of RCC were prospectively enrolled. Patients with completely resected disease were followed without adjuvant therapy, independent of TNM stage. **Results:** 62 eligible patients enrolled (35 male: 27 female; median age 13.2 yr (range 0.17 - 22.1)). Histology was TFE-associated RCC (TRCC; 33, 53.2%), RCC NOS (21, 33.9%), papillary RCC (5, 8.1%) and Renal Medullary Carcinoma (RMC; 3, 4.8%). 58 (93.5%) patients had all disease completely resected at diagnosis with stages 1 (27, 43.5%), 2 (7, 11.3%), and 3 (24, 38.7%) disease. Three patients with stage 4 (M1) and one with stage 3 had an incomplete resection. Surgery included radical nephrectomy (50) and partial nephrectomy (12). Lymph node (LN) status was N0 (21 (33.9%)), N1 (19 (30.6%)), and Nx (22 (35.5%)). Histology for patients with N1 disease was: TRCC (13, 68.4%), RCC NOS (4, 21.1%) and RMC (2, 10.5%). Four-year EFS and OS for the completely resected group were: 87.2% (95% CI 77.0 – 97.4) and 94.6% (87.6-100), respectively; and by stage were: 1 (92.4% (80.7-100) and 96.2% (87.7-100)), 2 (100% and 100%), and 3 (77.6% (57.6 – 97.6) and 91.3% (77.1-100)) (EFS p-value 0.294, OS p-value 0.722). Four-year EFS and OS by histology for the overall group were: TRCC: 87.7% (74.2-100) and 93.6% (83.3-100), papillary RCC: 100% and 100%, RCC NOS: 87.7% (70.3-100) and 100%, and RMC: 33.3% (0-86.7) and 33.3% (0-86.7). For the 15 patients with completely resected N1M0 disease (of which 13 had TRCC), the four-year EFS and OS were 86.7% (64.7-100) and 93.3% (76.6-100), respectively. **Conclusions:** Favorable outcomes can be achieved without adjuvant therapy in children and adolescents with completely resected RCC, including those with locally advanced disease and lymph node involvement. Clinical trial information: NCT00335556.

10517 Oral Abstract Session, Sun, 8:00 AM-11:00 AM

Hope and benefit-finding among adolescents and young adults with cancer: Results from the PRISM randomized controlled trial. *First Author: Abby R. Rosenberg, Seattle Children's Cancer and Blood Disorders Center, Seattle, WA*

Background: Adolescents and Young Adults (AYAs) with cancer are at risk for poor psychosocial outcomes, perhaps because they have not acquired the skills to navigate illness. We previously reported that a novel, brief, age-appropriate, skills-based intervention ["Promoting Resilience in Stress Management" (PRISM)] was associated with improved quality of life and psychological distress. In this secondary analysis, we aimed to determine if PRISM also improved targeted skills of hopeful thinking, benefit-finding, and goal-setting. **Methods:** PRISM consists of 4, 30-60 minute, in-person, 1:1 sessions plus a facilitated family-meeting targeting stress-management, goal-setting, cognitive reframing, and meaning-making. English-speaking AYAs (ages 13-24 years) with cancer were randomized to receive either PRISM or psychosocial usual care (UC). Participants completed surveys upon enrollment and 6 months later. Mixed effects regression models estimated associations between PRISM and hopeful patterns of thought (Snyder Hope Scale), benefit-finding (benefit-finding scale for children), and goal-setting (queried with open-ended items about short- and long-term goals, then evaluated by 3 blinded coders with a 10-point, *a priori* defined tool to identify specific, measurable, and actionable goals) at 6 months. **Results:** Of N = 92 enrolled AYAs (48 PRISM and 44 UC), 73% were 13-17 years-old, 43% were female, and 62% had a diagnosis of leukemia or lymphoma. Attrition was similar in each arm and primarily due to medical complication or death; n = 36 (72%) PRISM and n = 38 (76%) UC participants completed 6 month surveys. After adjusting for baseline scores, PRISM was associated with improved hope and benefit-finding with moderate-to-large effect sizes: Hope: +3.6 points, 95% CI 0.7,6.4, Cohen's *d* effect size = 0.6, p = 0.01; Benefit-finding: +3.1 points, 95% CI 0.0,6.2, *d* =0.6, p = 0.05. We did not detect changes in goal-setting (Goals: -0.5 points, 95% CI -1.2,0.3, *d* = -0.3, p = 0.23). **Conclusions:** A novel intervention targeting skills for AYAs with cancer was associated with significant improvements in hope and benefit-finding, 2 key skills which may mitigate later psychosocial risk. Clinical trial information: NCT023408.

10518 Poster Discussion Session; Displayed in Poster Session (Board #191), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Matched targeted therapy for pediatric patients with relapsed, refractory or high-risk leukemias: A report from the LEAP consortium. *First Author: Yana Pikman, DFCI, Boston, MA*

Background: Despite the remarkable pace in characterizing the genomics of acute leukemias, integration of sequencing into clinical practice is lagging. With increased availability of targeted therapies, optimism exists in matching a patient's genetic lesion to a targeted drug with goals of improving survival and decreasing toxicity. **Methods:** We established the first pediatric leukemia genomics consortium, Leukemia Precision-based Therapy (LEAP) Consortium, which includes 13 major US pediatric cancer institutions. Using a combination of a next-generation sequencing panel and gene fusion testing, we are conducting a feasibility clinical trial aimed to identify, in real-time, actionable alterations with a matched targeted therapy for patients with high-risk leukemias. **Results:** To date, we have enrolled 84 pediatric patients. Based on targeted sequencing results, 68% of the patients had a recommendation for targeted therapy, tiered based on the level of evidence for the mutation within the patient's specific leukemia type. Of the 44 patients with clinical follow-up data, 5 (11%) have had changes in therapy based upon our genomic results. Targetable lesions identified include mutations resulting in RAS signaling pathway activation and mutations/translocations involving *ABL1*. These genomic data refined diagnosis and supported additional germline assessment in a subset of patients. We are establishing mouse patient-derived xenograft models in which to conduct correlative preclinical targeted therapy studies. We are further deploying *in vitro* drug and siRNA sensitivity assays to study response of leukemia cells to targeted therapies and to assess correlation with underlying genetic events. **Conclusions:** This first multi-institutional prospective pediatric leukemia genomics trial brings state-of-the-art clinical genetic testing to pediatric patients with leukemia, impacting diagnosis, treatment and selection of patients for germline testing. Moreover, our collaboration brings together cutting edge correlative biology studies to impact pediatric leukemia discovery and to inform future genomics-guided therapeutic trials and drug discovery efforts. Clinical trial information: NCT02670525.

10519 Poster Discussion Session; Displayed in Poster Session (Board #192), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Aqueous humor genomics predicts eye salvage in retinoblastoma. *First Author: Liya Xu, University of Southern California, Los Angeles, CA, US*

Background: Retinoblastoma was one of the first cancers to demonstrate a genetic basis to the development of cancer. However, unlike many cancers, Rb cannot be directly biopsied due to the high risk of extraocular cancer spread. Therefore, unless the eye is enucleated, tumor tissue is not evaluated for genetic and genomic changes and these alterations are not used to inform diagnosis or prognosis for this disease. However, in a recent publication in JAMA Ophthalmology,(Berry JL, Xu L et al. JAMA Ophthalmol, 2017) we demonstrated that tumor-derived cell-free DNA can be extracted from the aqueous humor (AH) of Rb eyes, which is safe to extract even with active intraocular disease. The purpose this current study was to identify somatic chromosomal copy number alterations (sCNA) in tumor-derived cell-free DNA in the AH of Rb eyes and to correlate with clinical outcomes particularly tumor relapse requiring enucleation. **Methods:** AH was extracted via paracentesis from Rb eyes during intravitreal injection of chemotherapy or enucleation. Shallow whole genome sequencing was performed to assess for cell-free tumor DNA fractions and highly-recurrent sCNAs in Rb which include gain of 1q, 2p, 6p and loss of 13q and 16q. Globe salvage was recorded. **Results:** 26 patients were included; 3 patients had both eyes included for 29 eyes. From these, 63 samples of AH were analyzed; 5 post-enucleations and 58 during intravitreal chemotherapy injection. Ultimately 13 eyes required enucleation and 16 eyes were salvaged. Follow-up ranged from 8-43 months (median 17 months). 6p gain was the most common sCNA found in 10/13 enucleated eyes (77%) compared to 4/16 (25%) of salvaged eyes (p = 0.009). The mean amplitude of 6p gain was 1.47 in the enucleated group versus 1.07 in the salvaged group (p = 0.001). The presence of a detectable sCNA in enucleated eyes was 92% while in salvaged eyes was 38% (p = 0.022). The probability of globe salvage was improved in eyes without detectable sCNAs (p = 0.0028). **Conclusions:** This is the first study to correlate globe salvage with highly-recurrent sCNAs in the AH from Rb eyes. This study suggests that not only can the AH serve as a surrogate to tumor biopsy but could contribute to prognostication of tumor response to therapy.

10520 Poster Discussion Session; Displayed in Poster Session (Board #193), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Parallel genomic and immune profiling of relapsed and metastatic osteosarcoma to reveal bases of low immunogenicity. *First Author: J Andrew Livingston, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Despite the high levels of point mutations, rearrangements, and other genomic instability events such as kataegis and chromothripsis, immune checkpoint inhibitors have shown limited clinical activity in osteosarcoma (OS). We completed in-depth parallel genomic and immune profiling in a cohort of 48 patients with high-grade osteosarcoma (relapsed or metastatic in 42) to determine potential mechanisms of primary resistance to immunotherapy and identify strategies to enhance immunogenicity. **Methods:** We utilized whole-genome sequencing (average coverage 75X), RNA sequencing, and immune profiling by T-cell receptor (TCR) sequencing and immunohistochemistry to analyze mutation load, cytotoxic and suppressive cell activity, relevance of checkpoint-related genes, and characterize immune infiltration in a clinically annotated set of primary resection, local relapse, and metastatic OS tumor specimens and matched normal tissue. **Results:** We observed high levels of gene rearrangements in approximately 60% of OS patient samples, however transcriptome sequencing showed a lack of fusion transcript expression from these rearrangements. Further, $<$ 10% of point mutations were expressed, generating few neoantigens. Immune-related pathways, including immunosuppressive *PD-L1* were upregulated in samples from older patients as compared to younger patients. Higher numbers of deleted genes were associated with higher immune infiltrate. Overall TCR clonality was low and did not correlate with mutation burden. T cell clonality did not differ by PTEN or HLA status. **Conclusions:** In the majority of OS, there is a lack of neoantigen expression and presentation. However, a subset of patients exhibit increased PD-L1 expression associated with lower levels of T-cell clonailty, for which immune checkpoint blockade may be beneficial and warrants further investigation.

10521 Poster Discussion Session; Displayed in Poster Session (Board #194), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The influence of surgical excision on survival in high-risk neuroblastoma revisited after introduction of ch14.18/CHO immunotherapy in the HR-NBL1/SIOPEN trial. *First Author: Keith Holmes, St George's Hospital, London, United Kingdom*

Background: The effect of complete macroscopic excision (CME) of the primary tumour on event free survival (EFS) in high-risk neuroblastoma remains controversial. We therefore investigated the influence of CME in patients enrolled on the HR-NBL1/SIOPEN Trial and compared the effect in the pre immunotherapy era. **Methods:** Eligibility criteria were: inclusion in HR-NBL1/SIOPEN Trial between 2002-2015, stage 4 disease; completion of Rapid COJEC induction $\pm$ 2 courses of TVD; no progression/relapse/death; no prior attempt at resection and complete operation data. Intended therapy following operation comprised: HDT/SCT (BuMel or CEM, after 2011 BuMel), 21Gy radiotherapy to the primary site, 13-cis RA and after 2009 ch14.18/CHO antibody $\pm$ IL2 in addition. 1504 patients fulfilled these criteria; 737 were treated prior to ch14.18/CHO availability (2002-2009) and 767 in the immunotherapy era. Median observation time was 4.9 years (0.1-14 years). **Results:** CME was achieved in 77%, incomplete macroscopic excision (IME) in 21% and 2% were inoperable (0E). Surgical mortality was 0.46% (7/1504). Five year event-free survival (5y-EFS $\pm$ standard error) was 39%$\pm$2% with CME and 30%$\pm$3% with IME or 0E ($p = 0.002$). The cumulative incidence of local relapse (CILR) was 0.17$\pm$0.01 (CME); 0.31$\pm$0.03 (IME) and 0.42 $\pm$0.10 (0E) ($p < 0.001$). 88% of patients received radiotherapy (78% CME; 21% IME and 1% 0E). 5y-EFS for patients with CME who received radiotherapy was 44$\pm$2%, but 31$\pm$6% without (reasons included very young age and very large primary tumours) ($p = 0.013$) and 35$\pm$3% with less than CME compared to 20$\pm$1% without radiotherapy (NS). CILR was 0.14$\pm$0.01 in patients with CME who received radiotherapy compared to 0.28$\pm$0.06 in patients who did not ($p = 0.005$). 5y-EFS was significantly higher (42$\pm$2%) for patients enrolled after 2009 compared to before (32$\pm$2%) ($p = 0.000$). 5-y EFS for patients after 2009 who achieved CME was 45$\pm$2% vs. 36$\pm$2% after IME and 26$\pm$13% after 0E respectively ($p = 0.034$); compared to 33$\pm$2% vs. 26$\pm$4% (IME) and 17$\pm$11% (0E) ($p = 0.059$) prior to 2009. **Conclusions:** In the immunotherapy era, CME in Stage 4 patients who received local radiotherapy resulted in improved 5-EFS. Clinical trial information: NCT01704716.

10522 Poster Discussion Session; Displayed in Poster Session (Board #195), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

A phase I NANT study of lenalidomide with ch14.18 and isotretinoin (RA) in patients with refractory/recurrent neuroblastoma (RR-NB). *First Author: Araz Marachelian, Children's Hosp Los Angeles, Los Angeles, CA*

Background: Ch14.18 (dinutuximab) increases event free and overall survival in patients with high-risk NB when given in a regimen with GM-CSF/IL-2. However, this therapy has significant toxicities, and 40% of patients relapse. LEN has immunomodulatory effects in pediatric solid-tumor patients and is well tolerated. The combination of LEN with ch14.18, was supported by preclinical data that demonstrate the activity in NB. We conducted a phase I trial to determine the tolerability of LEN with ch14.1 and RA in patients with RR-NB. **Methods:** LEN dose escalation followed a 3+3 design (25, 50, 75 and 100mg /m2/day). The administration schedule is: LEN days 1-21, ch14.18 (17.5mg/m2/day) days 8-11, and RA (160mg/m2/day) days 15-28 (Dose level 2-5). **Results:** 27 patients enrolled with a median age of 8 years (range: 3-20), of whom 23 were evaluable for dose escalation. The median number of courses was 4 (range 1–12). No MTD was identified. There were 7 patients with dose limiting toxicities (course): grade 3 diarrhea(C1), grade 3 diarrhea/delayed neutrophils(C1), delayed neutrophils(C2), grade 4 ALT(C8), anaphylaxis(C5), delayed platelets(C5), delayed neutrophils(C4), delayed neutrophils/grade 4 sinus bradycardia(C6). Overall regimen was tolerable with no grade 3 capillary leak, 7% grade 3 hypotension and 4% grade 3 fever. there was 1 complete response, 3 partial responses, 3 minor responses, 8 stable diseases and 6 progressive diseases in 21 patients evaluable for response. Immunomodulation was seen with statistically significant increases in frequency of circulating effector NK cells, an increase in the frequency of CD4+ (T-helper) effector memory T lymphocytes and increased antibody dependent cytotoxicity (ADCC) in patients. Plasma protein concentrations demonstrated statistically significant therapy-associated increases in granzyme B, IL-15, IFNg, CXCL9, CXCL10, CXCL11, sIL-2R, and GM-CSF as well as IL-6, IL-8, IL-10, MCP-1, and M-CSF. **Conclusions:** LEN 100 mg/m2 QD for 21 days per cycle is tolerable with ch14.18 and RA, and is associated with antitumor response and immunomodulatory effects. Further studies are warranted in studying this combination. Clinical trial information: NCT01711554.

10523 Poster Discussion Session; Displayed in Poster Session (Board #196), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

ROR1-specific CAR for neuroblastoma using *sleeping beauty*-modified t cells. *First Author: Fiorela Natali Hernandez Tejada, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Adoptive transfer of chimeric antigen receptor (CAR)-modified T cells is predicted to provide a treatment option for advanced/refractory neuroblastoma. One potential target, receptor tyrosine kinase-like orphan receptor-1 (ROR1), is a cell surface protein that is aberrantly expressed on solid organ tumors including neuroblastoma. **Methods:** A ROR1-specific CAR was developed by linking a ROR1-specific scfv to a mutated IgG4-Fc stalk and co-stimulatory endodomains CD3-zeta and CD28 (ROR1R*CD28 CAR). Human T cells were genetically modified to express the ROR1-CAR by electro-transfer of DNA plasmids from *Sleeping Beauty* system and (i) directly injected the next day under technology designated as point-of-care (P-O-C) or (ii) numerically expanded for 14 days on $ROR1^+$ activating and propagating cells (AaPC). Redirected specificity for ROR1 was assessed *in vitro* by chromium release assay and cytokine release. To demonstrate therapeutic potential, the ROR1R*CD28 CAR manufactured under the two conditions, were infused into NSG mice bearing disseminated CHLA 255 $ROR1^+$ neuroblastoma cells expressing firefly luciferase. **Results:** The day after electroporation, T cells had 20-30% CAR expression from episomal and integrated transgene and by day 14, 90% of $CD3^+$ T cells expressed CAR. CAR^+ T cells were able to lyse neuroblastoma lines and produce IFN-gamma in a ROR1-specific manner. *In vivo*, POC and 2-stim manufactured CAR^+ T cells both exhibited similar antitumor activity. This antitumor effect was confirmed by histological evaluation of metastatic liver lesions and correlated with the presence of circulating human $CD3^+$ T cells. **Conclusions:** Genetically modified T cells with CAR infused after being manufactured under P-O-C or propagated on AaPC can specifically target and lyse neuroblastoma cells significantly reducing the tumor burden in mice. These data reveal that shortening the manufacturing time from 14 days to 1 day result in anti-tumor effects with CARs that signal via chimeric CD28. Shortening the manufacturing from 14 days to 1 day is predicted to broaden the application of CAR^+ T cells as this avoids the need for *ex vivo* tissue culture and thus reduced the costs and expense of manufacture.

10524 Poster Discussion Session; Displayed in Poster Session (Board #197), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Survival and delayed effects of risk-stratified hepatoblastoma patients treated in the JPLT-2 trial. *First Author: Eiso Hiyama, Hiroshima University, Hiroshima-Shi, Japan*

Background: The Japanese Study Group for Pediatric Liver Tumor (JPLT) -2 trial (2000-2012) has been conducting to evaluate the efficacy of the CITA regimen, consisting of cisplatin/pirarubicin, in patients with hepatoblastoma (HB) stratified by risk according to the PRETEXT staging system. **Methods:** In JPLT-2, PRETEXT I/II tumors were initially resected or underwent two courses of low-dose CITA before resection and an additional four courses of CITA after resection. Of the PRETEXT III/IV or metastatic tumors, those that responded to two courses of CITA underwent four more courses of CITA, and the non-responsive tumors received four courses of a second-line regimen consisting of ifosfamide, pirarubicin, etoposide, and carboplatin. Highly metastatic or refractory tumors were treated with high-dose chemotherapy and stem cell transplantation. **Results:** Among the 360 patients who were eligible in the JPLT-2 trial, 5-year event-free/overall survival rates of patients with PRETEXT I/II/III HB were 94/82%, while those of patients with PRETEXT IV and metastatic HB were 65.4/74.6% and 44.3/60.9%, respectively (Table). Except for 40 patients who underwent primary resection, complete resection of the primary tumor after CITA was achieved in 86%, 66%, and 56% of patients with PRETEXT II/III, PRETEXT IV, and metastatic tumors, respectively. The outcomes of the patients who received high-dose chemotherapy did not improve. Of those patients who survived, 68 experienced late-phase complications with otoxicity, 12 cardiotoxicity, 5 maldevelopment, and 12 second malignancies. **Conclusions:** Compared with other multicenter cooperative protocols, treatment with the CITA regimen achieved similar rates of survival and resectability. However, the rates of otoxicity and a second malignancy were higher and that of cardiotoxicity lower compared with other studies. Reduction of the chemotherapy dose should be considered in low-risk patients, while more promising strategies such as novel targeted drugs should be developed for intermediate- and high-risk patients with HB. Clinical trial information: UMIN000001116.

Summary of JPLT-2.

PRETEXT	(n)	5y- EFS (%)	5y-OS (%)
I M-	22	75.2	95.5
II M-	108	83.5	90.5
III M-	113	80.0	91.5
IV M-	56	65.4	74.6
M	61	44.3	60.9

M: metastasis

10525 Poster Discussion Session; Displayed in Poster Session (Board #198), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

KEYNOTE-051: An update on the phase 2 results of pembrolizumab (pembro) in pediatric patients (pts) with advanced melanoma or a PD-L1–positive advanced, relapsed or refractory solid tumor or lymphoma. *First Author: Birgit Geoerger, Gustave Roussy, Villejuif, France*

Background: In the phase 1 portion of KEYNOTE-051 (NCT02332668), the 2-mg/kg-Q3W dose of pembro was identified as the pediatric recommended phase 2 dose. We provide an update on the safety and efficacy of this dose by tumor type in the ongoing phase 2 trial. **Methods:** Pts aged 6 mo to $<$ 18 y with advanced melanoma or a PD-L1–positive, advanced relapsed/refractory solid tumor or lymphoma and measurable disease per RECIST v1.1 received pembro 2 mg/kg Q3W until confirmed disease progression per irRECIST by investigator review, intolerable toxicity, or pt/investigator decision to discontinue. Key efficacy end points were ORR and PFS per RECIST v1.1 by investigator and OS (data cutoff Oct 10, 2017). **Results:** 689 of 748 prescreened pts had PD-L1–evaluable tumors. Of these, 229 (33.2%) were PD-L1–positive; 125 pts (median age, 13 y [range, 1-17]) were enrolled and treated (10 Hodgkin lymphoma [HL]; 115 other tumors). Median follow-up was 5.7 mo (range, 0.2-29). Primary diagnoses were other non–central nervous system (CNS) solid tumors (46%), sarcoma (19%), CNS tumors (26%), and lymphoma (9%). Seven (6%) pts experienced grade 3-5 treatment-related AEs; of these, 2 (1.6%) discontinued (1 due to increased aspartate aminotransferase; 1 with renal medullary carcinoma died of treatment-related pulmonary edema). No major untoward effects on the developing immune system were observed. One pt (10.0%) with HL achieved CR and 5 (50%) achieved PR. Six (5.2%) pts with other tumors achieved prolonged PR (2 adrenocortical carcinoma and 1 each epithelioid sarcoma, mesothelioma, malignant ganglioglioma, and lymphoepithelial carcinoma). ORR was 60.0% (95% CI, 26.2-87.8) in pts with HL and 5.2% (95% CI, 1.9-11.0) in pts with all other tumor types. Median PFS was 12.2 mo in HL and 1.9 mo in any other tumor type; 12-mo PFS was 56.3% and 8.3%, respectively. Four (40.0%) pts with HL and 19 (16.5%) with any other tumor type survived $\geq$12 months. **Conclusions:** Pembro was well tolerated and showed response in HL and in a few rare tumor types, which warrants further study. Enrollment in KEYNOTE-051 is ongoing. Clinical trial information: NCT02332668.

10526 Poster Discussion Session; Displayed in Poster Session (Board #199), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The association between atopy and Hodgkin's lymphoma in teenagers and young adults: A UK nationwide case control study. *First Author: Meena Rafiq, University College London (UCL), London, United Kingdom*

Background: Hodgkin's Lymphoma (HL) is the commonest cancer in teenagers and young adults (TYAs). Incidence in this age group has been increasing since the early 1990s in the UK, Australia, Canada and several US states. The cause in the majority of cases remains unknown. Previous studies have shown conditions involving impaired immune regulation, including HIV, immunosuppressive treatment and some autoimmune conditions, are associated with increased HL risk. However, few studies have investigated the link between atopy, the commonest form of childhood immune dysregulation, and HL and the results have been conflicting and inconclusive. This study uses large scale, UK data to investigate the association between atopic disease and immunosuppression with development of HL in TYAs. **Methods:** We conducted a case control study using primary care data from the UK Clinical Practice Research Database linked to hospitalization data. 1,238 cases with HL diagnosed between the ages of 0-49 years were individually matched using concurrent sampling to six controls each by age, sex and follow up time (7,428 controls). Multivariable logistic regression was used to investigate the association between atopic diseases (asthma, eczema, hay fever) and immunosuppression with HL incidence. **Results:** A prior diagnosis of asthma was associated with 26% increased odds of developing HL (Adjusted Odds Ratio (AOR):1.26, 95%CI 1.08-1.49 p = 0.005). There was weak or no evidence for an association between eczema or hay fever and HL (AOR:1.15, 95%CI 0.98-1.34 p = 0.09; AOR:0.88, 95%CI 0.73-1.05 p = 0.15, respectively) or that HL risk was increased in individuals with more than one atopic diagnosis (p = 0.07). Consistent with previous studies, immunosuppressed individuals had 14 times the odds of developing HL (AOR:13.79, 95% CI 5.67-33.50 p $<$ 0.001). **Conclusions:** This study has identified asthma as a risk factor for developing HL in early life. These findings add to the growing evidence that immune dysregulation is involved in development of HL in TYAs. Understanding the immune components and pathways underlying this relationship could help uncover markers for HL detection, recurrence and to develop new therapeutic interventions.

10527 Poster Discussion Session; Displayed in Poster Session (Board #200), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

Intravenous fosaprepitant for the prevention of chemotherapy induced vomiting in children: A double blind placebo controlled, phase III randomized trial. *First Author: Archit Joshi, Cancer Institute (WIA), Chennai, India*

Background: Fosaprepitant, is a Neurokinin-1 (NK-1) receptor antagonist, approved in adults for the prevention of vomiting associated with administration of moderately or highly emetogenic chemotherapeutic agents. The efficacy and safety of fosaprepitant in children is not known. Therefore, we conducted a phase III randomized trial to assess the safety and efficacy of fosaprepitant in children. **Methods:** The study was a phase III, single centre, double blind, randomized placebo controlled trial. Children aged 1-12 years with documented malignancy, who were scheduled to receive moderately or highly emetogenic chemotherapy, were randomly assigned to arm A (Fosaprepitant) or arm B (Placebo). Arm A received intravenous ondansetron (0.15 mg/kg) plus dexamethasone (0.075 mg/kg) followed by fosaprepitant (3 mg/kg) short infusion. Arm B received intravenous ondansetron (0.15 mg/kg) plus dexamethasone (0.15 mg/kg) followed by normal saline as placebo. Oral ondansetron and dexamethasone were continued for 48 hours after completion of chemotherapy. Primary end-point of the study was the proportion of patients who achieved a complete response (defined as no vomiting, no retching) during the 25–120 hours (delayed phase) after administration of fosaprepitant. Secondary end-points were proportion of patients who achieved complete response during the acute (0–24 hours) and overall phases after administration of fosaprepitant. **Results:** 135 patients were analyzed (68 in fosaprepitant arm and 67 in placebo arm). Complete response rates were significantly higher in fosaprepitant arm compared to placebo arm during acute phase (84% vs. 57%, p $<$ 0.001), delayed phase (79% vs. 51 %, p $<$ 0.001) and overall phases (69% vs. 42%, p = 0.0014). Three (4%) patients in fosaprepitant arm and fourteen (21%) patients in the placebo arm required rescue anti-emetics (p = 0.004). No fosaprepitant related grade 3-4 adverse events were observed. **Conclusions:** Addition of fosaprepitant to ondansetron with dexamethasone is safe and effective for the prevention of chemotherapy induced vomiting in children being treated with moderately or highly emetogenic chemotherapy. Clinical trial information: CTRI/2017/02/007925.

10528 Poster Discussion Session; Displayed in Poster Session (Board #201), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The challenge of pediatric oncology: New business models to accelerate innovation. *First Author: Sonya Das, MIT Laboratory for Financial Engineering, Cambridge, MA*

Background: Few patient populations are as helpless and in need of advocacy as pediatric cancer patients. Pharmaceutical companies have historically faced significant financial disincentives to pursue pediatric oncology therapeutics, including low incidence, high costs of conducting pediatric trials, and a lack of funding for early-stage research. One way to accelerate innovation in this field is the formation of a collaborative business model involving private, public, and philanthropic stakeholders. We explore this idea by simulating the financial returns of a hypothetical collection of pediatric cancer drug projects under several different business structures. **Methods:** Using published studies of pediatric oncology research and the cost of drug development, and existing clinical trials of pediatric oncology therapeutics at clinicaltrials.gov, we identified 77 potential drug development projects to be included in a hypothetical portfolio. The returns of this portfolio were simulated so as to compute the financial returns and risk. Simulated business strategies include combining projects at different clinical phases of development, obtaining partial funding from philanthropic grants, and obtaining government guarantees to reduce risk. **Results:** The purely private-sector portfolio exhibited expected returns ranging from -34.2% to 0.0%, depending on the model parameters assumed. This suggests significant financial disincentives for pursuing pediatric oncology therapeutics and implies that financial support from the public and philanthropic sectors is essential. Phase diversification increases the likelihood of a successful drug, and yielded expected returns of -17.8% to 36.4%. Standard philanthropic grants had a marginal impact on expected returns. Government guarantees were more effective by reducing downside exposure, with returns ranging from -9.5% to 12.8%. **Conclusions:** A combination of financial and business strategies has the potential to maximize expected return while eliminating some downside risk—in certain cases enabling expected returns upwards of 36.4%—which can overcome current financial disincentives and accelerate the development of pediatric oncology therapeutics.

10529 Poster Discussion Session; Displayed in Poster Session (Board #202), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 1:15 PM-2:30 PM

The social value of tisagenlecleucel, a CAR-T cell therapy, for the treatment of relapsed or refractory pediatric acute lymphoblastic leukemia in the United States: What are consequences of treatment delays? *First Author: Julia Thornton Snider, Precision Health Economics, Oakland, CA*

Background: Despite the recent approval of tisagenlecleucel, a CAR-T cell therapy, to treat pediatric and young adult patients with relapsed or refractory acute lymphoblastic leukemia (pALL) in the United States, patients have faced barriers to treatment. This study quantifies the social value of tisagenlecleucel and the value lost from treatment delays. **Methods:** The social value of tisagenlecleucel reflects its economic value to patients and the manufacturer, relative to the standard of care (clofarabine). To quantify the social value, we obtained estimates of life expectancy, quality-adjusted life years (QALYs), and healthcare costs from a cost-effectiveness model for tisagenlecleucel and valued each QALY gained at $150,000. Health and monetary values were discounted at 3.0%, and costs were inflated to 2016 US dollars. The social value of tisagenlecleucel was calculated using a price of $475,000. To quantify lost value from monthly treatment delays, we assumed patients would start clofarabine treatment while awaiting access to tisagenlecleucel. Expected survival for patients on clofarabine was obtained from a clinical trial, and social value and QALYs gained with tisagenlecleucel were calculated conditional on surviving to receive it. **Results:** Our study population included 20 incident cohorts of 500 patients with pALL. Patients treated with tisagenlecleucel gained 37,018 QALYs. The total social value was $4.6 billion. However, when treatment was delayed 1- 3 months, $452 million to $2.1 billion of social value and 3,634 to 17,100 QALYs were lost. Over half the social value, value to patients, and QALYs from tisagenlecleucel were lost when treatment was delayed 4 months. **Conclusions:** Innovative therapies such as tisagenlecleucel have the potential to provide substantial social value from improvements in life expectancy, QALYs and productivity. However, the magnitude of benefit depends upon the ability of patients to access these treatments promptly. Efficient payment mechanisms and sufficient technological capabilities will be required to minimize treatment delays for patients.

10530 Poster Session (Board #203), Sat, 8:00 AM-11:30 AM

Association of regulatory- and helper-T- cells with inferior survival of neuroblastoma patients treated with long-term infusion of ch14.18/CHO combined with interleukin-2. *First Author: Holger N. Lode, University Medicine Greifswald, Greifswald, Germany*

Background: Long-term infusion (LTI) of the anti-GD_2 antibody (Ab) ch14.18/CHO in combination with interleukin-2 (IL-2) prolongs survival in patients (pts) with high-risk neuroblastoma compared to historical controls. We investigated a correlation between lymphocyte subsets, functional immune-parameters and survival in treated patients. **Methods:** 53 pts received 5 cycles (35 days (d)) of $6x10^6$ IU/m^2 subcutaneous IL-2 (d1-5; 8-12), LTI of 100 mg/m^2 ch14.18/CHO (d8-18) and 160 mg/m^2/d oral 13-cis RA (d22-35) in a closed single center program (APN311-303). The counts of cytotoxic NK cells ($CD16^{++}/CD56^{dim}$), helper T cells ($CD3^+/CD4^+$), cytotoxic T cells ($CD3^+/CD8^+$), regulatory T cells (Treg; $CD4^+/CD25^+/CD127^-$) and granulocytes ($CD64^+$) were determined by flow cytometry (cycle 1; d1, 8 and 15). Ab-dependent cellular cytotoxicity (ADCC) was determined and correlation between cell counts and progression-free survival (PFS) was analyzed. **Results:** IL-2 treatment resulted in a strong increase of cytotoxic NK cells, cytotoxic- and helper T cells and Treg on d8 compared to baseline (d1) (2.4-, 3.9-, 2.6- and 15.0-fold increase, respectively). Subsequent combined treatment with IL-2 and ch14.18/CHO did not further increase lymphocyte counts on d15. In contrast, elevation of granulocytes occurred during the combined treatment. We did not observe any correlation between cell counts and ADCC on d15 as well as between cytotoxic NK and cytotoxic T cells and PFS. Similar observations were made for granulocytes. In contrast, pts with low Treg ($\leq$ 138 cells/μl) on d15 (n = 11) showed a better PFS compared to high Treg pts (n = 31) (P = 0.072). The 5-year PFS was 44% (95% CI [0.13, 0.74]) and 19% (95% CI [0.05, 0.33]) for low and high Treg counts, respectively. On d15, pts with low helper T cells (n = 11, $\leq$ 365 cells/μl) also showed an improved PFS compared to those who had high helper T cells (n = 31; P = 0.013). The 5-year PFS was 53% (95% CI [0.23, 0.83]) and 16% (95% CI [0.03, 0.29]) for low and high helper T cell count, respectively. **Conclusions:** IL-2-dependent elevation of helper T- and Treg-cells may negatively affect efficacy of ch14.18/CHO combined with IL-2.

10531 Poster Session (Board #204), Sat, 8:00 AM-11:30 AM

Evaluation of pegaspargase (PEG-ASP) adverse events among adolescents and young adults (AYAs) and younger patients with lymphoid malignancies (LM) at the Children's Hospital of Eastern Ontario (CHEO). *First Author: Nicole Mathies, University of Ottawa, Ottawa, ON, Canada*

Background: PEG-ASP is a common component of the chemotherapy regime for LM, but with significant side effects. The aim of this study was to determine the prevalence of major adverse events: allergic reactions, pancreatitis and thrombosis/hemorrhage among pediatric patients treated with PEG-ASP, and whether there is an association between age and a specific adverse event. **Methods:** Patients aged 0-18 years diagnosed with LM from January 1, 2007 to June 30, 2017 at CHEO, a tertiary care pediatric hospital, were eligible for this retrospective cohort study. A stratified, discrete-time, multivariable Cox regression model was fitted to elucidate the relationship between age at diagnosis and risk to adverse event. Model covariates included sex, body mass index and route of PEG-ASP administration (intravenous versus intramuscular). **Results:** Among 186 eligible patients, the median duration of follow-up was 2.0 years (IQR: 1.0-3.0). There were 34 allergic reactions, 8 cases of pancreatitis, and 32 cases of thrombosis/hemorrhage were observed. Estimates of 4-year cumulative incidence were 18.9% [95%CI:13.9, 25.4], 4.5% [95%CI:2.3, 8.7], and 19.4% [95%CI: 13.8, 26.9] for the three adverse events, respectively. Cox regression revealed a significant association between age at diagnosis and risk of allergic reaction (adjusted Hazards ratio (HR) = 2.18 [95%CI:1.45, 3.28], $p < .001$ for a 5-year increase in age) and risk of pancreatitis (adjusted HR = 1.93 [95%CI:1.02, 3.63], p = 0.04 for a 5-year increase in age), but not the risk of thrombosis/hemorrhage (adjusted HR = 1.25 [95%CI: 0.84, 1.85], p = 0.28, for a 5-year increase in age). The Cox model concordance index was 0.58. **Conclusions:** Evidence of an association between age at diagnosis and 2 of 3 adverse events (allergic reaction and pancreatitis) was revealed among pediatrics patients treated with PEG-ASP. In light of the study results, cautious observation is further warranted when administering PEG-ASP particularly to AYAs with lymphoid malignancies.

10532 Poster Session (Board #205), Sat, 8:00 AM-11:30 AM

Predictors of differential response to induction chemotherapy in high-risk neuroblastoma: A report from the Children's Oncology Group (COG). *First Author: Navin R. Pinto, Seattle Children's Hospital, Seattle, WA*

Background: Induction chemotherapy plays an important role in the management of patients with high-risk neuroblastoma. Predictors of response to Induction therapy itself are largely lacking. We sought to describe clinical and biological features associated with differential response to Induction. **Methods:** Patients from the following COG high-risk trials with at least one disease evaluation during Induction were included: A3973; ANBL02P1; ANBL0532; and ANBL12P1. Response at end-Induction was evaluated by the 1993 International Neuroblastoma Response Criteria. The primary endpoint was partial response (PR) or better. A series of univariate analyses (Fisher's exact or chi-squared tests) were performed to compare response as a function of clinical or biologic predictor variables. For each predictor variable, the Holm-Bonferroni method was used to correct for multiple testing, using an overall α=0.05. A multivariate logistic regression model using significant predictors from univariate analyses was constructed to model PR or better. **Results:** The analytic cohort included 1,242 patients (79.8% with PR or better; 20.8% with CR; 9.1% with PD). Baseline factors significantly associated with a PR or better included age <18 months (87.4% with PR or better vs. 78.7% if older; p=0.0103), age <5 years (82.0% vs. 70.6% if older; p<0.0001), INSS <Stage 4 (89.0% vs. 78.4% if Stage 4; p=0.0016), *MYCN* amplification (85.5% vs. 77.1% if non-amplified; p=0.0006), 1p loss of heterozygosity (LOH; 85.6% vs. 76.0% if no LOH; p=0.0085), no 11q LOH (84.8% vs. 70.9% if 11q LOH; p=0.0004), and high mitosis-karyorrhexis index (MKI); 84.5% vs. 77.5% if low-intermediate MKI; p=0.0098). On multivariate analysis (n=407), the absence of 11q LOH was the only factor that remained significantly associated with PR or better (odds ratio: 1.962 compared to 11q LOH; 95% confidence interval 1.104-3.487; p=0.0216). **Conclusions:** Clinical and biological factors are associated with differential response to Induction chemotherapy. These findings may further improve our ability to predict treatment response.

10533 Poster Session (Board #206), Sat, 8:00 AM-11:30 AM

The addition of cycles of irinotecan/temozolomide (i/T) to cycles of vincristine, doxorubicin, cyclophosphamide (VDC) and cycles of ifosfamide, etoposide (IE) for the treatment of Ewing sarcoma (ES). *First Author: Paul A. Meyers, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Treatment for ES in North America has evolved to include cycles of VDC and IE. A regimen including these 5 agents with interval dose compression has achieved 5 year EFS of 73% for localized ES. At Memorial Sloan Kettering (MSK) we have instead used the strategy of increasing doses of alkylating agents to achieve dose intensification and reported similar results. The combination of i/T given as irinotecan 20 mg/m2/day for 10 days with temozolomide 100 mg/m2/day for 5 days has achieved objective responses for patients who recur after initial therapy with the 5 drug combination. Our prospective protocol incorporates cycles of i/T with cycles of VDC and IE for the treatment of newly diagnosed patients with ES. **Methods:** We have enrolled patients with and without clinically detectable metastatic disease at initial presentation. For patients with localized ES we administer high dose alkylator therapy with 4 cycles of VDC and 3 cycles of IE, followed by 6 cycles of i/T. For patients who present with metastases we intercalate 10 cycles of i/T with the same 7 cycles of high dose alkylating agent therapy. **Results:** We have enrolled 22 patients with localized and 16 patients with metastatic ES. With a median followup of 14 (3-51) months, patients with localized ES have achieved a 3 year EFS of 95% and overall survival (OS) of 95%. With a median followup of 20 (8-51) months, patients with metastatic ES have achieved a 3 year EFS of 55% and OS of 70%. **Conclusions:** The addition of multiple cycles of i/T to conventional 5 drug therapy for ES is feasible and may be associated with an improved probability for both EFS and OS. Clinical trial information: NCT01864109.

10534 Poster Session (Board #207), Sat, 8:00 AM-11:30 AM

Rhabdomyosarcoma in the first year of life: outcome data from five trials and one registry of the Cooperative Weichteilsarkom Studiengruppe (CWS). *First Author: Monika Sparber-Sauer, Klinikum Stuttgart - Olgahospital, Stuttgart Cancer Center, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany*

Background: Infantile soft tissue sarcoma (STS) has been associated with worse survival than STS in older children. Age, histology, molecular phenotype and treatment adjustment according to age may affect the outcome of patients with rhabdomyosarcoma (RMS) diagnosed during the first year of life. **Methods:** The records of 5 trials and one registry, conducted by the Cooperative Studiengruppe (CWS) between 1981–2016, were reviewed to identify children diagnosed with RMS during the first year of life. Patient characteristics, treatment data and outcome were evaluated. **Results:** A total of 155 infants ≤ 12 months with histological diagnosis of RMS were identified, including 115 cases of embryonal RMS (RME), 38 cases of alveolar RMS (21/25 PAX7/3:FOXO1-positive (PF+)), 1 case of botryoid RMS and 1 case of spindle-cell RMS. 144 infants presented with localized disease (LD); 11 with metastatic disease (MD). 150 children received age- and weight-adapted chemotherapy (1/3 dose reduction in infants ≤6 months): VAIA/VACA/CEVAIE (n = 100), IVA/VA/VAC/other (n = 50). Resections were achieved R_0 (n = 64), R_1 (n = 37), R_2 (n = 37) and biopsies (n = 17). Adjuvant radiotherapy (RT) was administered to 37 children. After a median follow-up of 7.55 years [0.24- 30], the 5-year overall survival (OS) and event-free survival (EFS) rates were 66% and 49% for the whole group. Significant prognostic factors were LD (OS 69% vs 12% in MD, p = 0.000), tumor size and resection status. For patients with LD, tumor size and best resection (R_0/R_1/R_2) were no prognostic factors and RT did not improve survival. 2nd malignancy occurred in 6 infants. OS and EFS rates of newborns (≤1 month, n = 15) were significantly worse (31% and 17%, respectively) compared to those > 1 month and ≤ 12 months (n = 140, OS 69% and EFS 52%, p = 0.001 and 0.001). Children with RMA (41% and 24%) and/or PF+-RMS achieved significantly worse regarding OS and EFS (36% and 19%) than those diagnosed with RME (72% and 56%; p = 0.018 and 0.003). **Conclusions:** Survival of infants with RMS is comparable to older children. Metastatic disease, RMA histology/ PF+ status and age below 1 month are factors relevant for inferior outcome. RT did not improve survival in LD.

10535 Poster Session (Board #208), Sat, 8:00 AM-11:30 AM

Phase 1/2 intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma, or leukemia. *First Author: Cornelis Martinus van Tilburg, KiTZ Clinical Trial Unit, Hopp Children's Cancer Center at the NCT Heidelberg (KiTZ), German Cancer Research Center (DKFZ) and Heidelberg University Hospital, Heidelberg, Germany*

Background: In preclinical pediatric cancer models, the HDAC inhibitor vorinostat showed significant activity only at higher concentrations compared with those achieved with currently recommended dosing regimens. The aim of this trial was to intra-individually dose escalate to an individual maximum tolerated dose (MTD) in order to increase the likelihood of response whilst keeping toxicity acceptable. **Methods:** Children 3 – 18 years old with relapsed or therapy-refractory solid tumor, lymphoma or leukemia were eligible. In phase 1 an intra-patient dose (de)escalation was performed until the MTD was reached. After identification of MTD, patients did continue treatment in phase 2 at their individual MTD until progression. **Results:** Fifty-two patients were enrolled and 50 received treatment. 27/50 patients completed the intra-patient (de)escalation phase 1 part and entered phase 2. A safe starting dose of 130mg/m^2/day with weekly increments of 50mg/m^2 was determined (maximum: 580mg/m^2/day). 46/50 (92%) patients experienced treatment related AEs, in 44 patients (88%) ≥ CTCAE grade 3. Of the patients who reached phase 2, 24/27 patients (89%) experienced treatment related AEs, in 17 patients (63%) ≥ grade 3. Most of the grade 3-4 AEs were reversible hematologic toxicity (mostly thrombocytopenia), fatigue, nutrition and gastrointestinal disorders and weight loss. The median MTD was 280mg/m^2/day (range 130 - 580mg/m^2/day). Overall response rate (CR + PR + SD) in the phase 2 was 6/27 (22%). 5 patients stayed on treatment for > 12 months receiving doses of 280 – 580mg/m^2/day. 3 patients with histological high grade glioma and one with metastasized SETTLE tumor showed PR, one with a medulloblastoma showed prolonged SD. 1 patient was on drug for > 4 years. **Conclusions:** A safe starting dose of 130mg/m^2/day for individual dose escalation with weekly increments of 50mg/m^2 was identified. This resulted in higher drug exposure associated with responses and long-term disease stabilization confirming that activity can only be expected at doses higher than currently recommended. The toxicity profile was compatible with published adult and pediatric safety data. PK, PD and biomarker analysis are ongoing. Clinical trial information: NCT01422499.

10536 Poster Session (Board #209), Sat, 8:00 AM-11:30 AM

Phase 1 study of entrectinib (RXDX-101), a TRK, ROS1, and ALK inhibitor, in children, adolescents, and young adults with recurrent or refractory solid tumors. *First Author: Ami Vijay Desai, University of Chicago Medical Center, Comer Children's Hospital, Chicago, IL*

Background: Entrectinib (RXDX-101) inhibits TRKA/B/C, ROS1, and ALK tyrosine kinases with $IC_{50} < 2$ nM. *In vivo*, entrectinib is active in several fusion-driven solid tumor and TRKB-expressing neuroblastoma (NB) models. Central nervous system (CNS) penetration enables targeting of CNS metastases and primary tumors. Entrectinib has clinical activity in adults with malignancies harboring *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions [Drilon 2017]. **Methods:** Patients (age 2-21 years) with recurrent or refractory extracranial solid tumors were eligible for this multicenter Phase 1 study. 4 doses levels (250, 400, 550, 750 mg/m^2) were evaluated using a 3+3 design to determine the recommended phase 2 dose (RP2D). Entrectinib capsules were administered orally, once daily, on continuous 4-week cycles. Adverse events were graded using CTCAE v4.03; response assessed by RECISTv1.1 and detailed pharmacokinetic sampling was completed. **Results:** 16 patients enrolled; 15 were evaluable (9 male, 6 female) with median (range) age 10 (4-20) years. Diagnoses included NB (n = 10), inflammatory myofibroblastic tumor (IMT; n = 2), salivary gland adenocarcinoma (n = 1), synovial sarcoma (n = 1), and infantile fibrosarcoma (IFS, n = 1). Somatic target gene fusions were identified in IMTs (*DCTN1-ALK, TFG-ROS1*) and IFS (*ETV6-NTRK3).* Dose-limiting toxicities included grade (G) 2 creatinine increase > 7 days in 1/6 patients receiving 550 mg/m^2 and 1 patient each with G2 dysgeusia/fatigue > 7 days and G3 pulmonary edema out of 3 patients receiving 750 mg/m^2, thus confirming the pediatric RP2D as 550 mg/m^2. Overall toxicity profile and drug exposure were comparable to the adult RP2D. 4 patients (2 IMT, 1 IFS, 1 NB) continue protocol therapy. All 3 fusion-positive patients have experienced an objective response. **Conclusions:** The RP2D of entrectinib in children, adolescents, and young adults with solid tumors is 550 mg/m^2 daily. Preliminary antitumor activity has been seen in gene fusion-positive patients. Entrectinib continues to be investigated in expansion cohorts of patients with primary CNS tumors, extracranial solid tumors harboring *NTRK*, *ROS1*, or *ALK* fusions, and patients with NB. Clinical trial information: NCT02650401.

10537 Poster Session (Board #210), Sat, 8:00 AM-11:30 AM

Phase 1 trial of trametinib alone and in combination with dabrafenib in children and adolescents with relapsed solid tumors or neurofibromatosis type 1 (NF1) progressive plexiform neurofibromas (PN). *First Author: Birgit Geoerger, Gustave Roussy, Villejuif, France*

Background: Mitogen-activated protein kinase (MAPK) pathway aberrations are common in cancer and NF1 PN. Dabrafenib, a BRAF inhibitor, is active in children with *BRAF* V600–mutant tumors; however, activation of MAPK signaling in *BRAF* WT cells increases skin toxicity. Trametinib, a MEK inhibitor, targets MAPK activation in tumors harboring *BRAF* fusions and *NF1* gene loss. This trial sought to establish the trametinib dose alone and in combination with dabrafenib in patients (pts) with relapsed solid tumors or progressive PN. **Methods:** Part A: safety and pharmacokinetics (PK) of trametinib (0.0125, 0.025, 0.04 mg/kg daily) were evaluated. Dose-limiting toxicity (DLT) during the first 4 wk and trough concentrations were used to determine the recommended dose (RD). Three age groups (< 2 y, 2-12 y, > 12 y) were evaluated based on initial PK; trametinib 0.032 mg/kg was assessed in pts < 6 y. Part C: pts with *BRAF* V600–mutant tumors received the trametinib RD in combination with 50% or 100% of the established age-specific dabrafenib RD. **Results:** Part A: 40 pts (median age, 8 y [range, 0-18 y]) were enrolled. Median treatment (Tx) duration was 81 wk (range, 3-124 wk); 21 (53%) continue on Tx. DLTs (mucositis [n = 3 overall]) occurred in 5/15 pts receiving 0.04 mg/kg and 3/19 receiving 0.025 mg/kg. Frequent Tx-related adverse events (TRAEs) were paronychia (58%), diarrhea (48%), and rash (45%). Tx-related serious AEs (TRSAEs) occurring in > 1 pt included hyponatremia and pyrexia (2 each). The trametinib RD is 0.025 mg/kg daily for pts ≥ 6 y and 0.032 mg/kg for pts < 6 y. Part C: 12 pts (median age, 12 y [range, 2-18 y]) were enrolled. No DLTs were observed at 50% or 100% of the dabrafenib age-specific RD in combination with trametinib 0.025 mg/kg in pts ≥ 6 y. Median Tx duration was 41 wk (range, 11-67 wk); 8 pts continue on Tx. Frequent TRAEs were rash (67%) and pyrexia (50%). Decreased ejection fraction (n = 2) was the only TRSAE in > 1 pt. Assessment of pts < 6 y is ongoing. **Conclusions:** Age-specific dose, safety, and tolerability of trametinib alone and combined with dabrafenib were defined for children and adolescents; $> 50\%$ of pts continue on Tx. Clinical trial information: NCT02124772.

10538 Poster Session (Board #211), Sat, 8:00 AM-11:30 AM

G_{D2} as a circulating tumor biomarker (CTB) for neuroblastoma (NBL). *First Author: Frank M. Balis, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: CTBs that reflect tumor burden or viability can improve the accuracy and sensitivity of assessing tumor response in phase 2 trials and substantially shorten the timeline of phase 3 trials if they are predictive of relapse or survival. G_{D2} is a ganglioside present in the plasma membrane of NBL tumor cells, is measurable in the serum of patients with high-risk NBL, and could serve as a CTB. **Methods:** We developed and validated a sensitive and specific high-pressure liquid chromatography/tandem mass spectroscopy assay for G_{D2} in serum and plasma and quantified its circulating lipoforms that differ in the chain length of the fatty acid moiety (C_{18} and C_{20}) in the ceramide portion of the molecule. We measured G_{D2} lipoforms in serum or plasma from 40 normal children (controls) and pretreatment samples from 128 (86 high-risk) children with NBL and 8 to 12 children each with 10 other childhood cancers. **Results:** The C_{18} lipoform was the predominant circulating form of G_{D2} in controls and in patients with NBL. The median concentration of the C_{18} lipoform in children with high-risk NBL at diagnosis was 156 nM (range, 4-1060 nM), which was > 25-fold higher than the median concentration (5.6 nM) in controls. G_{D2} was not measurable (< 2.4 nM) in 16 of 40 controls, and the highest concentration in controls was 15 nM. G_{D2} was not elevated in children with 10 other childhood cancers except for medulloblastoma (median, 34 nM; range, 6-111 nM). *MYCN* amplification ($p < 0.0001$), high-risk disease ($p < 0.0001$), and INSS stage 4 ($p < 0.0001$) were associated with higher G_{D2} concentration. Median G_{D2} concentration in non-high-risk NBL was 9.9 nM. **Conclusions:** These preliminary data indicate that G_{D2} may be a sensitive and specific CTB for high-risk NBL. G_{D2} will be studied prospectively and longitudinally in new COG frontline, high-risk NBL treatment trials to determine if pretreatment G_{D2} concentration or change in G_{D2} concentration post-treatment are predictive of response or survival and if G_{D2} concentration is predictive of response to G_{D2}-targeted immunotherapy. Although our focus is on developing G_{D2} as a surrogate clinical trial endpoint, the associations noted above with other prognostic markers also suggest it may also be useful as a diagnostic or prognostic CTB.

10539 Poster Session (Board #212), Sat, 8:00 AM-11:30 AM

Immunotherapy with anti-GD2 antibody ch14.18/CHO±IL2 within the HR-NBL1/SIOPEN trial to improve outcome of high-risk neuroblastoma patients compared to historical controls. *First Author: Ruth Lydia Ladenstein, St. Anna Children's Hospital and Department of Paediatrics, Medical University, Vienna, Austria*

Background: Randomization of immunotherapy versus standard was not possible in the HR-NBL1/SIOPEN trial. In order to explore an impact of immunotherapy on outcome, we used trial patients prior to availability of ch14.18/CHO as control. **Methods:** Trial patients received rapid COJEC, two courses of TVD if needed, surgery, HDT/SCT (BuMel or CEM) and radiotherapy. MRD treatment (MRDT) consisted of isoretinoin alone from 2002 - 2009 (control population, CP) and from 2009 - 2013 with ch14.18/CHO (5 cycles ch14.18/CHO, ± IL2) (immunotherapy population, IP). Patients (844) were ≤9 months between diagnosis and HDT/SCT, PR or better prior to HDT/SCT and had no progression after HDT/SCT until start MRDT (median time 109 days) (CP 466, IP 378). Sex, age groups, stage 4 MycN amplified (MNA) and response prior HDT/SCT were balanced between cohorts. Imbalanced (IP vs CP) were metastatic compartments (MC > 1) [80% vs 71%; $p = 0.0034$)], TVD given [12% vs. 32%; $p < 0.001$], MNA localised disease [8% vs. 13% $p = 0.0019$], type of HDT = CEM [8% vs. 45%; $p < 0.001$)], time point of surgery $<$ day120 after diagnosis [60% vs. 73%; $p < 0.0001$] and radiotherapy given [94% vs. 88%; = 0.0034]. Median follow up was 5.8y (0.05-13.8y). **Results:** The 5y-EFS was 57%±3% for the IP and 42%± 2% for the CP ($p < 0.001$). Univariate analysis of risk factors identified no 5y-EFS difference for sex, stage 4 ± MNA and was borderline for radiation given (5y-EFS if yes: 50%±2%, no: 38%±6%, $p = 0.073$). Risk factors with 5y-EFS differences were age, stage, MC > 1, delayed surgery, response pre HDT/SCT and type of HDT. However, MVA analysis identified patients at a higher risk without immunotherapy ($p = 0.0002$, HR 1.573), with CEM ($p = 0.0029$; HR 1.431), response $<$ CR prior MRD ($p = 0.0043$, HR 1.494) and $>$ 1MC at diagnosis (< 0.001 HR 2.665). After adjustment for age, stage, MC, TVD and pre-MRD response, a benefit for immunotherapy was confirmed in BuMel- ($p = 0.0066$; HR 1,439) with 5yEFS of , 56±3% vs 48±3% (IP vs CP) and in CEM-treated patients ($p = 0.0107$; HR 2.334) with 5yEFS of 67±9% vs 35±3% (IP vs. CP). **Conclusions:** Introduction of ch14.18/CHO immunotherapy achieved a major improvement in outcomes for patients on the HR-NBL1 trial. Clinical trial information: NCT01704716.

10540 Poster Session (Board #213), Sat, 8:00 AM-11:30 AM

Cediranib phase II study in children with metastatic alveolar soft part sarcoma (ASPS). *First Author: John Glod, National Cancer Institute at the National Institutes of Health, Bethesda, MD*

Background: ASPS, a rare, highly vascular sarcoma with a clinically indolent course, frequently presents with metastases at diagnosis. Standard sarcoma chemotherapy is ineffective. Vascular endothelial growth factor (VEGF) is a promising therapeutic target. In a phase II trial of the VEGF receptor inhibitor cediranib for adults with ASPS, the partial response (PR) rate (RECIST v1.0) was 35% (15/43;95% CI:21-51%); (Kummar S,et al. ***J Clin Oncol*** 2013; **31**(18): 2296-302). We evaluated the objective-response rate [PR + complete response] of cediranib in the pediatric population (NCT00942877). **Methods:** Patients (pts) ≤16 years old (yo) with metastatic, unresectable ASPS received cediranib at the pediatric maximum tolerated dose of 12 mg/m^2 (≅70% of the fixed adult phase II dose of 30 mg) orally daily [1 cycle (cy) = 28 days]. Response was assessed every 2 cy (RECIST v1.0). A Simon two-stage optimal design (target response rate 35%, rule out 5%, alpha = 0.1, beta = 0.1) was used. With ≥ 1 response in 6 pts, enrollment would expand to 12 pts; with responses in ≥2/12pts, cediranib would be considered active. **Results:** 7 pts (4 female), median age 13 yo, (range 9-15), all with pulmonary metastases, enrolled on stage 1. Best response was stable disease (SD) (median cy number = 18). 2 pts were removed from study for disease progression (cy 4 and 5), and one pt for surgical resection of primary tumor (cy 16) per pt and local oncologist choice. 5 of 7 pts had SD for ≥14 months. 4 pts with SD remain on study after 18-44+ cy. Each of these pts had 1 (n = 3) or 2 (n = 1) cediranib dose reductions for grade 2 hypertension (n = 1, cy 2), fatigue (n = 2, cy 2), and proteinuria (n = 1, cy 38), and grade 3 ALT elevation (n = 1, cy 1). No growth plate toxicity was detected on MRI. **Conclusions:** Cediranib did not reach the target response rate in this small pediatric cohort; thus, no additional pts were enrolled. This is in contrast to the adult 35% PR rate. Pediatric dosing was 30% lower compared to adult dosing, which may have contributed to response differences. Prolonged SD was observed in 5 pts, but given the indolent nature of ASPS, SD cannot be clearly attributed to cediranib. Cediranib has an acceptable safety profile, with no growth plate toxicity, with several pts experiencing prolonged SD. Clinical trial information: NCT00942877.

10541 Poster Session (Board #214), Sat, 8:00 AM-11:30 AM

Phase 1 study of olaratumab as monotherapy and in combination with doxorubicin, vincristine/irinotecan, or high-dose ifosfamide in pediatric patients with relapsed or refractory solid tumors: Part A results. *First Author: Steven G. DuBois, Dana-Farber Cancer Institute/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Olaratumab (O), a PDGFRα antagonist, is a targeted human IgG1 monoclonal antibody that specifically binds PDGFRα, blocking PDGF-AA, -BB, and -CC binding and receptor activation, and has improved survival outcomes in adults with advanced sarcoma. **Methods:** This ongoing Phase 1, multicenter, dose-escalation study (NCT02677116) enrolled patients (pts) aged < 18 years, with a diagnosis of relapsed or refractory solid tumors, to 2 dose levels (Parts A and B) of O combined with fixed doses of standard chemotherapy with doxorubicin (D), vincristine/irinotecan (VI), or high-dose ifosfamide (I). Pts in Part A received 1 cycle (21 days) of O monotherapy at 15mg/kg IV on Days 1 and 8 followed by O + (D, VI, or I) for subsequent 21-day cycles. Each combination arm was complete when 6 pts received 2 full cycles. The primary objective of Part A was to determine the safety and tolerability of O 15mg/kg + (D, VI, or I) based on any dose-limiting toxicity (DLT) and O serum exposure matching between adult and pediatric pts. **Results:** Pts enrolled by O + chemotherapy regimen (n) were D (11), VI (10), and I (9). One pt (3.3%) experienced a DLT during the DLT period (Cycles 1 and 2), which consisted of grade (G) 4 elevated ALT while on O monotherapy. No ≥G3 infusion- or cardiac-related treatment emergent adverse events (AEs) occurred. Treatment-related AEs (TRAEs) ≥G3 reported in ≥2 pts are presented (Table). Serum concentrations of O in pediatric pts were within expected ranges based on adult exposure. **Conclusions:** Based on Part A results,O 15mg/kg as monotherapy or in combination with D, VI, or I is tolerable in pediatric pts with relapsed or refractory solid tumors. Part B of this trial is currently enrolling. Clinical trial information: NCT02677116.

	O + D		O + VI		O + I	
TRAE, n (%)	**G3**	**G4**	**G3**	**G4**	**G3**	**G4**
ALT increased	0	0	1 (10.0)	0	0	1 (11.1)
Anemia	1 (9.1)	0	1 (10.0)	1 (10.0)	3 (33.3)	0
Leukopenia	0	2 (18.2)	0	1 (10.0)	0	3 (33.3)
Lymphopenia	0	1 (9.1)	1 (10.0)	0	1 (11.1)	4 (44.4)
Neutropenia	0	3 (27.3)	2 (20.0)	1 (10.0)	1 (11.1)	1 (11.1)
Thrombocytopenia	0	1 (9.1)	0	1 (10.0)	3 (33.3)	1 (11.1)
Vomiting	0	0	1 (10.0)	0	1 (11.1)	0

10542 Poster Session (Board #215), Sat, 8:00 AM-11:30 AM

Phase I multicenter trial of CUDC-907 in children and young adults with relapsed/refractory solid tumors, CNS tumors, and lymphomas. *First Author: David Stephen Shulman, Dana-Farber Cancer Institute/Boston Children's Hospital, Boston, MA*

Background: CUDC-907 is a first-in-class small molecule inhibitor of histone deacetylases and phosphatidylinositol-3-kinases. Data from pediatric preclinical models, and adult clinical studies suggest that CUDC-907 can downregulate Myc/Mycn, providing a potential therapeutic strategy for Myc/Mycn-driven pediatric tumors. **Methods:** Using a 3+3 dose escalation design, CUDC-907 was administered at 3 dose levels to patients 1-21 years of age with relapsed/refractory solid tumors, brain tumors and lymphomas (NCT02909777). Primary objectives were to determine the pediatric recommended phase II dose (RP2D), describe toxicities, and describe PK parameters. Other endpoints included antitumor activity and pharmacodynamic effects. Patients received CUDC-907 orally on a 5 days on / 2 days off ("5/2") schedule in 28-day cycles, with a pediatric mini-tab formulation for children who could not swallow pills. **Results:** As of 11/16/2017, 15 patients enrolled, with a median age of 15 (4.6-20.9) years. Diagnoses included: osteosarcoma (n = 4); alveolar rhabdomyosarcoma (n = 3); DIPG (n = 2); ependymoma (n = 2); Ewing sarcoma (n = 2); CNS germ cell tumor (n = 1); and alveolar soft part sarcoma (n = 1). Patients received a median of 2 (1-7+) cycles. No DLTs were observed in 3 evaluable patients each at dose levels 1 and 2. A single first cycle DLT (grade 3 metabolic acidosis) was observed in 1 of 6 evaluable patients at dose level 3 (45 mg/m2; 128% of the adult RP2D). The most common treatment-related AEs were: thrombocytopenia (87%), nausea (80%), lymphopenia (80%), diarrhea (73%), leukopenia (73%), anemia (67%), tachycardia (67%), vomiting (67%), fatigue (67%), and anorexia (67%). The mean T_{max} was 2.5 hrs and $T_{1/2}$ was 1.4 hrs. No objective responses were seen. One patient with Ewing sarcoma and one patient with ependymoma had stable disease for 6 and 7+ cycles, respectively. Pharmacodynamic studies are pending. **Conclusions:** CUDC-907 was well tolerated with a pediatric RP2D of 45 mg/m2 administered orally on a 5/2 schedule. An expansion stage will evaluate this dose in groups of interest: mature B-cell lymphoma; *MYCN* amplified neuroblastoma; and solid tumors with *MYC/MYCN* amplification/high-copy gain. Clinical trial information: NCT02909777.

10543 Poster Session (Board #216), Sat, 8:00 AM-11:30 AM

First-in-child trial of celyvir (autologous mesenchymal stem cells carrying the oncolytic virus ICOVIR-5) in patients with relapsed and refractory pediatric solid tumors. *First Author: Manuel Ramirez, Hospital Universitario Niño Jesús, Madrid, Spain*

Background: Outcome for relapsed/refractory pediatric solid tumors is dismal so there is an urgent need for new therapies. Immunotherapy with oncolytic viruses show great promise in adult cancers but have scarcely been explored in children. The results of a first-in-man, first-in-child trial (NCT01844661) using Celyvir, autologous mesenchymal stem cells (MSC) carrying an oncolytic adenovirus are presented. **Methods:** Patients (1-18 yrs) with advanced relapsed/refractory solid tumors, adequate organ function and performance status were included. Autologous MSCs were collected from a bone marrow aspirate (BMA). Celyvir was manufactured within 6 weeks from BMA and then given IV weekly for 6 weeks at doses from 2x10^6 cells/Kg and 2x10^4 viral particles (vp) per cell. Dose was based in a previous compassionate use program (Melen et al. 2016;371:161). Primary objective was to determine safety and toxicity. Secondary objective was preliminary antitumor activity. Biomarker studies included oncolytic viral replication and immune response. **Results:** Fifteen patients had BMA performed, 6 progressed before treatment could be started, 9 received Celyvir and completed the planned 6 weeks treatment and were evaluable. The total number of cells administered ranged from 89 to 468 million, 1,78 – 8,36x10^{12} vp. Celyvir was well tolerated showing no grade 3/4 toxicities. Most frequent adverse event was pyrexia (37,5% patients). Adenoviral replication detected by PCR was found in all but two patients and humoral antiadenoviral response was detected in all but one patient. Circulating T lymphocytes numbers raised with Celyvir administration, mostly CD8 effector cells. No radiological responses were seen. Two patients with neuroblastoma showed disease stabilization per RECIST, one of them continued on treatment for up to 6 additional weeks. **Conclusions:** Celyvir, the combination of MSCs and oncolytic adenovirus is safe and warrants further evaluation in the pediatric phase 2 setting. The use of MSCs may be a strategy to increase the amount of oncolytic virus administered to patients, minimizing toxicities and avoiding direct tumor injections. Clinical trial information: NCT01844661.

10544 Poster Session (Board #217), Sat, 8:00 AM-11:30 AM

Various checkpoint proteins, and tumor infiltrating lymphocytes in common pediatric solid tumors: Possibilities for novel immunotherapy. *First Author: Kazuhiro Mochizuki, Fukushima Medical University, Fukushima, Japan*

Background: Despite the significant improvements of long-term survival rates for pediatric cancers, prognosis of refractory/relapsed solid tumors are extremely poor, and novel strategies are desired. Recently, tumor immunotherapies such as anti-PD-1/PD-L1 antibodies have been recognized as an effective option for many intractable cancers. However, there are still a substantial number of patients who do not show objective responses to the PD-1/ PL-L1 blockades. On the other hand, like PD-1/PD-L1, other immune checkpoint pathways such as TIM3/GAL9, LAG3/MHC-II, and BTLA/HVEM have been reported to regulate immune responses in tumor microenvironment. Although these pathways could be alternative targets for novel immune therapies, almost no information is available whether pediatric solid tumors express these molecules. Herein, we characterized the expression of various checkpoint proteins, and tumor infiltrating lymphocytes (TILs) in tumor specimens from untreated children with common pediatric solid tumors. **Methods:** Sections cut from formalin-fixed, paraffin-embedded tissue blocks were processed and evaluated for GAL9, MHC-II, and HVEM on tumor cells, and TIM3, LAG3, and BTLA on TILs by immunohistochemistry. **Results:** Specimens from 65 patients, including 16 neuroblastomas, 11 rhabdomyosarcomas, 12 osteosarcomas, 10 hepatoblastomas, 10 Wilms tumors, and 6 Ewing sarcomas were evaluated. Although in neuroblastoma and Ewing sarcoma, checkpoint proteins on the tumor were rarely detected, 64% of the patients with rhabdomyosarcoma and 83% with osteosarcoma expressed moderate to high levels of HVEM. TILs were detected in all tumor types among which CD8 positive T cells were the most dominant population following CD4 positive T cells. Interestingly, in rhabdomyosarcoma, and osteosarcoma, more than 70% of the TILs expressed moderate to high levels of BTLA. **Conclusions:** A subset of pediatric solid tumors demonstrated tumor associated checkpoint expressions, and TILs also expressed corresponding ligands of the checkpoints, which suggested immunogenic environments may be created, and the checkpoint blockades could induce favorable immune responses.

10545 Poster Session (Board #218), Sat, 8:00 AM-11:30 AM

Visceral primary non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) in patients < 30 years of age: Findings of Children's Oncology Group (COG) study ARST0332. *First Author: Meena Kadapakkam, Stanford University School of Medicine, Stanford, CA*

Background: Little is known about the clinical features, optimal management, and prognosis of young patients with primary visceral NRSTS. **Methods:** We analyzed clinical features, treatment, and outcomes of patients with visceral tumors (defined as intrathoracic, intraperitoneal, retroperitoneal, pelvic and perineal) enrolled in COG ARST0332, which evaluated a risk-based treatment strategy for NRSTS patients aged < 30 years (surgery +/- radiotherapy +/- chemotherapy based on tumor size, grade, extent of surgery, and extent of metastases). Variables analyzed included gender, age, race, ethnicity, tumor grade/size/invasiveness, extent of metastases, extent of surgery, and event-free and overall survival. **Results:** Visceral tumors occurred in 114/551 enrolled patients (21%), were most likely to occur in patients > 10 years (67%) and be > 5 cm (92%), high-grade (89% by POG, 73% by FNCLCC), non-metastatic (78%), and grossly resected prior to study entry (58%). Compared to patients with non-visceral tumors, those with visceral tumors were more likely to have high-risk features: high POG and FNCLCC grade, > 5 cm diameter, deep location, and invasiveness (all $p < 0.001$), metastases ($p = 0.03$), and microscopic residual tumor after gross total resection ($p = 0.01$). Due to these features, they were more often assigned to intermediate-/high-risk therapy (87% vs. 50%). Event-free and overall survival by risk group were 85.1% and 82.5% (low), 67.9% and 82.8% (intermediate), and 44.0% and 44.0% (high), and did not differ significantly from outcomes for the rest of the population. **Conclusions:** Patients with primary visceral tumors were more likely than those with tumors at other anatomic sites to have high risk features such as > 5 cm tumor diameter, high grade, deep location, invasiveness, metastases, and microscopic disease after gross resection. However, with risk-adapted therapy, their event free and overall survival were similar to those of patients with non-visceral tumors. Clinical trial information: NCT00346164.

10546 Poster Session (Board #219), Sat, 8:00 AM-11:30 AM

Risk group accurately predicts outcome in primary extremity non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) in patients <30 years of age: Findings from Children's Oncology Group study ARST0332. *First Author: Sara Regina Kreimer, Stanford University School of Medicine, Stanford, CA*

Background: Data are limited on primary extremity NRSTS in pediatric patients. **Methods:** This ARST0332 subset analysis evaluated the clinical features and outcomes of extremity (including shoulder/hip girdle) NRSTS in < 30 year old patients risk-stratified to receive surgery +/- radiotherapy +/- chemotherapy based on clinicopathologic characteristics including tumor size, grade, extent of surgery, and presence of metastases. Other variables analyzed included age, gender, race, tumor invasiveness, and depth. **Results:** Primary extremity tumors comprised 297/551 cases (100 upper and 197 lower extremity) treated with surgery only (n = 137), adjuvant radiotherapy (n = 9), adjuvant chemoradiotherapy (n = 38), or neoadjuvant chemoradiotherapy followed by surgery if feasible (n = 113). Extremity site correlated with older age ($p = 0.0059$), diameter < 5 cm ($p = 0.0421$), lower grade ($p < 0.0001$), superficial location ($p = 0.0314$), and non-invasiveness ($p < 0.0001$). However, among patients with extremity tumors, older patients more commonly had > 5 cm ($p < 0.0001$), deep ($p = 0.0010$), invasive ($p = 0.0037$) tumors, and distant metastases ($p = 0.0003$). Estimated 5-year cumulative incidence of local and distant recurrence was 5% and 20%, respectively. Five-year overall survival (OS) for low-, intermediate- and high-risk patients was 96.7%, 78%, and 25.4%, respectively, and was not statistically significantly different than for non-extremity tumors. Older age, size > 5 cm, invasiveness, and higher risk group predicted inferior event-free survival; only higher risk group predicted inferior OS. **Conclusions:** Although extremity NRSTS are more likely to have low-risk features (size < 5 cm, lower grade, superficial location, non-invasiveness) compared to non-extremity tumors, their outcomes are similar with risk-adapted therapy. Older patients had more high-risk features. Risk group was the most important predictor of overall survival. Clinical trial information: NCT00346164.

10547 Poster Session (Board #220), Sat, 8:00 AM-11:30 AM

Nasopharengeal carcinoma in children: Demographic, clinical, therapeutic characteristics and long term outcome of 97 patients. *First Author: Rejin Kebudi, Istanbul University, Cerrahpasa Faculty of Medicine and Oncology Institute, Pediatric Hematology-Oncology, Istanbul, Turkey*

Background: The aim of this study is to evaluate the demographic, clinical and therapeutic characteristics and long-term outcome in childhood nasopharyngeal carcinoma (NPC) in a single center. **Methods:** Data of 97 patients < 18 years with NPC, treated in the Istanbul University Oncology Institute from November 1989 to January 2018 were evaluated retrospectively. All patients received three courses of neoadjuvant chemotherapy (1989-1991; cisplatinum, 5-fluorouracil; 1992-2008: Bleomycin, epirubicin and cisplatinum- BEP; since 2008-EP) followed by radiotherapy given both to the primary tumor and to the metastatic cervical lymph nodes. **Results:** Sixty-nine boys and 28 girls (M:F = 2.5) with a median age of 14 yrs (6-18), presented mostly with a lump in the neck, headache, and ear and nose problems. Median follow-up was 83 months (3 months-26.6 years). Ninety percent of the biopsies of NPC were WHO type III tumors. Most patients had advanced stage tumors, 5 had distant metastatis. Chemotherapy was followed with radiotherapy 60-66 Gy to the primary tumor and involved lymph nodes, and 50-54Gy to the uninvolved cervical nodal region. The 10-year overall survival (OS) rate was 79%. There was no significant difference in OS in patients who received BEP or EP. Seventeen patients died, 2 due to accident/suicide, 3 with second primary cancer, 12 with recurrent/progressive disease. Seven second malignancies developed in six patients, six in the irradiated field at a median of 12 years (5- 25 years). Late effects included hypothyroidism, neck fibrosis, xerostomia, bony hypoplasia, skin problems and hearing loss. **Conclusions:** Children with advanced NPC treated with neoadjuvant chemotherapy and radiotherapy have a high locoregional control rate and much higher long-term survival (OS 79 %) than that reported in our center before 1990's when most recieved only radiotherapy (46%) or radiotherapy and adjuvant chemotherapy (58 %) (IJ Radiation Oncology Biol Phys 1996). Neoadjuvant therapy with EP chemotherapy seems to be as effective as BEP. Survivors should be followed for long-term morbidities, including second malignancies.

10548 Poster Session (Board #221), Sat, 8:00 AM-11:30 AM

Outcomes for young children with molecularly defined ependymoma treated on the multi-institutional SJYC07 clinical trial. *First Author: Santhosh Upadhyaya, St. Jude Children's Research Hospital, Memphis, TN*

Background: Retrospective reports of poor outcomes of ependymoma (EPN) subgroups, posterior fossa A (PF-EPN-A) and supratentorial *C11orf95–RELA* (ST-EPN-RELA), need confirmation in prospective trials. **Methods:** Fifty-four children (median age 1.6 y, range 0.4–3.1) with newly diagnosed EPN (WHO grade II/ III) were treated (2008–2016) with maximal safe surgical resection + chemotherapy (high-dose methotrexate, vincristine, cisplatin and cyclophosphamide), consolidation using focal conformal radiation therapy (RT) to 54Gy (M0) or additional cyclophosphamide/topotecan with no RT (M+) and 6 months of oral maintenance chemotherapy. DNA methylation was performed using Infinium MethylationEPIC BeadChip and profiled on the DKFZ MN2.0 classifier. Fluorescent in-situ hybridization was used to determine tumor 1q status. **Results:** No participant had imaging evidence of metastatic disease at diagnosis (M0 = 40, M1 = 1, CSF not obtained = 13). At a median follow-up of 3.6 y (range, 1.0-9.3), 49 patients (91%) were alive with a 4-y PFS = 77.0%±7.5% and OS = 91.3%±5.2%. There was no significant difference in outcomes by subgroup [4-y PFS: PF-EPN-A (n = 42), 74.3%±8.2%; ST-EPN-RELA (n = 8), 80%±20.7%; ST-EPN-YAP (n = 4), 100%, p = 0.42]. Five patients with PF-EPN-A had 1q gain but no difference in outcome (p = 0.59 for OS and p = 0.15 for PFS). For 6 patients with subtotal resection (STR) prior to RT, outcome was inferior to those of the 48 with gross-total or near-total resection (4-y PFS = 27.8%±16.7% vs 81.7%±7.3%, p = 0.047). Fourteen patients experienced progression at a median time of 28 mos (range, 1.7m–7.3 y). Recurrence was distant (n = 7), local (n = 6), or combined (n = 1), 3/14 recurred at 6 (n = 2) and 7 years post diagnosis. **Conclusions:** In a uniformly treated, prospective EPN cohort, we found no significant difference in PFS or OS by molecular subgroup; however, the number of ST-EPN-RELA was small. In our data, 1q was not associated with outcome in PF-EPN-A, though only 5 subjects had 1q gain. Patients with STR prior to RT had inferior outcomes. Close surveillance and follow-up beyond 5 years is warranted due to risk of metastasis and late progression. Clinical trial information: NCT00602667.

10549 Poster Session (Board #222), Sat, 8:00 AM-11:30 AM

Final results of the phase II, single arm trial of irinotecan and cisplatin in children with high-risk glial tumors. *First Author: Ofelia Cruz, Hospital Sant Joan de Déu, Esplugues Llobregat-Barcelona, Spain*

Background: We conducted an open label, single arm phase II clinical trial with irinotecan and cisplatin (I/C) for pediatric patients with glial tumors (EudraCT:2009-010742-59). **Methods:** Patients diagnosed with high-risk (HR) gliomas at diagnosis (HGG, Ependymomas, DIPG, or HR-LGG) received sixteen weekly outpatient iv cycles of Cisplatin (30mg/m2) and Irinotecan (65mg/m2). Malignant gliomas received radiation upon progression. Objective response was evaluated by MRI volumetric analysis. Clinical and neurological changes were assessed. **Results:** From November 2009 until December 2012 39 patients aged 7m to 17y (mean 84 months) diagnosed with DIPG (n = 7); HGG (n = 5); Ependymoma (n = 6); atypical neurocytoma (n = 1); LGG (n = 22); pilocytic (n = 7) or pilomyxoid Astrocytoma (n = 1); Astrocytoma NOS (n = 5); Ganglioglioma (n = 2); and NF1 related LGG (n = 3) were included. Most frequent events were nausea/vomiting (5/39 grade $>$ 2); 17 patients (43.6%) with grade-1 diarrhea. Three of 31 (9.7%) evaluable patients developed hypoacusia, all grade 1. Five (45.5%) patients with HGG, 1 relapsed HGG (100%), 7 DIPG (100%) and 3 LGG (15%) progressed during treatment. Objective response rate (ORR) at the end of therapy (week 21) is 54.4% for HGG; 0% for DIPG; and 85% for HR-LGG. After a median follow-up of 67.5 months OS/EFS for relapsed HGG and DIPG is 0%/0%; for high-grade glial tumors 62%/23%; and 95%/43% for HR-LGG. Radiation was avoided in 19 of 20 HR-LGG patients. **Conclusions:** The I/C regimen was well tolerated and showed anti-tumor activity and clinical benefit for children with HR-LGG. Clinical trial information: NCT01574092.

10550 Poster Session (Board #223), Sat, 8:00 AM-11:30 AM

Risk prediction based on post induction bone marrow response and genomic profile: A new way to stratify stage M neuroblastoma patients? *First Author: Stefan Fiedler, St. Anna Kinderspital, Veinna, Austria*

Background: So far, and apart from minor adaptations, high-risk neuroblastoma patients have been treated uniformly by not taking biological features of the tumor into consideration. To mend this oversight and address the lack of biological data, we evaluated the prognostic relevance of a combined analysis of genomic aberrations of tumor cells and minimal residual disease (MRD) of stage M neuroblastoma patients. **Methods:** Diagnostic/post-induction bone marrow (BM) samples from 115 (83 fulfilled all criteria) stage M patients enrolled in the HR-NBL1/SIOPEN high-risk neuroblastoma trial were automatically searched for GD_2/CD56/DAPI positive disseminated tumor cells (DTCs), which provided excellent sensitivity and specificity. Information on somatic copy-number aberrations (SCNAs), *MYCN* amplification, aberrations in *ATRX*, *TERT*, and *PTPRD* genes from 139 patients was generated by high-density single-nucleotide polymorphism (SNP) arrays. **Results:** The 3-year event-free survival (EFS) of 184 patients was 39±4% with a 3-year cumulative incidence of relapse (CIR) of 56±6% (median observation time: 55.5 months). BM-MRD negative patients had a 3-year EFS of 67±9% (CIR:39±7%), whereas non-clearing patients had only 27±7% EFS (CIR:71±7%) (p = 0.001). Genomic analysis found a higher relapse incidence in patients whose tumors showed a gain/loss on chromosome 1q and/or aberrations in the *TERT* and/or *PTPRD* genes. Patients lacking these genomic markers and with BM clearing had the most favorable outcome (3-year EFS 92±7%) whilst those with two or more of the above mentioned genomic markers and positive BM-MRD fell into the ultra-high risk group (3-year EFS of 0%; p = $<$ 0.001). **Conclusions:** Combination of BM-MRD monitoring and genomic analysis enables early risk assessment and merits further evaluation.

10551 Poster Session (Board #224), Sat, 8:00 AM-11:30 AM

Pediatric preclinical testing consortium evaluation of the EZH2 inhibitor tazemetostat in orthotopic PDX models of pediatric brain tumors. *First Author: Xiao-Nan Li, Laboratory of Molecular Neuro-Oncology, Program of Preclinical Neuro-Oncology Research, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX*

Background: Tazemetostat (EPZ-6438) is an EZH2 inhibitor that has entered clinical trials both in pediatric and adult patients. Over-expression of EZH2, the catalytic subunit of Polycomb Repressive Complex 2 that catalyzes H3K27me3, has been detected in a series of pediatric malignant brain tumors. **Methods:** Expression of EZH2 mRNA was examined in 23 patient derived orthotopic xenograft (PDOX) mouse models (10 GBMs, 11 medulloblastomas and 1 ATRT) with comparison to normal tissue levels. H3K27me3 was evaluated with immunohistochemical staining and Western blotting. Tazemetostat (250 mg/kg and 400 mg/kg) was tested in 4 PDOX models (1 GBM, 2 medulloblastomas and 1 ATRT) both as a single agent and in combination with cisplatin (5mg/kg days 8 and 11) and/or radiation (2 Gy/day x 5 days). Kaplan-Meier estimate of median time-to-event, ratio in median time-to-event between the treated and control groups (EFS T/C), and EFS p values were calculated and compared between the treatment groups. **Results:** Over-expression of EZH2 mRNA was detected in all GBM models (34.6±12.7) and medulloblastoma models (6.2±1.7 in group 3, 6.0±2.4 in group 4) accompanied by increased H3K27me3. INI1 mutation was confirmed in the ATRT model. In 3/4 models, tazemetostat at 250 mg/kg caused significant extension of median survival times ($P<$ 0.05), with EFS T/C ranging from 1.32 to 1.39. Increasing drug dose from 250mg/kg to 400mg/kg resulted in significant EFS prolongation only for the ATRT model (EFS T/C 1.39 vs 2.01). When compared with cisplatin and radiation used alone, tazemetostat was not significantly more active. When combined with cisplatin and/or radiation, tazemetostat did not significantly prolong survival compared to the standard therapy used alone. A group 3 medulloblastoma was not responsive to any treatment tested. **Conclusions:** Tazemetostat prolonged survival times in 3/4 PDOX models tested, with the greatest treatment effect observed in the INI1 mutant ATRT model at the higher 400 mg/kg dose. These data are consistent with the BBB in these PDOX models not preventing anti-tumor activity of tazemetostat. The addition of tazemetostat to standard therapies did not lead to improved survival.

10552 Poster Session (Board #225), Sat, 8:00 AM-11:30 AM

Preclinical effect of selinexor (KPT-330), a selective inhibitor of nuclear export, in pediatric rhabdoid tumors. *First Author: Lianna Jean Marks, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Malignant rhabdoid tumors (MRTs) are rare, aggressive pediatric solid tumors characterized by a 22q11 chromosome rearrangement that inactivates the SMARCB1 gene. Outcomes remain poor despite multimodality treatment. MRTs are among the most genomically stable cancers and lack therapeutically targetable genetic mutations. We used the Virtual Inference of Protein-activity by Enriched Regulon analysis (VIPER) algorithm to computationally infer protein activity from MRT whole transcriptomic data available in the TARGET database to identify candidate non-genetically encoded vulnerabilities. This approach identified markedly aberrant activation of the nuclear export protein Exportin-1 (XPO1) in MRTs compared to other tumor types. We hypothesized that MRTs may be dependent on high XPO1 activity and this dependence can be co-opted as a novel non-oncogene directed therapeutic approach using the XPO1 inhibitor selinexor. **Methods:** A panel of 6 MRT and 3 atypical teratoid/rhabdoid tumor (ATRT) cell lines were used for *in vitro* studies. Two patient-derived xenograft (PDX) mouse models of MRT were treated with selinexor to determine anti-tumor effects. **Results:** All MRT cell lines demonstrated marked baseline activation of XPO1. The median IC_{50} following 72 hour selinexor treatment was 200 nM (IQR 175-435 nM) for MRT, 460 nM (IQR 400 nM-1.4 μM) for ATRT and 1.1 μM (IQR 580 nM-1.4 μM) for 5 non-MRT cell lines. There was a correlation between inferred XPO1 activity and IC_{50} with cell lines with the highest inferred activity being the most sensitive to selinexor. Treatment with selinexor *in vitro* led to cell cycle arrest and induction of apoptosis in MRT cell lines. Post-perturbation RNAseq of selinexor treated cell lines with VIPER dynamic protein activity inference demonstrated decreased activity of XPO1, SWI/SNF complex proteins, kinetochore regulators and cell cycle regulators. *In vivo* treatment of two MRT PDXs with oral selinexor for 15 days significantly inhibited tumor growth in both models ($p < 0.0001$ and $p = 0.0002$). **Conclusions:** Selinexor demonstrates efficacy in preclinical models of MRT. These results supports further investigation of selinexor in a phase II study in children with MRT.

10553 Poster Session (Board #226), Sat, 8:00 AM-11:30 AM

Identification and validation of a 24-gene expression signature for subtype classification of medulloblastoma. *First Author: Qinghua Xu, Institute of Machine Learning and Systems Biology, College of Electronics and Information Engineering, Tongji University, Shanghai, China*

Background: Medulloblastoma is the most common malignant brain tumor in children accounting for about 10% of all pediatric cancer deaths. According to the 2016 WHO Classification, four molecular subtypes of medulloblastoma including WNT, SHH, Group 3 and Group 4 were characterized by high-throughput gene expression profiling. These molecular subtypes display distinct clinical, demographic and genetic features that are associated with prognostic and therapeutic differences. Because it is currently impractical to perform microarray analysis in clinical settings, distinguishing the four molecular subgroups of medulloblastoma in the daily treatment of patients, as well in the setting of clinical trials, remains an important challenge. **Methods:** Three medulloblastoma microarray datasets were curated to perform integrative analysis. To identify a reliable biomarker, a training - validating approach were adopted in this study. The gene expression profiles of 103 samples were selected as a training set for signature identification. Additional 358 samples were used for signature validation.The Gene Ontology and KEGG pathway analysis were performed to reveal the biological features of candidate genes. **Results:** A 24-gene expression signature derived from the training set was strongly associated with the molecular subtypes of medulloblastoma. The 24-gene expression signature was validated in 8 WNT, 61 SHH, 62 Group 3 and 227 Group 4 samples. With the 24-gene expression signature, 8 samples were classified as WNT, 63 as SHH, 73 as Group 3 and 214 as Group 4. The gene expression-based assignments reached a 95.5% overall agreement with the reference diagnoses (342 of 358; 95% CI: 0.928 to 0.974). Sensitivity ranged from 94% to 100%, while specificity ranged from 96% to 100%. The functional enrichment analysis showed that 24 genes were significantly associated with signal transduction and WNT signaling pathway. **Conclusions:** A 24-gene expression signature that could accurately discriminate molecular subtypes of medulloblastoma was identified in this study. Our results may prompt further development of this gene expression signature into a molecular assay amenable to routine clinical practice.

10554 Poster Session (Board #227), Sat, 8:00 AM-11:30 AM

Plasma cell-free DNA for noninvasive molecular profiling in high-risk stage 4 neuroblastoma. *First Author: Prachi Kothari, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cell-free DNA (cfDNA) allows real-time molecular analysis of solid tumors. Neuroblastoma, the most common extracranial pediatric solid tumor, is known to have a higher mutational burden at relapse. In this study, we evaluate the value of cfDNA profiling in a cohort of 21 high-risk stage 4 neuroblastoma (NB) patients. **Methods:** Plasma cfDNA samples were collected near diagnosis or at time of relapse from 21 patients. FISH analysis confirmed 5/21 patients were MYCN amplified. Tumor mutational profiles are known from targeted NGS analysis in 19/21 patients. Plasma cfDNA was analyzed by MSK-IMPACT (468 genes panel) to profile somatic mutations, and shallow whole genome sequencing (sWGS) to look for MYCN amplification. We also evaluated the utility of sWGS to assess tumor-derived mutant allele fractions (MAF) in cfDNA using genomewide z-scores (GWZ). Matched control samples were used to filter germline variants. **Results:** We detected somatic mutations in tumor tissue and cfDNA of 17/19 and 12/21 patients, respectively. These included recurrent drivers such as ALK and ATRX. In 5 patients with MYCN-amplified NB, sWGS sequencing confirmed the same finding in 4. The patients with a GWZ above 2.5 at the time of blood draw were associated with a decreased overall survival. In 1 patient, longitudinal samples were collected after 1 cycle of chemotherapy and pre-/post-surgery, the GWZ decreased as the patient responded to therapy. Two patients with GWZ > 5 (MAF~10%) were selected for WES to perform more comprehensive analysis. WES revealed FGFR1, ARID1A and FOXP1 mutations which have been reported in relapsed high-risk NB patients. Mutational signature analysis using WES data from cfDNA also revealed signature 18 that has previously been reported predominantly in neuroblastoma. **Conclusions:** This study shows the utility of cfDNA analysis through multiple platforms to noninvasively profile the genetic heterogeneity of neuroblastoma, reveal somatic copy number alterations and monitor response to therapy. These findings call for cfDNA analysis to be incorporated in clinical trial to further evaluate its utility for clinical management of NB patients.

10555 Poster Session (Board #228), Sat, 8:00 AM-11:30 AM

Prospective study of ophthalmic artery chemosurgery (OAC) as alternative to enucleation in retinoblastoma. *First Author: Isabelle Aerts, Institut Curie, Paris, France*

Background: Over the past twenty-five years, the introduction of systemic chemotherapy combined to local treatments has enabled to dramatically increase globe retention for retinoblastoma (RB) patients (pts) without using external beam radiation (EBR). OAC has more recently emerged as a primary conservative treatment of RB. **Methods:** We conducted a prospective phase II non randomized study to determine (i) the efficacy of Melphalan OAC in terms of globe salvage rates, without EBR 18 months after inclusion, (ii) patient survival and (iii) adverse events. Pts with unilateral RB group B, C or D without diffuse vitreous seeding or very asymetric bilateral RB including one group D eye were eligible. Pts were nationally referred to Institut Curie and treated by OAC at the Interventional Neuroradiology Department of the Fondation Rothschild. **Results:** Between February 2012 and December 2016, 39 pts with unilateral RB classified by the International Classification of Retinoblastoma as Group B (10.3%), Group C (33.3%), Group D (56.4%), were included. Two pts did not receive OAC, one due to initial catheterization failure, the second to prolonged general anesthesia contra-indication (severe RSV bronchiolitis). Median age at OAC was 19.3 months (3.2-61.6). Median number of OAC cycles was 4 (range 1-6). For 31 pts, OAC was associated to ophthalmological local treatment, starting after the second cycle, by diode laser (31) or cryotherapy (10). All pts are alive, with a median follow-up of 27.1 months from inclusion (2.9 -60.2). Twelve pts did not receive the planed complete treatment: 2 because of secondary catheterization failure, 1 for progressive disease, 3 for medical decision, 4 for intra-arterial procedure related serious complications, 1 for ptosis, 1 for retinal hemorrhage. Twelve serious adverse events were declared including 4 vascular retinal occlusions. 8 pts presented leucopenia. No extraocular RB, second cancer or life-threatening complication occurred. As follow-up of the last pts is actually under 18 months, enucleation rate cannot be yet assessed. **Conclusions:** For advanced RB focal OAC is feasible and generally well tolerated but may expose to some systemic and retinal vascular toxicity. Clinical trial information: NCT02866136.

10556 Poster Session (Board #229), Sat, 8:00 AM-11:30 AM

ADVL1513: Results of a phase 1 trial of entinostat, an oral histone deacetylase inhibitor, in pediatric patients with recurrent or refractory solid tumors. *First Author: Suman Malempati, Oregon Health and Science University, Portland, OR*

Background: Histone modification plays a key role in oncogenesis and progression of malignancy. Histone deacetylase (HDAC) inhibition has shown promise as anti-cancer therapy. Entinostat is an oral small molecule inhibitor of class I and IV HDACs that has not previously been evaluated in pediatric patients. We report the results of a phase 1 study of entinostat in children and adolescents with solid tumors. **Methods:** Children and adolescents (age £ 21 years) with relapsed or refractory solid tumors, including CNS tumors were eligible. Body-surface area ³ 1.17 m^2 was required. Entinostat (1 or 5 mg tablets) was administered orally, once weekly, in 4-week cycles. A rolling 6 design was used to evaluate two dose levels of 3 or 4 mg/m^2. A pharmacokinetic (PK) cohort was enrolled at the recommended dose. **Results:** Twenty eligible patients (10 male, 10 female), median (range) age 14.4 (8 -20) years were enrolled. Diagnoses included patients with CNS tumors (n = 11), sarcomas (n = 6) or other solid tumors (n = 3). Twelve patients were evaluable for DLT. Eight patients were not evaluable due to progression of disease prior to receiving the required percent of protocol prescribed therapy. No DLTs were observed at 3 mg/m^2 (n = 3) or among 9 patients (6 in dose escalation and 3 in the PK cohort) at the 4 mg/m^2 dose level. Grade 3 toxicities included neutropenia (n = 4), lymphopenia (n = 1), and leukopenia (n = 1). Most common non-hematologic toxicities (all grade £ 2) were elevated AST, fatigue, and hypophosphatemia (n = 4 each) and elevated ALT, hypoalbuminemia, and vomiting (n = 3 each). Pharmacokinetics of entinostat were evaluated and will be reported. **Conclusions:** Entinostat was well-tolerated with no DLTs observed. The recommended phase 2 dose in pediatric patients with solid tumors is 4 mg/m^2. Evaluation of entinostat in combination with other agents is planned. Clinical trial information: NCT02780804.

10557 Poster Session (Board #230), Sat, 8:00 AM-11:30 AM

In vitro and xenograft anti-tumor activity, target modulation and drug synergy studies of PV-10 against refractory pediatric solid tumors. *First Author: Lucy Swift, Alberta Children's Hospital, Calgary, AB, Canada*

Background: Children with refractory malignancies who fail conventional treatment protocols endure significant morbidity and mortality. Therefore, studies to identify tolerable and effective therapeutic agents are urgently needed. PV-10 (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein) is a novel therapeutic that in adult tumors induces direct cytotoxicity and stimulates tumor specific immune activation via immunogenic cell death, and is the subject of ongoing clinical study in combination with checkpoint inhibition (NCT02557321). Our studies aim to identify the potential of PV-10 in future clinical trials for refractory pediatric malignancies. **Methods:** A panel of cell lines derived from relapsed pediatric neuroblastoma, Ewing sarcoma, rhabdomyosarcoma and osteosarcoma (n = 20) were treated with increasing concentrations of PV-10 and cell viability was measured by alamar blue assay. Target modulation and induction of cell death pathways were investigated by western blots. The activity of PV-10 in combination with either radiation or a panel of chemotherapeutic agents was measured by cell survival assays and time-lapse microscopy. Mouse xenografts of pediatric solid tumors were injected with PV-10 and tumor growth dynamics were quantified by bioluminescence imaging. **Results:** PV-10 induced cell death in all pediatric solid tumor cell lines (IC50: 20-100 mM) with a measurable therapeutic-window. Western blot analyses showed dose dependent activation of caspases 3, 7 and 9 and PARP cleavage, indicating induction of apoptosis. Drug combination studies showed synergy with DNA damaging agents (including radiation) and agents that target mitosis and cytokinesis such as vincristine and inhibitors of Plk1 and Aurora A kinase. Xenograft studies showed significant reduction of tumor burden in treated mice by comparison to control animals, with corresponding increase in overall survival. **Conclusions:** Our studies provide pediatric solid tumor directed preclinical data for the activity, mechanisms of action, drug synergy and *in vivo* activity of PV-10, to support the formulation of an early phase clinical trial in this population.

10558 Poster Session (Board #231), Sat, 8:00 AM-11:30 AM

NANT 2012-01: Phase 1 study of DFMO and celecoxib with cyclophosphamide and topotecan for relapsed or refractory high-risk neuroblastoma. *First Author: Araz Marachelian, Children's Hosp Los Angeles, Los Angeles, CA*

Background: *MYC* drives polyamine expansion to support its oncogenic functions. Ornithine decarboxylase (Odc) is a direct *MYC* target that is rate-limiting for polyamine synthesis, and is itself amplified in a poor-outcome subset of NB. Difluoromethylornithine (DFMO) is an Odc inhibitor with preclinical activity via protein translation and immunomodulatory effects. We studied dose-escalated DFMO added to celecoxib (polyamine export inducer), Cyclo/Topo. **Methods:** Patients 2-30 years with RR HR NB were eligible. DFMO was studied at four dose levels (DL1-3,000; DL2/2A-4,500; DL3A-6,750; and DL4A-9,000mg/m^2/day po daily) with celecoxib (500mg/m^2/daily), Cyclo (250mg/m^2/day) and Topo (0.75mg/m^2/day) IV for 5 days, with G-CSF. DFMO pharmacokinetics and biomarkers of *ODC* regulation (promoter SNP) and polyamine depletion were performed. **Results:** Twenty-four patients enrolled; median age 6.8 years. Patients received 124 total cycles (range, 1-17). DL1 and 2 used 21d cycles (DFMO given 14/21d). Due to delayed platelet recovery, DL 2A-4A used 28d cycles (DFMO given 21/28d). Toxicities were predominantly hematologic/fever-related. There were three cycle-1 DLTs (hematologic; anorexia; transaminitis) and two DLTs in later cycles (cycle-2 hematuria; cycle-11 hypotension). Eight patients stopped therapy by choice; two due to DLT; 9 due to PD; 3 completed therapy (CR = 1, PR = 2; all at dose-levels ≥4500 mg/m^2/day DFMO); and 2 remain on therapy. Median time-to-progression was 19.8 months. Dose-level 4A exceeded tolerability (2/6 with DLT). Dose-level 3A (6,750mg/m^2/day) is the RP2D. Steady-state C_{min} for DFMO increased by dose-level with median C_{min} of 125mM at DL3A, equivalent to DFMO concentrations achieved in preclinical murine studies in water, and above the exposure needed to inhibit protein translation. **Conclusions:** DFMO and celecoxib added to Cyclo/Topo is tolerable in heavily pretreated NB patients, with a RP2D of 6,750mg/m^2/day. Achievable DFMO concentrations at this dose have demonstrable bioactivity using in vitro and in vivo preclinical models. Further testing with DFMO in combination with chemotherapy in this population is warranted. Clinical trial information: NCT02030964.

10559 Poster Session (Board #232), Sat, 8:00 AM-11:30 AM

Gene expression analysis for improved subtyping of high-risk neuroblastoma. *First Author: Jacob Pfeil, UCSC Genomics Institute, Santa Cruz, CA*

Background: One of the hallmarks of neuroblastoma is molecular heterogeneity, which leads to spontaneous remission in some patients and aggressive, resistant disease in others. Patients with low or intermediate risk have a high 5-year survival rate (90-95%), but high-risk neuroblastoma patients have a survival rate of 40% despite receiving high intensity therapies. **Methods:** Genome-wide transcriptome profiling can be used to stratify high-risk neuroblastoma patients and identify opportunities for molecularly targeted therapies. We developed a gene expression analysis for identifying molecular subtypes in large cancer gene expression cohorts (n > 100). Our method does not rely on a reference normal sample and thus can be applied to pediatric cancers where adequate normal samples are lacking. We applied the method to the TARGET NBL gene expression dataset (N = 162). **Results:** Our analysis identified 6,736 differentially expressed genes. We recapitulated amplification status of the transcription factor MYCN as originally determined in DNA-based assays by TARGET investigators (F1 score = 91%). We also identified two NTRK1 expression subtypes. The first was characterized by over-expression of MYCN, which downregulates expression of NTRK1. Tumors of the second subtype have lower activity for transcription factors that activate NTRK1 expression. Samples with the second subtype also have worse event-free survival than samples with higher NTRK1 expression (Log-rank test: p = 0.013). Thus, the low NTRK1/non-MYCN amplified subtype may benefit from an alternative treatment strategy. Finally, we used our gene expression approach to characterize the immune infiltrate of neuroblastoma patients and identified a subset of samples (~20%) with elevated expression of cytotoxic and regulatory T cell markers, including expression of inhibitory receptors and ligands. **Conclusions:** Our gene expression subtyping approach can tbe used to stratify high-risk neuroblastoma patients and identify opportunities for immunotherapy. Validation of this approach in preclinical models may lead to novel therapeutic strategies for high-risk neuroblastoma.

10560 Poster Session (Board #233), Sat, 8:00 AM-11:30 AM

Impact of survivorship care plans (SCPs) on adherence to surveillance for second malignant neoplasms (SMNs) and cardiac dysfunction in the Childhood Cancer Survivor Study (CCSS). *First Author: Adam Paul Yan, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Since specific treatments increase the risk of SMN and cardiac dysfunction in childhood cancer survivors, the Children's Oncology Group (COG) has published guidelines for SMN and cardiac surveillance. In 2006, the Institute of Medicine recommended that survivors receive a SCP documenting their required surveillance in order to maximize their adherence. The impact of this recommendation on adherence is not known. **Methods:** A survey completed between 2014-2016 by 10,791 survivors in the CCSS ascertained adherence to COG guidelines among those for whom surveillance for breast cancer (N = 657; mammogram/MRI), colorectal cancer (N = 951; colonoscopy), skin cancer (N = 5468; skin exam) and cardiac dysfunction (N = 4310; echocardiogram) was recommended. We estimated adherence rates and identified factors associated with adherence using multivariable logistic regression. **Results:** Median age at diagnosis was 7 years (range 0-21) and time from primary cancer diagnosis was 36 years (16-66). Adherence to recommended breast, colorectal, skin and cardiac surveillance was 45.7% (95 % CI 41.9-49.5%), 38.2% (CI 35.1-41.3%), 22.6% (CI 21.6-23.7%) and 42.3% (CI 41.0-43.6), respectively. 26.9% of survivors and 19.8% of primary care providers (PCPs) had a copy of the SCP. Providing the PCP with a SCP was associated with increased skin cancer surveillance (OR 1.4, CI 1.1-1.7) only. Survivors' having a SCP was associated with increased cardiac surveillance (OR 1.8, CI 1.5-2.2) only. Visiting a specialized survivor clinic in the last year (vs. never) was associated with increased breast (OR 2.0, 95% CI 1.1-3.8), skin (OR 1.3, CI 1.1-1.7) and cardiac (OR 8.9, CI 6.4-12.7) surveillance. **Conclusions:** Less than half of survivors at high risk for SMN or cardiac dysfunction adhere to surveillance guidelines. Few survivors and PCPs have SCPs, and possession of SCPs has limited impact on surveillance. Adherence was most strongly associated with attending a specialized survivor clinic. New initiatives to improve adherence must be developed and tested.

10561 Poster Session (Board #234), Sat, 8:00 AM-11:30 AM

Cardiac outcomes in childhood cancer survivors (CCS): A population-based study. *First Author: Ashna Khanna, University of Toronto, Toronto, ON, CA*

Background: CCS are at an elevated risk for cardiac morbidity due to cancer treatments such as anthracycline chemotherapy and thoracic radiation. Morbidities include congestive heart failure (CHF), arrhythmias, valve abnormalities, pericarditis, and coronary artery disease (CAD). However, cohort-based studies have focused primarily on CHF risk. We conducted a population-based study to determine the incidence of all types of cardiac disease in CCS. **Methods:** Using a provincial pediatric cancer registry, we identified all children $<$ 18 years of age at cancer diagnosis who were treated at a pediatric cancer center in Ontario, Canada between 1987- 2010, and who survived $\geq$5 years from diagnosis. Each CCS was matched to population controls in a 1:5 ratio by age, sex and geographic region. The index date was 5 years after cancer diagnosis. Administrative health datasets were linked to determine the incidence of CHF, arrhythmias, valve disorders, pericardial disease, CAD (including myocardial infarction), and cardiac-related death using established algorithms. Cumulative incidence of cardiac events was calculated in both cohorts, accounting for competing risks of non-cardiac death and adult cancer events. **Results:** We studied 7,354 CCS (median diagnosis age 6 years, IQR 2-12) and 36,647 matched controls. During median follow-up of 11 years (IQR 5-17) from index, 2.5% of survivors vs. 0.8% of controls experienced $\geq$1 cardiac event. At 15 years from index, the cumulative incidence of any cardiac disease was 3.7% (95% CI 3.2-4.3%) in survivors and 1.2% (95% CI 1.1-1.4%) in controls (HR 3.3, CI 2.8-3.9, $p < 0.0001$). Among survivors, the 15-year cumulative incidence of morbidities was: CHF (2.0%, CI 1.6-2.4%), arrhythmias (1.5%, CI 1.2-1.9%), valve disorders (0.5%, CI 0.3-0.7%), pericardial disease (0.5%, CI 0.3-0.7%), and CAD (0.2%, 95% CI 0.1-0.4%). The 10-year incidence of cardiac-related death was 0.1% (CI 0-0.2%) vs $<$ 0.01% (CI 0-0.03%) in controls. **Conclusions:** CCS are at elevated risk for multiple types of cardiovascular disease. Their absolute risk at 15-year follow-up is low, but is expected to increase as they age. Follow-up care of CCS should assess and manage general cardiovascular risk rather than limiting to CHF.

10562 Poster Session (Board #235), Sat, 8:00 AM-11:30 AM

The effect of medical social rehabilitation on quality of life in children with brain tumors: Interim results of observational prospective study. *First Author: Grigory Ja. Tseitlin, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation*

Background: Medical social rehabilitation is promising to support cancer children with the re-entry into 'normal' life. We aimed to study quality of life (QoL) changes in children with brain tumors (BT) after rehabilitation and identify independent predictors of QoL changes. **Methods:** Children of 6–17 y.o. underwent 4-week medical social rehabilitation after the end of cancer treatment (EOT). Children filled out child form of PedsQL and parents – parent form of PedsQL before and after rehabilitation. Statistical analysis included Generalised Estimation Equations (GEE), univariate logistic regression and multiple linear regression. **Results:** In total 82 survivors and their parents (44.4±11.1 y.o., 85% mothers) were enrolled. Mean age of children – 11.8±3.1 y.o.; 57% boys; 19 (23%) pts have overweight/obesity and other 19 (23%) pts have underweight/depletion according to the Body Mass Index (BMI); median duration time after EOT – 26 mos (1–123). According to child-reports QoL increased mainly in terms of emotional and psychosocial functioning ($p < 0.05$); according to parent-reports social, school and psychosocial functioning of children improved ($p < 0.05$). In general, child QoL improvement was revealed with adjustment for age, gender, time after EOT and baseline QoL (GEE, $p < 0.05$). Meaningful QoL improvement (QoL total score change $\geq$4.4) was observed in 58% of survivors. In the final logistic regression model ($\chi 2 = 6.9$, $p < 0.05$), overweight/obesity was independently associated with negative QoL changes after rehabilitation (OR = 6.71, p = 0.008). In multiple regression analysis, overweight/obesity (β -5.52, p = 0.05) and long period ($\geq$5 yrs) after EOT (β -9.56, $p < 0.01$) were associated with negative QoL changes after rehabilitation (R^2= 0.32, $p < 0.05$). **Conclusions:** Medical social rehabilitation is accompanied with QoL improvement in surviving children with BT. Rehabilitation program is not effective in terms of QoL in survivors with overweight/obesity and in those having long period after EOT. It might be taken into account for optimizing rehabilitation in survivors with childhood BT.

10563 Poster Session (Board #236), Sat, 8:00 AM-11:30 AM

Neurofibromatosis type 1 and risk of late outcomes after a primary tumor: A report from the Childhood Cancer Survivor Study. *First Author: Peter de Blank, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH*

Background: It is not known whether survivors of childhood cancer with neurofibromatosis type 1 (NF1) are at increased risk for poor long-term health outcomes. **Methods:** 1,936 $>$ 5yr survivors of childhood cancer diagnosed between 1970-1999 (176 with NF1 and 1,760 non-NF1 survivors matched on diagnosis and diagnosis era) and 5,051 siblings were compared on self-reported chronic medical conditions (CTCAE v 4.0) and cognitive impairment (defined as $> 90^{th}$ percentile of siblings on the CCSS Neurocognitive Questionnaire) using logistic and Poisson regression to adjust for age at survey, age at diagnosis, sex, race, CNS radiation and other treatment exposures. **Results:** Among survivors with NF1, CNS astrocytoma was the most common primary tumor (n = 142, 78%). Compared to non-NF1 survivors, NF1 survivors were more likely to report a serious health condition (grade 3-4; RR[95% CI] 2.2[1.9-2.6]) and multiple chronic conditions (grade 2-4, 1.9[1.6-2.2]). Specific health risks (grade 1-5) are shown below. Curiously, diabetes and abnormal thyroid were less common in NF1 survivors compared to non-NF1 survivors and siblings. Survivors with NF1 were more likely to report impaired organization (OR 1.9 [1.0-3.4]), task completion (1.7 [1.1-2.8]) and learning/memory (1.6 [1.3-1.8]). NF1 survivors were less likely to attend college (0.4 [0.2-0.7]) and be employed (0.6 [0.4-0.9]). **Conclusions:** NF1 impacts risk of health/cognitive outcomes in adult survivors of childhood cancer. Further research should investigate the underlying mechanisms of these risks.

	RR [95%CI]	
Condition	vs nonNF1 survivor	vs Sibling
Diabetes	0.14 [0.07-0.27]	0.22 [0.12-0.43]
Abnormal Thyroid	0.25 [0.19-0.33]	0.54 [0.41-0.73]
Speech Deficit	0.38 [0.18-0.81]	0.64 [0.30-1.35]
Hearing Loss	0.57 [0.48-0.68]	1.24 [1.05-1.4]
Hyperlipidemia	0.69 [0.57-0.83]	1.71 [1.42-2.06]
Osteoporosis/Osteopenia	1.25 [1.05-1.49]	14.9 [12.4-17.9]
Epilepsy	1.71 [1.51-1.95]	7.99 [7.06-9.05]
GI Disease	1.79 [1.57-2.05]	2.80 [2.47-3.18]
Sensory impairment	1.89 [1.69-2.11]	1.66 [1.49-1.84]
Motor impairment	2.05 [1.84-2.29]	4.87 [4.41-5.38]
Heart Disease	2.07 [1.71-2.50]	1.05 [0.88-1.25]
Vision Loss	2.06 [1.81-2.35]	6.26 [5.53-7.09]

10564 Poster Session (Board #237), Sat, 8:00 AM-11:30 AM

Radiation dose and volume to the pancreas and subsequent risk of diabetes mellitus: A report from the Childhood Cancer Survivor study. *First Author: Danielle Novetsky Friedman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Childhood cancer survivors exposed to abdominal radiotherapy (abdRT) are at increased risk for diabetes mellitus (DM). We examined the association between DM risk and pancreatic radiation dose and dose-volume metrics. **Methods:** Participants included 4,527 5-year survivors (median age 35 years, range 10–58; median follow-up 21 years, range 2–34) diagnosed 1970–1999 and treated with abdRT, excluding total body irradiation. We estimated maximum radiation dose to the abdomen, whole pancreas, pancreatic head, body and tail, and volume of the pancreas absorbing ≥10, 20, and 30 Gy (V10, V20, V30). Prevalence of DM, defined by DM medication use, was compared to 4,853 siblings and 15,944 survivors without a history of abdRT using a GEE model with a Poisson distribution adjusted for attained age. **Results:** Survivors exposed to abdRT were 2.9 times more likely than siblings (95% confidence interval [CI] 2.0–4.3) and 1.6 times more likely than survivors not exposed to abdRT (95% CI 1.3–2.1) to have DM. Among those treated with abdRT, the prevalence of DM was 2.9% for survivors aged 31–40 years and 4.7% for those over 40. In multivariable analysis of survivors treated with abdRT, attained age (RR = 1.09, 95% CI 1.06–1.11, $p < 0.001$); body mass index (< 18.5: RR = 1.1, 95% CI 0.4–2.7; 18.5–24.9: reference; 25–29.9: RR = 2.7, 95% CI 1.6–4.6; ≥30, RR = 7.7, 95% CI 4.8–12.4, $p < 0.001$); and pancreatic tail dose (0.1–9.9 Gy: reference; 10–19.9 Gy: RR = 6.3, 95% CI 2.1–18.8; 20–29.9 Gy: RR = 4.7, 95% CI 1.4–16.3; ≥ 30 Gy: RR = 11.4, 95% CI 3.6–36.3, $p < 0.001$) were associated with increased DM risk. An interaction was noted between age at diagnosis and pancreatic tail dose ($p < 0.001$), with the largest differences between tail doses found among those diagnosed at age < 10. Radiation to other regions of the pancreas, by dose or volume, as well as exposure to cranial irradiation, alkylating agents, and corticosteroids, were not associated with DM risk. **Conclusions:** Among survivors treated with abdRT, DM risk is associated with higher pancreatic tail dose, but not with other dosimetric or volumetric factors. Research is needed to identify interventions to decrease cardiometabolic risk in survivors treated with abdRT.

10565 Poster Session (Board #238), Sat, 8:00 AM-11:30 AM

Exercise intolerance among survivors of childhood cancer exposed to cardiotoxic therapy: Identification of survivors at increased risk through myocardial strain and ejection fraction. *First Author: Kirsten K. Ness, St. Jude Children's Research Hospital, Memphis, TN*

Background: Exercise intolerance is an established risk factor for heart failure and death in the general population. Exercise capacity and factors associated with intolerance have not been extensively studied in adult survivors of childhood cancer exposed to cardiotoxic therapy. **Methods:** Survivors exposed to cardiotoxic therapies, without clinical heart failure (N = 577, 52% male, mean age 35.8±8.2 years), and community controls (N = 286, 48% male, mean age 34.4±10.0 years) completed maximal cardiopulmonary exercise testing to determine exercise capacity ($pkVO_2$; intolerance defined as < 20^{th} % tile of age- and sex-specific predicted values) and echocardiography for EF and global longitudinal strain (GLS). EF < 50% and GLS ≥2 SD above age and sex normative values were evaluated for associations with exercise intolerance among survivors in models adjusted for race, pulmonary function, neuropathy, strength, physical activity and smoking. **Results:** Exercise intolerance (93.7%) and abnormal EF (7.6%) and GLS (27.6%) were common among survivors, differing significantly from controls: lower mean $pkVO_2$ (25.8±8.0 vs. 32.9±9.4, $p = 0.001$) and EF (57.6±5.5 vs. 60.3±5.5, $p < 0.001$) and higher GLS (-19.6±2.6 vs. -20.4±3.2, $p < 0.001$). **Conclusions:** Survivors exposed to cardiotoxic agents have dose dependent impairment in exercise capacity. Abnormal GLS, but not EF, is associated with exercise intolerance among survivors, and should be considered in screening guidelines for survivors.

	$pkVO_2$	EF	GLS
Control	32.9±9.4	60.3±5.5	-20.4±3.2
1-199 mg/m^2 anthracyclines	28.7±6.4*	58.4±5.4*	-20.2±2.8
200-349 mg/m2 anthracyclines	27.6±6.5*	58.4±5.4*	-20.2±2.8
350+ mg/m^2 anthracyclines	25.4±6.1*	57.2±4.9*	-19.5±2.6*
Chest RT, any anthracyclines	27.5±4.8*	57.0±3.9*	-19.5±2.0*
Chest RT, no anthracyclines	25.4±7.1*	58.2±6.0*	-19.1±3.0*

*$p < 0.05$ for comparison with control In adjusted models, EF < 50% was not (OR 2.2, 95% CI 0.4-11.1), but GLS ≥2 SD was (OR 3.0, 95% CI 1.1-8.2) associated with exercise intolerance among survivors. In models limited to survivors with EF > 50% GLS identified survivors with exercise intolerance (OR 3.7, 95% CI 1.1-13.0).

10566 Poster Session (Board #239), Sat, 8:00 AM-11:30 AM

Long-term renal function after treatment for Wilms tumor: A report from the St. Jude Lifetime Cohort (SJLIFE) study. *First Author: Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN*

Background: The impact of specific treatment modalities on long-term renal function among adult survivors of Wilms tumor (WT) has not been well-documented. **Methods:** We clinically evaluated 40 WT survivors and 35 non-cancer controls (NCC) with creatinine and cystatin C, estimated the glomerular filtration rate (eGFR) using the Chronic Kidney Disease – Epidemiology (CKD-EPI) equations with and without cystatin C, and, among survivors only, measured ^{99m}Tc diethylenetriamine pentaacetic acid (DTPA) plasma clearance. WT survivors consisted of 20 treated with unilateral nephrectomy (UN), non-nephrotoxic chemotherapy (NNC) and whole abdomen radiation therapy (WART) (mean – 20.2 Gy; standard deviation (SD) – 9.12 Gy), and 20 treated with UN, no radiation therapy, and NNC. Pairwise comparisons between WT survivors treated with and without WART, and of each group to NCC were performed using two-sample t-test. **Results:** WT survivors were female (n = 26), non-Hispanic white (n = 33). Results are shown in the Table. **Conclusions:** Among WT survivors who have undergone UN, long-term renal function is normal in those without WART, and only mildly impaired in some with WART. These data can guide development of future surgical recommendations for patients with WT.

	WART Mean (SD)	No WART Mean (SD)	Controls Mean (SD)	WART vs. No WART p-value	No WART vs Controls p-value	WART vs Controls p-value
Age at diagnosis (years)	4.0 (2.5)	2.3 (1.6)	-	0.013		
Age at evaluation (years)	33.7 (5.2)	28.8 (4.0)	31.5 (5.6)	0.002	0.069	0.152
Elapsed time from diagnosis (years)	30.1 (5.0)	26.9 (4.5)	-	0.040		
Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.2)	0.8 (0.1)	0.754	0.190	0.078
Cystatin C (mg/L)	1.0 (0.2)	0.9 (0.2)	0.9 (0.1)	0.494	0.139	0.024
24-hour urine protein (mg/24 hours)	59.5 (35.7)	146.3 (312.2)	18.5 (80.3)	0.231	0.087	0.013
eGFR (CKD-EPI) (creatinine only) (ml/min/1.73m^2)	88.7 (17.0)	96.9 (22.7)	99.9 (19.2)	0.204	0.606	0.035
eGFR (CKD-EPI) (creatinine and cystatin C) (ml/min/1.73m^2)	90.3 (15.3)	87.4 (14.8)	102.9 (13.8)	0.147	0.173	0.003
^{99m}Tc DTPA plasma clearance (ml/min/1.73m^2)	75.6 (12.1)	91.2 (17.9)	-	0.004		

10567 Poster Session (Board #240), Sat, 8:00 AM-11:30 AM

Racial/ethnic differences in neurocognitive, emotional and quality of life outcomes in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Stephanie Dixon, St Jude Children's Research Hospital, Memphis, TN*

Background: Survivors are at risk of impaired neurocognitive/emotional functioning and health related quality of life (HRQOL). The impact of CNS-directed therapy by race/ethnicity has not been reported. **Methods:** Analyses included 12,257 ≥5-yr survivors of childhood cancer: median age at follow-up 31.2 yrs (range 16.1-54.1), 490 non-Hispanic Black (NHB), 725 Hispanic (H) survivors and 2994 siblings. Self-reported neurocognitive (working memory, task efficiency, emotional regulation, organization), emotional (depression, anxiety, somatization) and HRQOL (components assess physical, emotional and mental health, social functioning, pain and vitality) outcomes were evaluated using the CCSS Neurocognitive Questionnaire, BSI-18 and SF-36. Impact of cranial radiotherapy (CRT) was investigated using general linear models adjusted for clinical/demographic factors to estimate differences in mean scores between survivors and siblings within racial/ethnic stratum. The magnitude of differences for NHBs and Hs were compared to those of non-Hispanic Whites (NHW). **Results:** Among non-CRT exposed survivors, no significant differences were observed between NHB, H and NHW for all neurocognitive, emotional, and HRQOL outcomes. Among CRT exposed survivors, while there were no significant differences for neurocognitive outcomes by race/ethnicity, mean scores for depression differed between H survivors vs siblings (49.9. vs 46.5, $p < 0.001$), which was greater than NHW survivors vs siblings (49.2 vs. 47.7, $p < 0.001$; p comparing differences in means between H and NHW = 0.047). Survivor-sibling differences in mean HRQOL scores for social functioning for NHB (-7.70, $p = 0.02$) and H (-6.27, $p = 0.01$) survivors exposed to CRT were greater than for NHW (-1.48). **Conclusions:** After CRT exposure, there were no differential effects on neurocognitive outcomes based on race/ethnicity. However, minority survivors who received CRT had increased risk for depression and reduced social function. The role of environmental and socio-economic factors in helping survivors recover from CRT exposure should now be investigated.

10568 Poster Session (Board #241), Sat, 8:00 AM-11:30 AM

Chronic pain and disability in long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Cynthia Karlson, University of Mississippi Medical Center, Jackson, MS*

Background: Chronic pain has not been well characterized in survivors of pediatric cancer. The current study is the first to examine prevalence and predictors of chronic pain and pain-related disability in this population. **Methods:** Participants included 10,012 adult survivors (48.7% female; median age 31 years; *M* time since diagnosis 15.3 years) from the CCSS. Participants completed the Short-Form 36 and Brief Symptom Inventory-18 on two occasions between 2002 and 2011. Chronic pain was defined as self-report of moderate to severe pain at both time points. Pain-related disability was defined as pain that interferes with normal work at either time point. Covariates included sex, age, time since diagnosis, treatment, and grade 3-4 chronic health conditions. Multinomial logistic regression estimated relative risk (RR) and 95% confidence intervals (CI) for predictors. Structural equation models examined associations between pain, depression, anxiety, and vitality. **Results:** 29% of survivors reported moderate to severe pain at either time point, 32% reported moderate to severe pain-related disability, and 10% reported chronic pain. Compared to survivors of leukemia, survivors of sarcoma (RR 1.33, CI 1.32-1.34) and solid tumors (RR 1.04, CI 1.03-1.06) reported more chronic pain. Survivors with a history of amputation (RR 1.54, CI 1.52-1.56) and, in separate models, those with chronic health conditions (RR 1.57, CI 1.56-1.59) were more likely to report chronic pain. Survivors with symptoms of depression (RR 1.11; CI 1.09-1.12) and anxiety (RR 1.25; CI 1.24-1.27) were also more likely to report chronic pain. Similar patterns were observed for pain-related disability. Controlling for demographics, treatment, and chronic health conditions, vitality mediated the effects of depression and anxiety on chronic pain (RMSEA 0.011) and pain-related disability (RMSEA 0.000). **Conclusions:** Adult survivors of childhood cancer experience chronic pain and pain-related disability that is associated with amputation, chronic health conditions, depression, anxiety, and poor vitality. Increased screening and comprehensive treatment of pain is warranted, particularly for these risk factors.

10569 Poster Session (Board #242), Sat, 8:00 AM-11:30 AM

Is physical activity and cardiorespiratory fitness reduced among childhood cancer survivors? *First Author: David Mizrahi, UNSW Australia, Sydney, Australia*

Background: Survivors of childhood cancer experience an increasing incidence of late sequelae with age, with the effect on health likely compounded by limited physical activity and low cardiorespiratory fitness (CRF). This study aimed to determine survivors' physical activity levels and to objectively measure CRF, compared with controls. **Methods:** *Stage 1:* We collected physical activity data from parents of survivors aged 7-18 years, ≥5 years after diagnosis, from 11 Australian and New Zealand hospitals and from age-matched controls (International Physical Activity Questionnaire). We compared moderate-vigorous physical activity with American Cancer Society guidelines (≥300 min/week). *Stage 2:* We assessed CRF in survivors aged 8-18 years, ≥1 year after treatment completion, by cardiopulmonary exercise test (Bruce Protocol), 6-minute walk test (6MWT), and self-reported fitness (International Fitness Scale). **Results:** *Stage 1:* 192 parents of survivors (age = 12.9±2.3 years) and 111 parents of control children (age = 12.3±2.7 years) participated. Parents reported survivors participated in more physical activity than controls (248.4±217.6 vs 184.8±213.6 min/week, p = 0.036), with 31% of survivors meeting physical activity guidelines, compared with 22.7% of controls (p = 0.011). *Stage 2:* 31 survivors (age = 13.0±3.5 years) and 10 controls (age = 10.6±1.1 years) completed CRF assessments. Survivors appear to have similar CRF compared with controls in terms of VO2max (41.1 vs 46.8ml/kg/min, p = 0.09; 40^{th} vs 60^{th} percentile, p = 0.11) and 6MWT distance percentile (69^{th} vs 78^{th} percentile, p = 0.30). Among survivors, a weak linear relationship existed between self-perceived CRF and VO2max percentile (r^2= 0.20, p = 0.017). **Conclusions:** Only one-third of childhood cancer survivors met physical activity guidelines, whilst survivors and controls reported similar fitness. Considering the late-effects risks during aging in survivors, regularly assessing physical activity and CRF provides clinicians with vital information to monitor survivors. Although survivors accurately perceived their CRF, the weak relationship reinforces the need for accurate assessment to provide insight into cardiovascular risk.

10570 Poster Session (Board #243), Sat, 8:00 AM-11:30 AM

Neurologic morbidities, psychological distress, and functional independence in adult survivors of childhood cancer treated with CNS-directed therapies: A report from the Childhood Cancer Survivor Study. *First Author: Stefanie C. Vuotto, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of childhood cancer who received CNS-directed therapies are at risk for neurologic sequelae, which may adversely impact psychological functioning and independence in adulthood. **Methods:** Participants included 7,942 survivors of childhood cancer treated from 1970-99 with cranial radiation, intrathecal methotrexate or cytarabine (59% leukemia; 27% CNS tumor; 11% non-Hodgkin; 3% other; mean[SD] age = 25.5[5.8] yrs, time since diagnosis = 17.7[4.6] yrs). Self-reported neurologic conditions included stroke, seizure, sensory deficits, focal neurologic dysfunction, and severe headaches. Emotional distress symptoms (BSI-18) included anxiety, depression, and suicide ideation (SI). Functional independence was assessed using latent class analysis with six indicators (independent living, assistance with routine needs, assistance with personal care needs, ability to attend work/school, driver's license, marital status). Multivariable regression models, adjusted for age, sex, race, pain, and health status, estimated relative risks (RR) and odds ratios (OR) for associations of neurologic morbidity with emotional distress and functional independence. **Results:** Prevalence of neurologic conditions was: 3% stroke; 11% seizure; 25% sensory deficits; 29% focal neurologic dysfunction; 31% severe headaches. In multivariable models, risk of emotional distress was associated with focal neurologic dysfunction (anxiety: RR 1.6; 95% CI 1.3-2.1; depression: RR 1.4; CI 1.2-1.7), sensory deficits (anxiety: RR 1.3; CI 1.0-1.6; depression: RR 1.3; CI 1.1-1.5; SI: RR 1.3; CI 1.0-1.6), and severe headaches (anxiety: RR 1.5; CI 1.2-1.9; depression: RR 1.6; CI 1.4-2.0; SI: RR 1.5; CI 1.2-1.8). Stroke (OR 0.3, CI 0.2-0.5), seizure (OR 0.2, CI 0.2-0.3), and focal neurologic deficits (OR 0.26, CI 0.2-0.3) were associated with decreased likelihood of functional independence. **Conclusions:** Childhood cancer survivors who develop neurologic morbidities are at-risk of emotional distress symptoms, including suicide ideation, and failure to attain independence in adulthood.

10571 Poster Session (Board #244), Sat, 8:00 AM-11:30 AM

Longitudinal assessment of patient-reported cumulative symptom burden as an indicator of chronic health conditions in adult survivors of childhood cancer: A joint report of the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS). *First Author: I-Chan Huang, St. Jude Children's Research Hospital, Memphis, TN*

Background: Adult survivors of childhood cancer experience a high cumulative burden of therapy-related chronic health conditions (CHCs). However, longitudinal evaluation of patient-reported symptoms has not been examined as an indicator of CHCs in this population. **Methods:** 735 long-term adult survivors of childhood cancer completed three symptom surveys through participation in both SJLIFE and CCSS across 25 years (1992-2016). Surveys included 10 symptom domains: sensory, cardiac, pulmonary, musculoskeletal, memory, pain, fatigue, nausea, anxiety and depression. Domains were classified as present vs. absent at each time point and summated with possible scores ranging from 0 to 30. Cardiac, pulmonary and endocrine CHCs were clinically determined after the last survey and graded using modified CTCAE criteria. Poisson regression identified associations of cumulative symptom burden (dichotomized as high [top quartile of the symptom burden scores] vs. low [bottom three quartiles]) with each organ system-specific CHC (grades 2-4 vs. 0-1) and severe/life-threatening CHCs (any grades 3-4 vs. 0-2), adjusting for age, sex, race and education. **Results:** Across the three symptom surveys, survivors' mean ages were 27, 36 and 40 years; mean years from diagnosis was 31 years at the final clinical assessment. Survivors were mostly female (51%), Caucasian (90%) and treated for leukemia (46%). Survivors with high cumulative symptom burden had a 30% increased risk of hypertension/dyslipidemia (RR 1.3, 95% CI 1.1 1.6) and endocrine dysfunction (RR 1.3, 95% CI 1.0 1.7), and a 40% increased risk of respiratory disorders (RR 1.4, 95% CI 1.2 1.8) compared to survivors with low symptom burden. High cumulative symptom burden was associated with a 50% increased risk of having severe/life-threatening CHCs (RR 1.5, 95% CI 1.2 1.9) compared to those with low symptom burden. **Conclusions:** Routine symptom screening may help identify adult survivors of childhood cancer who are at concurrent and/or future risk of hypertension/dyslipidemia, endocrine and respiratory disorders.

10572 Poster Session (Board #245), Sat, 8:00 AM-11:30 AM

The impact of CMV reactivation on HSCT outcomes in children with malignancies: A 13 years single center experience. *First Author: Francesco Baccelli, University of Pisa, Pisa, Italy*

Background: After the introduction of pre-emptive therapy, the incidence of CMV disease dramatically decreased in HSCT recipients, while indirect effects of CMV infection (CMVI) are still under investigation. **Methods:** We retrospectively analyzed children (< 18 years) who underwent first allogeneic HSCT for malignancies at our institution between 01/2003 and 12/2016. CMVI was defined as the presence of pp65 or DNA in any body fluid. Patients were classified according to their CMVI status. 5-years probabilities of OS, DFS, GVHD-free relapse-free survival (GRFS) and infections were estimated using Kaplan-Meier method and log-rank test. Cumulative incidence and Gray's test were used to assess differences in relapse, NRM, aGVHD grades 2-4, extensive cGVHD (e-cGVHD), neutrophils and platelets engraftment. Cox regression was performed to identify possible correlations. Major endpoints are reported in Table 1 with standard errors (SE). **Results:** 92 HSCT were included (CMVI+ N = 40). Groups were homogeneous for age, sex, diagnosis, donors, HSC source and graft composition with the exception of lower median cellularity in UCBU. No significant differences were reported for OS, DFS, infections, GRFS, relapse, NRM, and both neutrophils and platelets engraftment ($p > 0.05$). The mean day of CMVI diagnosis was 39.6 (28.2-51.0). Although statistically non-significant aGVHD grade 2-4 was higher in CMVI+, suggesting a possible association. Noticeable, aGVHD has often preceded CMVI (N = 7 vs N = 1). In contrast, e-cGVHD was less frequent in CMVI+ patients. Remarkably, infections were slightly higher in the early period in CMVI+. **Conclusions:** Despite variations in HSCT procedures and the limited sample size, pre-emptive therapy determined a dramatical decrease in CMV indirect effects. Moreover, aGVHD is a possible risk factor for CMVI but not vice versa. However, further evidences are needed to enlighten the role of CMV in the modern era of pediatric HSCT.

Endpoints (SE)	CMVI+	CMVI-	p
OS	70.0 (.07)	64.5 (.07)	ns
DFS	59.9 (.08)	64.1 (.07)	
Relapse	25.1 (.07)	24.2 (.06)	
NRM	5.0 (.04)	4.1 (.03)	
aGVHD	20.0 (.06)	9.6 (.04)	
e-cGVHD	6.3 (.04)	13.1 (.07)	
GRFS	35.0 (.08)	46.4 (.07)	
Infections	58.3 (.09)	47.8 (.08)	

10573 Poster Session (Board #246), Sat, 8:00 AM-11:30 AM

Comprehensive molecular characterization of pediatric treatment-induced glioblastoma: Germline DNA repair defects as a potential etiology. *First Author: John Thomas Lucas, St. Jude Children's Research Hospital, Memphis, TN*

Background: Pediatric treatment-induced high grade glioma (TIGs) are an incurable late complication of cranial radiation therapy or combined radiation/chemotherapy. We now evaluate copy-number, sequence and epigenetic alterations in an expanded TIG cohort. **Methods:** Whole Genome (WGS) or Whole Exome Sequencing (WES), and Illumina Infinium 450/850K methylation profiling was performed on TIG (N = 34) and non-TIG (N = 29) pediatric high grade gliomas (pHGG) from a multi-institutional cohort and the Childhood Cancer Survivors Study Group. WGS/WES was performed on matched germline DNA from 15 TIGs and 23 non-TIG pHGG. **Results:** Survival between TIG and non-TIG pHGG was comparable (p = 0.43). On methylation profiling, 19/27 TIGs clustered into a subclass of IDH-wild type midline GBM. Recurrent copy number alterations included 1p loss (13/34), 1q gain (13/34), Ch.13 loss (13/34), PDGFRA gain/amplification (17/34), and CDKN2A loss (14/34). WGS identified a mean germline mutation load of 1.50 mut/Mb. There was no difference in the number of coding and noncoding mutations in TIG and non-TIG groups. Noncoding and coding region mutational spectrums seemed to be biased toward A–>G and C–>T respectively. TIG cases had frequent pathogenic germline alterations in DNA repair genes including BARD1, BRCA1, BRCA2, ATR, and PMS1. **Conclusions:** TIGs are enriched for specific defined epigenetic subgroups, and are characterized by recurrent chromosomal aberrations and frequent germline defects in DNA repair pathways.

10574 Poster Session (Board #247), Sat, 8:00 AM-11:30 AM

Retrospective study of age-adjusted growth patterns for height, weight and body mass index in pediatric acute leukemia and lymphoma. *First Author: Charles Phillips, Children's Hospital of Philadelphia, Philadelphia, PA*

Background: Pediatric patients with acute lymphoblastic leukemia (ALL) have a significantly higher body mass index (BMI) than their peers with an expected increase in age-adjusted mean Z-score of 0.81 after completion of cancer treatment. Growth patterns are less well understood for other types of pediatric hematologic malignancies including acute myeloid leukemia (AML), Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL). Understanding the differences in growth patterns between different pediatric malignancies is critical to discern who is most vulnerable to unhealthy weight changes and stunted growth. We describe a single institutional retrospective study of height, weight, and BMI patterns for patients with hematologic malignancies. **Methods:** Study population included patients at the Children's Hospital of Philadelphia from 2011-2017. Anthropomorphic measurements were abstracted from the electronic health record and contained in an electronic health record derived research network, PEDSnet. All acute leukemia and lymphoma patients who received at least one dose of chemotherapy were included. Anthropomorphic measurements were standardized with day 0 corresponding to the day of first chemotherapy administration and followed for 1 year. **Results:** A total of 650 patients met inclusion criteria with the following diagnosis frequency: ALL 377, AML 83, HL 93, NHL 97. As expected, mean BMI Z-score for ALL patients increased during therapy and increased by 0.5 at 1 year. At 1 year, mean BMI Z-score decreased for AML patients by 0.4, increased for NHL by 0.5, and was unchanged for HL. All four cancer groups had a mean weight Z-score change of < 0.3. HL was the only cancer not to have a mean weight Z-score fall during the first 6 months of treatment. Regarding height, ALL and AML patients had a decrease in mean height Z-score of about 0.4 while HL and NHL had no change. **Conclusions:** Acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin's Lymphoma, and Non-Hodgkin's Lymphoma have unique growth patterns in the first year after cancer diagnosis. Hodgkin's lymphoma had the smallest changes in mean height, weigh and BMI Z-scores while acute myeloid leukemia had the largest changes.

TPS10575 Poster Session (Board #248a), Sat, 8:00 AM-11:30 AM

Open-label, dose-escalation, phase 1 study of venetoclax in combination with navitoclax and chemotherapy in patients with relapsed acute lymphoblastic leukemia. *First Author: Thomas Alexander, Department of Pediatrics, University of North Carolina School of Medicine, Chapel Hill, NC*

Background: Acute lymphoblastic leukemia (ALL) relapse in children and adults is associated with poor prognosis. Venetoclax (VEN) is a potent, highly selective BCL-2 inhibitor, and navitoclax (NAV) inhibits various BCL family proteins, including BCL-2, BCL-W, and BCL-X_L. VEN and NAV have shown activity in a variety of ALL cell lines and xenografts, and their combination resulted in synergistic antitumor effect in most ALL xenografts (Khaw et al. Blood 2016;128:1382-95). This trial evaluates VEN in combination with NAV and chemotherapy in patients with relapsed ALL. **Methods:** This is an open-label, multicenter phase 1 dose-escalation trial (NCT03181126) in patients 4–45 years old with relapsed or refractory ALL. Patients receive daily oral VEN, weight-adjusted to match the adult-equivalent exposure of 400 mg. Daily oral NAV administration starts on day 3. Based on the patients' weight, up to 3 dose levels (25, 50, and 100 mg) will be explored. Chemotherapy consists of peg-asparaginase (1,250 IU/m^2 intravenous [IV] on days 9 and 22), vincristine (1.5 mg/m^2 IV on days 9, 15, 22, and 29), and dexamethasone (20 mg/m^2/day orally on days 9–13 and 22–26). At the investigator's discretion, chemotherapy may be delayed, not administered, or repeated for a second cycle. Dose escalation is guided by a Bayesian optimal interval design. For each weight group (< 45 kg and ≥45 kg), the initial cohort at each dose level enrolls ≥3 dose-limiting toxicity (DLT)-evaluable patients, and additional cohorts ≥2. DLTs are assessed during the first 42 days. In the absence of progressive disease, patients may receive VEN + NAV for up to 9 months; thereafter, therapy may be continued for those with ongoing benefit. Primary endpoints are safety and DLTs of VEN + NAV and chemotherapy, and safety and pharmacokinetics of VEN + NAV. Secondary objectives include assessments of antitumor activity and number of patients who proceed to stem cell transplantation. BH3 profiling and comprehensive genomic analysis will be performed to explore biomarkers of disease response. Approximately 42 patients are planned to be enrolled. As of Jan 5, 2018, 3 patients were enrolled at dose level one. Clinical trial information: NCT03181126.

TPS10576 Poster Session (Board #248b), Sat, 8:00 AM-11:30 AM

Phase 1 multicenter trial to assess the maximum tolerated dose, safety, pharmacokinetics, and pharmacodynamics of pazopanib in combination with irinotecan and temozolomide (PAZIT) for children and young adults with advanced sarcoma. *First Author: Kieuhoa Tran Vo, University of California San Francisco, San Francisco, CA*

Background: Sarcomas express pro-angiogenic factors that may represent therapeutic targets. Pazopanib, an oral multi-kinase inhibitor of VEGFR-(1-3), c-kit, and PDGFR, is FDA-approved for the treatment of advanced soft tissue sarcomas. In a phase 1 study of single-agent pazopanib in children with recurrent or refractory solid tumors, this agent was well tolerated and the clinical activity was encouraging in this heavily pre-treated population. Preclinical studies have demonstrated a potential additive or synergistic interaction between anti-angiogenic agents and cytotoxic chemotherapy. The combination of irinotecan and temozolomide is well tolerated and provides a modest degree of antitumor activity in heavily pre-treated sarcoma patients, thus making it a useful platform onto which new compounds may be tested. **Methods:** This is a phase 1, open-label, multicenter trial of pazopanib in combination with irinotecan and temozolomide (PAZIT) in children and young adults ages 6-30 years with relapsed or refractory sarcomas (NCT03139331). The primary objectives are to determine the recommended phase 2 dose, describe toxicities, and describe pharmacokinetic parameters in this population. Secondary and exploratory objectives include evaluation of disease response and exploration of pharmacodynamic effects of PAZIT. Pazopanib is administered orally on days 1-21 of 21-day cycles according to assigned dose level. All patients receive fixed doses of irinotecan IV (50 mg/m^2/day) or PO (90 mg/m^2/day) and temozolomide 100 mg/m^2/day PO on days 1-5. Oral cephalosporin diarrhea prophylaxis is required. Dose escalation follows a standard 3+3 design evaluating up to three pazopanib dose levels. Following dose escalation, up to 10 additional patients will be enrolled to the dose expansion cohort to obtain additional toxicity and efficacy data. Correlative studies include changes in plasma angiogenic factors and circulating tumor DNA. Enrollment began in May 2017 and is ongoing. Clinical trial information: NCT03139331.

11000 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Addressing the burden of cancer in East Africa through cascaded training and education by local doctors. *First Author: Jennifer Eastin, Royal College of Physicians of London (RCP), London, United Kingdom*

Background: Development of cancer services in low and middle income countries (LMIC) is a challenge. The Medical Education, Training and Fellowship (METAF) program aims to improve early detection, research and treatment of cancer in East Africa (EA). Through clinical training courses, participating physicians will be better equipped to diagnose, triage and manage cancer within local hospitals. **Methods:** The EADB, which is responsible for the development of infrastructure in EA, through the British Council, appointed the RCP as the technical partner in this 4-year project. During Year 1, a needs assessment was carried out in Kampala with oncologists from Kenya, Tanzania, Uganda and Rwanda. Course conveners were recruited, curricula developed and two intensive "training of trainers" (TOT) courses delivered with RCP volunteers teaching alongside local faculty. In Year 2, 5 training courses were delivered, including the first round of 'cascaded' courses, facilitated by trainers who participated in the previous TOT workshops, supported by a member of local faculty and an RCP volunteer. Quantitative feedback to evaluate learning was gathered using multiple choice tests at the beginning and end of training. Qualitative feedback was gathered from written evaluations at the end of each course. Course content is continually amended based on country specific needs and participant and faculty feedback. **Results:** Since the launch of the program in 2016, 7 clinical training activities have been delivered; 3 oncology ToT workshops and 4 oncology cascaded training courses. During Years 1 and 2 the total number of doctors trained across East Africa as part of the METAF programme was 137. Participant feedback suggests that over 935 clinical staff will benefit from the knowledge gained on the clinical courses through mentoring by course participants at home facilities. **Conclusions:** The TOT solution to the need for a rapid cascade of knowledge has been well received and demonstrated to be effective within this multinational program. The methodology may be applicable to similar needs in LMIC settings. Lessons learned to date will be implemented during Years 3 & 4.

11001 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Bridging the gap in global advanced radiation oncology training: Impact of a web-based open-access interactive three-dimensional contouring atlas on radiation oncology practice in Russia. *First Author: Natalia Dengina, Ulyanovsk Regional Cancer Center, Ulyanovsk, Russian Federation*

Background: Radiation oncologists (ROs) in Russia face a number of unique professional difficulties including lack of standardized training and continuing medical education. To combat this, under the auspices of the Russian Society of Clinical Oncology (RUSSCO), our group has developed a series of ongoing in-person interactive contouring workshops that are held during the major Russian oncology conferences in Moscow, Russia. Since November 2016 during each workshop, we utilized a web-based open-access interactive three-dimensional contouring atlas as part of our didactics. We sought to determine the impact of this resource on radiation oncology practice in Russia. **Methods:** We distributed an IRB-approved web-based survey to 172 practicing ROs in Russia. We inquired about practice demographics, RUSSCO contouring workshop attendance, and the clinical use of open-access English language interactive contouring atlas (eContour). The survey remained open for two months until November 2017. **Results:** Eighty ROs completed the survey with a 46.5% response rate. Mean number of years in practice was 13.7. Sixty respondents (75%) attended at least one RUSSCO contouring workshop. Of those who were aware of eContour, 76% were introduced during a RUSSCO contouring workshop, and 81% continue to use it in their daily practice. The greatest obstacles to using the program were language barrier (51%) and internet access (38%). Nearly 90% reported their contouring practices changed since they started using the program, particularly for delineation of clinical target volumes (57%) and/or organs at risk (46%). More than 97% found the clinical pearls/links to cooperative group protocols in the software helpful in their daily practice. The majority used the contouring program several times per month (43%) or several times per week (41%). **Conclusions:** Face-to-face contouring instruction in combination with open-access web-based interactive contouring resource had a meaningful impact on perceived quality of radiation oncology contours among Russian practitioners and has the potential to have applications worldwide.

11002 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

The teaching of multi-disciplinary cancer care: A flipped classroom approach. *First Author: Helen Sarah Winter, University of Oxford, Huntingdon, CAMBS, United Kingdom*

Background: Multi-disciplinary team (MDT) cancer care was introduced to improve cancer outcomes in UK. Teaching of MDTs involves observation from the "back of the room". A flipped classroom approach was used as a tool for experiential learning of participation in a meeting. Team dynamics, shared decision-making and representing patient views are important in MDTs. **Methods:** Four true-to -life cancer cases requiring a multi-modality approach were developed. A flipped classroom was developed following feedback from students. Participants were given cases; individual roles with speciality-specific information; links to cancer resources and guidelines for case discussions. Following preparation facilitators set the scene and supported the groups to run the case discussion. Observers gave feedback on the decision-making, team dynamics and how the patient's views were voiced. Participants gave feedback on their participation within the team, reflections on their role, and their learning of cancer care. **Results:** Eighty 4th year medical students each participated in two cases, with on average of 10 participants per case. Students compared their learning with their observational experiences of attending MDTs. Students rated this experience highly as a learning experience. Attendance was high, although not all students had prepared their roles. Feedback on the sessions was positive with the majority of students preferring this as a method for learning about MDTs. Results included reflections on how it felt be to be a member of the team with a different opinion, how group dynamics affected decision-making and suggestions for improvements for the flipped classroom approach. **Conclusions:** A flipped classroom approach to teaching cancer management was rated highly by students. This approach offers a flexible, learning tool that stimulates knowledge application and conceptual understanding. Other professional skills were developed by chairing, presenting evidence from prior preparation and considering the patient's wishes and values. The evaluation of a new innovative way to teach cancer care was well-supported by the students who overwhelmingly have advised to implement the pilot fully into the undergraduate clinical course

11003 Clinical Science Symposium, Sun, 11:30 AM-1:00 PM

Professional development improves geriatric focused oncology activities in settings across the nation. *First Author: Denice Economou, City of Hope, Duarte, CA*

Background: Although older adults represent the majority of patients with cancer, oncology nurses receive little training in the care of older patients. In an effort to bridge this knowledge gap, an NCI-funded R25 grant supported the development and implementation of an educational curriculum in geriatrics for oncology nurses. **Methods:** Competitively chosen 3-person nursing teams (manager, educator, and clinical provider) from cancer settings across the nation participated in a 2 $^1/_2$ day course in geriatrics for oncology nurses. Teams developed 3 goals aimed to improve geriatric oncology care in their settings. Goals were coded into detailed subcategories by PI and Co-Is. Code categories included: research-focused, clinical care, education, geriatric assessment, symptom focused, caregiver-related, infrastructure/team building, and other. Progress in implementing the goals was tracked at 6, 12, and 18 months post course. Goal completion rate over time was analyzed using generalized estimating equation for repeated measure. **Results:** 99 nurses (34 teams) participated in the 1st conference. A single goal may have had 2-3 codes applied and therefore 3 goals per 34 teams yielded a total of 181 codes. The most common goals focused on improving geriatric oncology clinical care (23%; N = 41 codes), professional education (23%; N = 41), geriatric assessment (9%; N = 16), infrastructure/team building (8%; N = 14) and resource development (7%; N = 13). Overall goal achievement at 6, 12, and 18 months was categorized as never started (29%, 7%, 4%), stopped (2%, 10%, 15%), stalled (9%, 20%, 13%), in process (48%, 38%, 30%) and completed (13%, 25%, 37%). Fourteen (8%) of the 41 clinical care goals and 8 (4%) of the education goals had stopped or stalled. Four teams had goals that were not started by 18 months. Goal completion rate increased significantly from 6 to 18 months ($P < .0001$). By 18 months, 67% of the goals were either in process or completed. **Conclusions:** An education curriculum in geriatrics for oncology nurses was implemented. Over the subsequent 18 months, nurses enacted goals to improve geriatric oncology care in their institutions. Continued follow-up and support is needed post course to foster goal completion.

11004 Poster Session (Board #1), Mon, 8:00 AM-11:30 AM

Quantitative assessment of learning behaviors for oncology providers. *First Author: Marie Wood, University of Vermont, Burlington, VT*

Background: Understanding how different types of providers choose topics and activities for learning is key to meeting their needs. We sought to identify these needs in a diverse group of oncology providers. **Methods:** An online focus group study was conducted between November 2015 and August 2016. Participants were ASCO members and chosen by convenience and stratified random sampling. Participants included international, domestic, academic, and private practice providers as well as physicians and advanced practitioners (AP). Providers were asked monthly to journal their learning needs and explain how they identified that need. They were then asked what learning activity they chose to meet that need and what informed their choice. **Results:** 201 journal entries from 32 providers were reviewed; 47% from academic settings, 9% APs, and 41% international. Individuals provided an average 6 entries (range 1 to 17). Learning needs were associated with practice setting and professional role, with a significant association between practice setting and a making a choice based on a self-identified knowledge gap ($p = .005$). Colleague recommendation impacted learning needs for APs ($p < .001$), and patient cases drove $> 50\%$ of identified learning needs across groups. Preference for learning activity type, formal versus informal, was associated with practice setting ($p = .02$). The choice of learning activity was associated with practice setting, professional role, and geographic location, with international providers more likely to consider cost ($p = .001$) and provider reputation ($p = .03$) when selecting activities. Colleague recommendation was important for APs ($p = .011$). Over 75% of learner responses identify convenience and quality of content as factors in choosing an activity. **Conclusions:** To our knowledge, this study represents the first quantitative assessment of learning behaviors for oncology providers and shows that identification of learning needs and activity selection differ among them. Our cohort was small and may limit the generalizability of our findings. Future research should focus on educational needs of different members of the oncology care team and rank priorities for learning.

11006 Poster Session (Board #3), Mon, 8:00 AM-11:30 AM

Development and implementation of an instrument for assessing the proficiency of oncology fellows in the delivery of bad news. *First Author: Mark Allan Hoffman, Long Island Jewish Medical Center, New Hyde Park, NY*

Background: Breaking bad news is the quintessential difficult communication task for oncologists. Baile et. al., (The Oncologist, 2000) published SPIKES, a six step protocol for delivering bad news. "S" stands for optimizing the environment and physical approach to the patient, "P" assessing the patient's perception, "I" obtaining invitation to give the news, "K" giving knowledge, "E" addressing emotion and "S" summary and strategy. **Methods:** At Northwell Cancer Center, we have recently developed a 2-month Communication Course for multidisciplinary first year oncology fellows, addressing core communication skills, spirituality/coping, assessing for depression, discussing sexuality, delivering bad news, communication with adolescents/young adults, communication with families and transition to palliative care. We have formulated a version of SPIKES, named "MR. SPIKES" for teaching bad news delivery. "MR." represents pre-encounter Mental preparedness and Rehearsal (agenda setting, anticipating patient's concerns). The "S" now encompasses six functions: Summary, Strategy, Survey of all concerns, Sustaining realistic hopes/goals, Support/reinforcement of coping systems and Statement of continuing partnership. A 21-item assessment tool was synthesized assessing the expanded SPIKES component of MR.SPIKES (2 items for setting, 6 items for emotion/empathy,1 item for perception, 1 for invitation,2 for preparation,4 for delivery of news, 1 for strategy, 1 for concerns,1 for hope/goals, 1 for coping assessment, 1 for partnership). The tool was then used by 4 experienced raters to assess videotaped encounters between trainees and standardized patients. **Results:** Preliminary assessment of inter-rater reliability using Gwet's $'AC_1$ resulted in coefficients ranging from moderate to substantial (0.47 to .075) agreement. Inter-item reliability was also good (Cronbach's alpha of 0.84). **Conclusions:** A 21 item instrument based a modified version of SPIKES has been developed to assess proficiency of trainees in breaking bad news, and has shown very promising reliability.

11007 Poster Session (Board #4), Mon, 8:00 AM-11:30 AM

Creation of a high-fidelity simulation tool to teach competency in radiation oncology treatment plan evaluation. *First Author: Jenna Adleman, Radiation Medicine Program Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Although treatment plan evaluation (TPE) is a core competency for radiation oncology residents, gaps in teaching exist. The purpose was to create an interactive TPE case bank for residents to improve competency. **Methods:** A needs assessment informed case bank development. Residents assessed their confidence in TPE using a 10-point Likert scale (1 = least, 10 = most confident). A list of clinically unacceptable plans were compiled and categorized by clinical site, reason for rejection and relevance. An interactive web-based DICOM-RT tool was used to query and interact with the case bank database. A companion software tool, acting as an interactive simulation platform, was created allowing user interaction. **Results:** Twenty-three participants (70%) responded to the needs assessment: 6 junior, 7 senior and 10 former residents. Opportunities for improving TPE were identified; the mean confidence scores were: target coverage assessment (6.3+ 2.7), doses to normal tissue (6.2+2.5), conformity (5.5 +2.6), plan acceptability (5.4+2.5) and ability to suggest improvements (4.8+2.3). Extracted themes for case bank development included incorporating diverse clinical sites, target coverage/normal tissue assessment, conformity and provision of feedback. Of the 677 clinically unacceptable plans, a final list of 50 were selected for inclusion. They were categorized, anonymized and imported. Additional (un)acceptable plans were generated to augment the case bank where required. The companion simulation software platform describes each clinical scenario and allows residents to enter their assessment and suggested corrective action (if applicable). The platform then provides immediate feedback, including error description and correction strategy. **Conclusions:** An innovative TPE case bank has been created to address a learning gap in radiation oncology training. The high fidelity simulation format allows case interactivity and feedback with the goal of improving TPE competency. This platform can be leveraged for teaching/assessment in competency based medical education. Future work will evaluate resident satisfaction with and effectiveness of the case bank as a learning tool.

11008 Poster Session (Board #5), Mon, 8:00 AM-11:30 AM

Implementation of a model for training and career development in the emerging academic field of global oncology. *First Author: Rebecca Deboer, University of California, San Francisco, San Francisco, CA*

Background: As interest in global oncology increases, the need to support early career investigators is a priority, as advocated by the ASCO Global Oncology Leadership Task Force. The Global Cancer Program (GCP) at UCSF strives to implement a novel multifaceted strategy to support trainees from UCSF and our partner institutions in low and middle-income countries in pursuing careers focused on global cancer research and capacity-building. **Methods:** In 2017, the GCP launched a Global Cancer Fellowship (GCF) for post-doctoral trainees, Future Global Cancer Leaders (FGCL) monthly seminar, and quarterly Global Cancer Lecture Series. GCF protects research time, provides mentorship, and lends credibility to an unprecedented career track in this emerging field. FGCL is a multi-disciplinary group of students, residents, fellows, and others who convene to share experiences, present works-in-progress (WIPs), and interact with faculty mentors and visiting experts. After one year GCP evaluated the feasibility and adoption of this strategy and measured early indicators of effectiveness with an anonymous survey administered to FGCL members. **Results:** Post-doctoral trainees in public health (DB; Nepal), medical oncology (RJD; U.S.), and surgery (MM; Kenya) were selected as inaugural GCF recipients in 2017-18. Monthly FGCL seminars were regularly attended; 21 trainees responded to the survey. Despite variable training levels and disciplines, 19 (90%) reported that the meetings were "just right" for their level. All meeting formats were rated as very or extremely valuable to career development (4-5 on a 5-point Likert Scale) by a majority of respondents. The most preferred formats were "town halls" with visiting experts (89% Likert 4 or 5), faculty lectures (85%), presenting a WIP (74%), and reviewing a WIP presented by a peer (70%). **Conclusions:** A multifaceted strategy to support trainees in pursuing global oncology careers is feasible, adopted with high fidelity, and effective by early measures. In 2018, the GCP aims to expand support for trainees at partner institutions; for example, providing funding and mentorship for pilot research projects submitted by trainees at our partner institution in Tanzania.

11009 Poster Session (Board #6), Mon, 8:00 AM-11:30 AM

Global oncology fellowship electives: The impact on cancer care and international collaborations. *First Author: John Butonzi, Ministry of Health, Butaro, Rwanda*

Background: To meet the rising demand for cancer care in low-middle-income countries (LMIC's), an accredited Global Health track in Hematology-Oncology Fellowship programs (HOFP) is needed. To determine feasibility, the Geisel School of Medicine at Dartmouth (GSMD) HOFP piloted a bi-annual, one-month elective in Rwanda supervised by GSMD faculty. Objectives included exchange of knowledge in a resource-stratified setting and engagement in scholarly collaborations. **Methods:** Program objectives were implemented by GSMD HOFP in partnership with the Rwandan Ministry of Health, the NGO Partners In Health, and the Butaro Hospital Cancer Center of Excellence (BCCOE) in Butaro, Rwanda. Mentorship opportunities, formal lectures, organizational changes, research projects and funding sources were tracked. Fellows were evaluated using ACGME clinical competencies. **Results:** The 2-year pilot program was 100% enrolled by fellows from 3 US HO programs and one rising first year HO fellow (N = 4). Seven educational, research and quality improvement projects and three organizational changes were implemented. Three grant proposals for research collaborations are in process. Fifty percent of participating fellows plan to pursue careers in Global Health. The HO fellows gained perspective on cancer care and capacity-building in a LMIC, and confidence in teaching. BCCOE staff gained knowledge and mentorship, ideas for quality improvement, and increased expertise with treatment protocols. Rwandan colleagues valued the solidarity generated by a long-term partnership. Faculty were funded by a combination of CME, Fellowship and Vacation time. **Conclusions:** A global oncology fellowship elective is feasible and has a qualitative impact on care delivery and collaboration in LMICs influencing fellows' career choices and professional growth of colleagues at partner sites. Long-term partnerships complement the task-sharing approach to cancer care. Financial sustainability requires formal institutional support for faculty participation. A Global Health track in HO that includes international applicants from LMICs will encourage multi-disciplinary collaboration and expand our capacity for quality global cancer care.

11010 Poster Session (Board #7), Mon, 8:00 AM-11:30 AM

Ten years of ASCO/ESMO global curriculum for training in medical oncology implementation at Instituto Oncologico Nacional in Panama City, Panama. *First Author: Omar Orlando Castillo Fernandez, Instituto Oncologico Nacional, Panama City, Panama*

Background: Cancer is a leading cause of death in Panama. In 2007 the Instituto Oncologico Nacional endorsed the ASCO/ESMO global curriculum core (GCC) for training in Medical Oncology with a view to address the lack of cancer specialists in the country. The aim of this study is to evaluate the benefit of GCC to our institution. **Methods:** We assess the benefit in three ways: Human resources benefit (the number of medical oncologist before and after the GCC implementation, numbers of fellows, number of fellows visiting from others countries/ programs), Academic benefit (papers published and posters presentations in International Oncology meetings) and Inter-institutional benefit (number of academic center outside Panama receiving our fellows for observership and clinical rotations). **Results:** The proportion of medical oncologist in the institution has increased in 300% (from 4 to 14). Over this decade 15 fellows have been admitted (12 from Panama, 3 from Dominican Republic. 10 graduated and 5 currently in training). We have hosted clinical rotation visits from others medical oncology regional programs: 3 from Dominican Republic, 1 from Peru, 1 from El Salvador, 1 pathologist from Colombia, 1 surgical oncology form Nicaragua and 1 interventional radiologist from Costa Rica. Eight papers have been published in collaboration with mentors from others institutions and 18 posters were presented in International Oncology Meetings (1 ASCO Annual Meeting , 4 ESMO Congress, 4 ENETS Conference, 2 SABCS, 2 IASLC WCLC, 2 ESMO-WCGC, 4 LALCA-IASLC). Our fellows have undergone clinical rotations in academic centers in United States (Memorial Sloan Kettering Cancer Center, Cleveland Clinic, Massachusetts General Hospital Cancer Center) and Europe (Vall d´Hebron University Hospital, Instituto Valenciano de Oncologia and Instituto Oncologico Rosell). **Conclusions:** To integrate ASCO/ESMO GCC to local training programs offers assistance and academic benefits to institutions in developing countries. Closer relations with mentors and academic centers in developed countries is key to inspire and motivate fellows and trainers.

11011 Poster Session (Board #8), Mon, 8:00 AM-11:30 AM

Use of medical simulation for cancer education in Nigeria. *First Author: Kelechi Ngozi Eguzo, University of Saskatchewan, Saskatoon, SK, Canada*

Background: Among the many limitations of cancer control in Nigeria are lower awareness/competence and poorer training of healthcare professionals (HCP). These manifest as deficiencies in advocacy, screening /diagnostic practices, and patient management. Medical simulation (MS) using models is an effective approach for sustainably improving the competence of HCP, especially regarding clinical breast examination (CBE), pelvic examination (PE) and digital rectal examination (DRE). Study evaluates the effect of MS during a Nigerian training course focusing on CBE, PE and DRE. It answers the question: what are the perspectives of HCP on use of MS for cancer education? **Methods:** Participants included a convenience sample of Nigerian physicians and nurses who attended the ASCO-sponsored Multidisciplinary Cancer Management Course. Intervention was MS using high-fidelity models. The models demonstrated normal anatomic and common pathologic features of the breast, cervical and prostate. Participants cycled through MS stations (i.e. CBE, PE and DRE). Pre-and post-training surveys with comments evaluating self-reported comfort levels were basis for comparison. Data analysis included descriptive statistics, Wilcoxon signed rank test, chi-square and thematic analysis. **Results:** Of the 92 course participants (physicians-36, nurses-16), 51 completed the course evaluation forms (response rate = 55.4%; 51/92), and average number of years in practice was 8 (±5.2) years. Pre-training survey showed non-significant differences in practices patterns; 71% (22/35) of physicians rarely performed PE (p = 0.92), and 93% (14/16) of nurses rarely performed DRE (p = 0.07). According to some participants, "the use of simulation is quite commendable as it gives room for improvement before using a human; "it is the best method of learning I have ever enjoyed." **Conclusions:** MS-based training significantly improved the comfort levels of participants regarding CBE and PE, as well as their likelihood to perform CBE, PE and DRE. Participants recommend widespread use of MS for continuing medical education and undergraduate training.

Comfort levels	Median	IQR	P-value
CBE (Pre)	4	4-4	< 0.01
CBE (post)	5	4-5	
PE (Pre)	4	2-5	< 0.01
PE (Post)	5	4-5	
DRE (Pre)	3	1-5	0.01
DRE (Post)	3	1-4	

11012 Poster Session (Board #9), Mon, 8:00 AM-11:30 AM

Assessing trainee's need and readiness for e-cancer education and training in Africa. *First Author: Omoruyi Credit Irabor, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: As a prerequisite to launching a virtual education and training platform, the African Organization for Research and Training in Cancer (AORTIC) assessed the educational needs and e-Learning readiness of Sub-Sahara African oncology staff before designing ICT support systems. **Methods:** Using existing assessment models, we developed a self-assessment tool for a cross-sectional survey. Competence areas assessed include basic knowledge, early detection and diagnosis, clinical skill, cancer registry, and cancer management respectively. Components of e-Learning readiness assessed include access to technology, technological skills/ competence, capacity for self-directed learning, confidence prerequisite skills, and motivation. We calculated an average score for each component as (Sum of positive response/Sum of responses). **Results:** There were 128 respondents. 33%, 44%, 48%, 58% and 60% felt they needed further training in the areas of basic knowledge, early detection and diagnosis, clinical skill, cancer registry, and cancer management respectively. Reported internet access for e-Learning is 100%, significantly higher than the 31.2% internet penetration of Sub-Sahara Africa. However, only 15.7% have a bandwidth of quality to support real-time visual learning. Weighted averages for technological access, skill, competence, capacity for self-directed learning, motivation, and prerequisite skills was 69%, 86%, 51% 42% and 80% respectively. **Conclusions:** There are deficiencies in the training of oncology health professionals in all five competency areas, and e-Learning can supplement ongoing traditional training to meet the gap. The low access to the internet in Africa may not be disruptive to asynchronous oncology training but may limit real-time video-based synchronous learning which involves more intense interaction between trainees and trainers. However, African bandwidth growth trend indicates this limitation is fast diminishing. African oncology health professionals are technologically competent for e-Learning and score high in the prerequisite skills. There is, however, a low ability for self-directed learning, and many may need a support system for the advanced virtual education.

11013 Poster Session (Board #10), Mon, 8:00 AM-11:30 AM

Impact of closed Facebook group participation on women hematology/oncology physicians. *First Author: Julia Lee Close, University of Florida, Gainesville, FL*

Background: Making meaningful connections is an important aspect of career satisfaction. The Hematology Oncology Women Physician Group (HOWPG) is a private Facebook (FB) group of 936 women who practice within the hematology and oncology (H/O) field. We hypothesized that HOWPG adds value to the education, emotional wellness, and practice of oncology for its membership. A survey was conducted within HOWPG to define the impact this group has on members. **Methods:** A voluntary, anonymous 12-question online survey was distributed to members of HOWPG by sharing the survey link in the FB group 4 times between 11/16/2017-1/03/2018. Participants were surveyed regarding demographic data, general FB use vs. exclusive use of HOWPG, and opinions regarding HOWPG value and impact. Survey was approved by University of Florida institutional review board. **Results:** Of the 936 members of the site, between , and 169 completed the survey. 9% were fellows, 65% in practice $<$ 10 years, 26% $>=$ 10 years. 62% were less than 40 years of age and 35% between the ages of 40-49. 85% practice adult H/O, and the remainder divided between pediatric H/O, radiation oncology, surgical specialty and palliative care. 90% use FB at least daily, with 82% accessing the HOWPG group at least daily, 16% using less than daily but at least twice per week. The most common uses for the site included education (65%-89%), advice on complex cases (65%), emotional support (65%), and networking (55%). On a scale of 1-10, learning from clinical cases (9.0) and emotional support (8.4) were rated the most beneficial aspects. The aspects of the group rated most important were: membership limited to women, physicians, in the H/O field, secret group. **Conclusions:** The HOWPG FB group has provided an opportunity for education, clinical and emotional support. Social media can be an effective venue to educate physicians, augment patient care via advice, foster networking, reduce burnout, and improve career satisfaction amongst women physicians in the field of hematology and oncology.

11014 Poster Session (Board #11), Mon, 8:00 AM-11:30 AM

Oncology education for family medicine (FM) residents and family physicians (FPs): A needs assessment survey. *First Author: Steven Yip, BC Cancer Agency Vancouver Cancer Centre, Vancouver, BC, Canada*

Background: Cancer care demands in FM continue to grow. This study aimed to determine the current state of oncology education in FM and examine opinions regarding optimal FM oncology education. **Methods:** A survey was designed to evaluate ideal and current oncology teaching, topics and objectives in FM post graduate medical education (PGME) and continuing medical education (CME). The survey was pilot-tested and sent to FM residents and FM program directors (PDs) across Canada and FP Cancer Care Committee members of the College of Family Physicians of Canada. **Results:** From May 1 - August 31, 2017, 131 FM residents and 15 FM PDs affiliated with 16 of 17 Canadian medical schools and 42 FPs completed the surveys. The PGME survey results are in Table 1. Residents reported that the best way to learn oncology is through clinical experiences alone. PDs stated that case-based and didactic teaching are also important. Residents and PDs agreed that the most important topics are cancer prevention, cancer screening, breaking bad news, and palliative care. These topics were taught to 89-100% of residents. Yet, the other important topics of appropriate cancer patient referrals, managing cancer complications and post-treatment surveillance were only taught to 52%, 40% and 36% of residents, respectively. According to 40% of FPs, the amount of oncology CME completed was inadequate; 21% reported that CME inadequately updates their knowledge in cancer patient management. **Conclusions:** Current FM PGME oncology education is sub-optimal across Canada, although the degree differs between the opinions of the residents and PDs. Sub-optimal oncology teaching is also likely for FM CME. FM oncology education can be improved using suggestions generated from this survey.

PGME results.

	Residents	PDs
There is an oncology clinical rotation	118/130 (91%)	15/15 (100%)
There are oncology learning objectives	17/130 (13%)	5/15 (33%)
Cancer topics are taught in clinic	73/127 (57%)	15/15 (100%)
Oncology education provided is adequate	10/130 (8%)	3/15 (20%)
Training adequately prepared me to care for cancer patients	11/130 (8%)	2/15 (13%)
Standardized oncology learning goals, objectives and competencies would be useful	93/128 (73%)	8/15 (53%)

11015 Poster Session (Board #12), Mon, 8:00 AM-11:30 AM

Utilization of a web-based supportive oncology training curriculum for healthcare professionals (HCPs). *First Author: Shelly S. Lo, Loyola University Medical Center, Maywood, IL*

Background: A challenge in supportive oncology, is training the HCP workforce. A collaborative funded by The Coleman Foundation of 30+ clinicians (faculty) from 25 institutions (academic, community & safety net) developed a unique and easily accessible supportive oncology training curriculum (Trosman JR JNCCN 2017). **Methods:** Using data provided by The National Comprehensive Cancer Network (NCCN) Continuing Education team, we evaluated completion rates of survivorship and supportive oncology education courses using simple frequencies. **Results:** Over 4748 on-line courses were completed (pretest, course, post-test, evaluation) of 7184 accessed. Of 4748 courses, nurses completed 45%, physicians 17%, advance practice clinicians 16%, and others 22% (social workers, chaplains, MAs). Course completion improved from 65% to 69% after articles describing collaborative work were published in Cure and Oncology Nursing News, p = 0.0014. **Conclusions:** A variety of HCPs successfully completed supportive oncology education via the NCCN's education portal. These on-line courses are an efficient way to train HCPs in supportive oncology. Curriculum advertising improves course completion.

Education Course	Accessed	Completed	Completion Rate
Distress: Impact on Care, Screening for and Addressing	621	456	73%
Survivorship Factors: Lifestyle/Behavior, Psychosocial Challenges, Late & Long-term Effects	569	404	71%
Primary Palliative Care vs. Specialized Palliative Care and Reasons to Refer to Hospice and Palliative Care	465	324	70%
Cancer Survivorship Defined, Patient Needs, and CoC Requirements for care plans	584	405	69%
Supportive Care and Documenting Patient's Supportive Needs	507	350	69%
How to Discuss Practical and Family Concerns	384	263	68%
Comprehensive Care for Cancer Survivors	485	326	67%
Cancer Survivor Screening and Genetic Testing	523	341	65%
Pain Assessment: The Basics	542	352	65%
Nausea/Vomiting, Constipation, Dyspnea & Shortness of Breath	690	441	64%
Goals of Care and Advance Care Planning over Time	408	248	61%
Pain Management: Beyond the Basics	619	373	60%
POLST Paradigm: Physician Orders for Life Sustaining Treatment Paradigm	284	169	60%
How to Communicate Prognosis	503	296	59%
Totals	**7184**	**4748**	**66%**

11016 Poster Session (Board #13), Mon, 8:00 AM-11:30 AM

Gender differences in faculty rank amongst radiation oncologists in United States: A cross-sectional study. *First Author: Irbaz Bin Riaz, Mayo Clinic, Rochester, MN*

Background: Female faculty in academic medicine is underrepresented in leadership positions and reportedly has fewer publications, lower h-indices and grant funding. However, there is a lack of evidence examining whether this gender disparity persists after adjusting for scholarly productivity and clinical experience among academic radiation oncologist. **Methods:** We used the Fellowship and Residency Electronic Interactive Database (FREIDA) to identify faculty members of radiation oncology residency training programs in the US . Faculty rank (assistant, associate and full professor) was obtained by review of program website. Data on physician gender, clinical experience in years, number of publications, *h*-index, clinical trial investigator, advance degree and ranking of medical school was collected using program websites, Doximity and Scopus databases. Primary outcome of the study was a binary outcome odd of professorship versus assistant plus associate professorship. We used a multivariable logistic regression model to estimate the gender difference in full professorship after adjusting for these factors. **Results:** A total of 906 radiation oncologists were included in the final analysis. 70.2% (n = 636) were men and 29.8% (n = 270) women. Women had less clinical experience (median of 10 years vs 14 years, $p < 0.0004$), fewer publications (median of 17 vs 32 publications, $p < 0.0001$), less *h*-index (median of 7 vs 12, $p < 0.0001$), less likely to be clinical trials investigator (41% vs 48%, p = 0.05), less likely holding advance degree (22% vs 28%, p = 0.067) but were more likely to be graduate of top 20 medical schools in research (27% vs 25%, p = 0.66). Women were under represented at higher faculty rank with 43 out of 270 (15.9%) were full professors compared to 194 out of 636 (30.5%) men with the absolute difference of 14.6% ($p < 0.001$). Moreover, women were found less likely to be full professors compared to men (odds ratio, 0.55; 95% confidence interval, 0.32-0.94; p = 0.029) in adjusted logistic regression analysis. **Conclusions:** Among radiation oncology faculty gender disparity exists at higher faculty ranks even after accounting for academically relevant factors influencing the academic progress.

11017 Poster Session (Board #14), Mon, 8:00 AM-11:30 AM

Opportunities for provider education in the use and interpretation of liquid biopsy. *First Author: Christine Elaine Lee, Guardant Health, Inc., Redwood City, CA*

Background: Increasingly affordable comprehensive genomic profiling (CGP) has exponentially expanded the amount of data available to oncologists, and liquid biopsy has made CGP more accessible. Given comprehensive liquid biopsy has only been commercially available since 2014, and the average age of a practicing oncologist is 52, liquid biopsy education was not a component in the majority of providers' formal training. Data from both community and academic settings suggests physicians' confidence around interpretation of genomic tests may play a critical role in clinical decision making. Physician knowledge is also a strong predictor of physicians' anticipated use of testing. Although liquid biopsy has gained in popularity and acceptability, little is known about providers' confidence in interpreting these results. **Methods:** Between 1/2016 and 1/2018, we prospectively documented provider calls with test-related questions. We then attempted to characterize major themes in provider inquiries related to genomic testing and liquid biopsy. **Results:** 811 consecutive provider contacts were recorded. Of those, 434 included completed survey data. Approx. 75% of these contacts originated from community-based practices and almost 70% of contacts were from providers who had ordered 5 or less tests. Of genomic questions, 49% were specific to liquid biopsy and most providers had ≥ 2 questions. Common questions about cfDNA results included: Is there enough mutation present to warrant treatment? (13%), What is the ideal timing of testing? (11%), Could this mutation be hereditary? (11%), What does mutant allele fraction mean? (8%). Interestingly, over 25% of all providers surveyed had questions regarding basic genomic principles not specific to liquid analysis. The remainder of questions varied, but many were related to NGS technology. **Conclusions:** Providers in both community and academic centers sought genomics support when interpreting a comprehensive liquid biopsy result. Questions regarding general genomics and liquid biopsy were asked at similar rates in this analysis. Though liquid analysis is an emerging field, our data suggests there is still a need for basic genomic education across provider types.

11018 Poster Session (Board #15), Mon, 8:00 AM-11:30 AM

Prospective study of the perceptions of oncology residents about learning from tumor boards. *First Author: Ramachandran Venkitaraman, Ipswich Hospital, Ipswich, United Kingdom*

Background: Tumor boards are a unique and integral component of oncology practice. Participation in the tumor board is an important aspect of education of oncology residents. This qualitative study based on phenomenological methodology, was conducted to assess the perception of residents and supervisors about how learning happens in tumor boards. **Methods:** Semi-structured interviews of ten oncology residents and five supervisors were conducted. The participants were requested to describe their experience of participating in and their perceptions of learning from tumor boards. The transcripts of the interviews were analysed by thematic analysis, to identify unifying themes which could explain how learning happens in tumor boards **Results:** All the residents and the supervisors perceived the tumor board meetings to be a good learning opportunity. The major underlying themes about learning from tumor boards that emerged from the interviews were: Educational gain (Positive experience vs Constraints), Involvement of the residents (Passive vs Active), Progression of residents (Junior vs Senior), Multi-Disciplinary Team dynamics (Integrated/Motivating vs Hierarchical/Intimidating), Background Reading and Learning (Pre-tumor board preparation vs Post- tumor board learning) and Feedback and Reflection (Formal vs Informal). **Conclusions:** Learning in tumor boards occur by active involvement of the residents. According to the residents, pre- tumor board preparation and post- tumor board reading are important for educational gain. The residents felt that their active involvement and learning from the tumor board meetings improved as they progress through their programme. Multi-disciplinary team dynamics was perceived to be an important determinant of resident learning in tumor boards

11019 Poster Session (Board #16), Mon, 8:00 AM-11:30 AM

The MD CaREs initiative: Tailoring oncology education to ethnically and culturally diverse students. *First Author: Zuanel Diaz, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Although more than 23,000 oncologists are practicing in the United States, a markedly small number of these are Hispanic/Latino. Related perhaps are statistics reflecting the poor representation of minorities in clinical trials, even for tumors from which minority outcomes are disproportionately poor compared to non-minority patients. **Methods:** To address these issues, we establish a partnership between a hybrid academic-community cancer center and a college of medicine, both with a history of addressing the needs of Hispanics/Latinos, a minority and typically underserved population. This partnership aims to increase participation of minority undergraduate, medical and graduate students in cancer research through a novel educational approach. Its curriculum concentrates on emerging fields in oncology, features research experiences, participation in execution of clinical trials and incorporates an outreach program to underserved populations. **Results:** Departing from well-established programs, we injected innovative education elements. We created a competency-based mixed modality course that includes an on-line interactive sessions for medical students to expand their skills in cancer screening and prevention at the individual, community, and health systems levels, with an emphasis on breast and cervical cancer, disparities and underserved populations. We also created an advanced Multidisciplinary Oncology Clinical Elective for 4th year medical students that introduces biospecimen banking science, tumor molecular profiling, medical physics, clinical research, and clinical cancer genetics. Finally, we enriched two long-standing programs which target undergraduate minority students, aimed at increasing the number of underrepresented candidates accepted to medical school, by providing opportunities to learn cutting-edge methodologies. **Conclusions:** A strong partnership that focuses on cancer research, education and training should contribute to a more diverse clinical and research workforce, an initiative that is ideally implemented in South Florida.

TPS11020 Poster Session (Board #17a), Mon, 8:00 AM-11:30 AM

A feasibility study to examine the role of a mindfulness-based wellness curriculum for early clinical trainees. *First Author: Monica Sheila Chatwal, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Physician wellness has become a topic of great interest within the medical field as rates of burnout, depression, and career dissatisfaction have increased. This topic is of particular interest in oncology, with 45%-80% of practicing oncologists worldwide reporting symptoms of burnout (Hlubocky et al. ASCO 2017). Despite the growing interest, there are few programs to address these issues in early clinical trainees, specifically hematology oncology fellows. Mindfulness is a strategy that can be used to recognize and cope with stress and burnout and foster resiliency. Several studies evaluate its use in chronic illness, but also physician burnout. The goal is not to focus on relaxation, but rather on self-awareness, thus extending into a form of "reflective practice" (Epstein, JAMA 1999). This may translate into more effective clinical experiences and stress management skills. **Methods:** This is a single-center, non-randomized pilot project to assess the feasibility and impact of a mindfulness-based wellness curriculum. All hematology oncology fellows at our institution are eligible for enrollment. A total of six monthly 30 minute sessions will be conducted within the framework of the existing didactic conferences. Each session is led by a social worker trained in mindfulness techniques. Participants will complete questionnaires pre- and post-intervention. Primary aim is feasibility determined through recruitment, participation, completion and compliance rates. This will also provide data for sample size estimation for a full-scale RCT. Secondary aim is acceptability, assessed using post-intervention questions addressing usefulness of the program. Exploratory aim is to collect and examine data on self-reported stress and self-awareness – Mindful Attention Awareness Scale (MAAS) (Carlson, 2005) and Perceived Stress Scale (PSS) (Cohen, 1983). Enrollment began in December 2017 and 27 of 28 eligible participants have enrolled and completed pre-session questionnaires. One session has been conducted to date. To our knowledge, this is the first study assessing this type of intervention in this population.

TPS11021 Poster Session (Board #17b), Mon, 8:00 AM-11:30 AM

Establishment of a medical student elective on the oncology consult service using the seven principles of teaching. *First Author: Hari Anant Deshpande, Yale Cancer Center, New Haven, CT*

Background: A busy academic oncology consult service has challenges for effective student teaching. The aim of this research is to establish an academic oncology elective through signature pedagogies - learning in the practice setting. **Methods:** The Seven Principles of teaching and learning will be used to develop an effective teaching model for the Inpatient Oncology Consult service. 1 Prior knowledge is the key to learning 2 Prior knowledge must be activated 3 Learners must be actively involved in constructing personal meaning (ie: understanding) – the links are more improtant than the elements 4 Making more and stronger links requires time 5 Context provides important cues for storing and retrieving information 6 - A Intrinsic motivation is associated with deep approaches to learning; B Extrinsic motivation and anxiety are associated with surface approaches to learning 7 - Teaching should be geared toward making the teacher increasingly unnecessary; that means the development of learner autonomy as well as intellect To address these principles: 1 - A short 10 question quiz to ascertain prior knowledge of general oncology 2 - Activate prior knowledge by asking about experiences or planting concepts at the beginning of the discussion. This should reflect the students' interests: e.g.. focusing on the disease, the social aspects, financial aspects, symptom management or end of life care. 3 - Encourage teachers to be guides, coaches or co-inquirers more than a source of knowledge during rounds to encourage deep and holistic rather than surface discussions. 4 - Allow students time to elaborate their knowledge base – make links between subjects as well as between theory and practice to focus on intrinsic motivation. Limit the size of the teaching service. 5 - Teach in the context from which they eventually use their knowledge. Observe patient encounters and critique their presentations. 6 - A flipped curriculum where the student studies an aspect that then can be discussed in more detail; this becomes the basis for constructing a management plan. 7- A feedback session to stay within the students' zone of proximal development and maintain in the course. Development of a smartphone app for assessment.

11500 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Phase III, randomized, double blind, placebo-controlled trial of sorafenib in desmoid tumors (Alliance A091105). *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: DT is a rare cancer of connective tissue affecting young patients (pts), arising in any location, with a wide natural histories. DT is locally infiltrative and may cause pain, loss of mobility, bowel obstruction and visceral organ compromise. Death is rare. There is no standard of care (SoC), but surgery, observation and systemic therapies are used. S is an oral drug inhibiting VEGFR2/PDGFRB/RAF, showing activity in DT in case series. **Methods:** We conducted an international prospective study to evaluate efficacy of S (400 mg qd) in unresectable progressive (PD) or symptomatic DT. Pts were randomized 2:1 (S:P) and crossover to S upon RECIST 1.1 PD. Stratification: pain-level and disease site. Primary endpoint was progression-free survival (PFS). 75 pts yielded 90% power (1-sided $\alpha = 0.025$, 1 interim analysis) to detect a hazard ratio (HR) of 0.4 (favoring S), assuming 6 month (mo) median (md) PFS for P and 15 mo for S, requiring 52 PFS events. Other endpoints: response rates (RR); toxicity (tox); overall survival; patient-reported outcome (PRO); tumor and imaging biomarkers. **Results:** 87 pts (37 P, 50 S) enrolled over 17 mo at 25 sites [69% female, md age 37 years (yr) (range 18-72), 62% chemo-naive, 9% prior RT]. Tumor location and pain level were balanced. 30% (11/37) P and 38% (19/50) S pts continue; 18% (9/50) ended S due to tox (0% P). 33% (16/49) S, 14% (5/36) P pts had grade 3-4 tox, primarily rash, hypertension, fatigue, pain. For the 1st 75 evaluable pts (med f/u 26 mo): PD 69% (22/32) P, 16% (7/43) S, 1 death (S); Durable partial RR 33% (14/43, 2–28 mo) on S and 21% (7/32, 4–17 mo) on P ($p = 0.3$); 1-yr PFS: 43%-P, 87%-S; Med PFS: 9.4 mo (95% CI 5.7-NE) for P, not reached for S [HR = 0.14 (95% CI 0.06-0.33), $p<0.0001$)]. Analyses of PRO, MRI T2 signal and tumor biopsy are ongoing. **Conclusions:** Phase III studies in rare cancers are feasible and rapidly conducted in an NCTN group setting. Here, S was well tolerated with significantly improved PFS. Spontaneous RR on P is consistent with observational trials in DT. The study exceeded its primary endpoint for PFS. DSMB recommended unblinding (P offered S). S may represent a new 1st-line or subsequent-line SoC in select pts with DT. Support: U10CA180821, U10CA180882, U24CA196171, R01FD005105. Clinical trial information: NCT02066181.

11501 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

DESMOPAZ pazopanib (PZ) versus IV methotrexate/vinblastine (MV) in adult patients with progressive desmoid tumors (DT) a randomized phase II study from the French Sarcoma Group. *First Author: Maud Toulmonde, Institut Bergonié, Department of Medical Oncology, Bordeaux, France*

Background: DT are a group of locally aggressive tumors of fibroblastic origin that can lead to significant morbidity. No randomized trial assessing systemic treatment activity in this rare disease has been reported previously. **Methods:** DESMOPAZ is a multicenter non-comparative randomized phase II trial based on a two-stage optimal Simon's design assessing safety and efficacy of PZ in DT adult patients (pts). All pts had to have documented progressive disease (PD) according to RECIST 1.1 based on two imaging within a 6-months interval. Pts were randomly assigned to receive PZ 800 mg/day orally continuously, or M (30 mg/m²) + V (5mg/m²) intravenously once a week for 6 months and then every 15 days for 6 months. Treatment was administered until PD (cross-over then permitted), unacceptable toxicity, and for a maximum of 1 year. The primary endpoint was 6-month non-PD rate according to RECIST 1.1. Based on the following hypotheses: P0 = 60%, P1 = 80%, $\alpha = 5\%$ and $\beta = 20\%$ and a 2:1 randomization, a total of 43 assessable pts were needed in PZ-arm and 22 pts in MV-Arm. PZ could be regarded as an active drug if at least 31/43 6-month non-PD. Archive FFPE samples of tumor tissue were mandatorily collected at baseline, and an on-treatment tumor biopsy at Cycle 2 was optional. **Results:** Accrual started in September 2012 in 12 centers of the French Sarcoma Group. As of December 2017, 72 pts (26 males, 46 females) were included: 48 in PZ-arm (46 assessable) and 24 in MV-arm (20 assessable). Median age was 40 years (18-79). The median number of previous lines of treatment was 1 (0-3). After central pathological and radiological review, 38 assessable pts (82.6%) in PZ-arm had tumor shrinkage, resulting in PR in 17 (37%) and SD in 21 (45.7%). In MV-arm, 11 assessable pts (55%) has tumor shrinkage resulting in PR in 5 (25%) and SD in 6 (30%). The 6-month non-PD rate was 86% (95%CI = 72.1-94.7) in PZ-arm (37/43) and 50% (95%CI = 27.2-72.8) in MV-arm (10/20). **Conclusions:** The primary endpoint of the DESMOPAZ study was reached. PZ has meaningful clinical activity in pts with progressive DT. Safety, quality of life and pharmacodynamics translational data will be presented at the meeting. Clinical trial information: NCT01876082.

11502 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Final results of ENLIVEN: A global, double-blind, randomized, placebo-controlled, phase 3 study of pexidartinib in advanced tenosynovial giant cell tumor (TGCT). *First Author: William D. Tap, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: TGCT is a rare neoplasm of the joint/tendon sheath associated with colony-stimulating factor 1 (CSF-1) overexpression. No approved systemic therapy is available. Pexidartinib (Pex), a selective inhibitor of CSF-1 receptor, KIT, and FLT3-ITD, showed promising Phase 1 activity in TGCT. Two severe liver toxicity cases (1 required liver transplant, 1 associated with death) have been observed with Pex across the non-TGCT development program. **Methods:** Patients (pts) ≥18 yr with symptomatic TGCT, for whom surgery would be associated with potentially worse function or severe morbidity, were randomized (1:1) to Pex or placebo (Pbo) 1000 mg/d x 2 wks then 800 mg/d PO x 22 wks (Part 1). Pts completing Part 1 could continue into an open-label Pex extension (Part 2). The primary endpoint was centrally reviewed overall response rate (ORR) by RECIST at Week 25 for which the study was powered to detect a 25% difference (35% vs 10%). **Results:** 120 pts were treated, 61/59 on Pex/Pbo. Due to 2 cases of nonfatal, serious hepatic toxicity, the DMC halted enrollment 6 pts short of target and stopped entry of pts on Pbo into Part 2. At the end of Part 1, ORR by RECIST in the ITT population was 39.3% vs 0% ($P< 0.0001$); after a median 6-mo follow-up (longest 17 mos), no responders have progressed. Secondary endpoints for Pex vs Pbo were ORR by tumor volume score (55.7% vs 0%, $P< 0.0001$), range of motion (+15.1% vs +6.2%, $P =0.0043$), PROMIS physical function (+4.06 vs -0.89, $P =0.0019$), worst stiffness (-2.45 vs -0.28, $P <0.0001$), and pain response (31.1% vs 15.3%, 1-sided $P= 0.032$). Hepatic toxicities were more frequent with Pex (AST ≥5X ULN 11.5%, ALT ≥5X ULN 19.7%, total bilirubin ≥2X ULN 4.9%). 8 pts discontinued Pex due to hepatic effects; 4 were serious nonfatal AEs with increased bilirubin, one lasting ~7 mos. Other AEs ≥15% and more common with Pex included hair color changes, vomiting, fatigue, dysgeusia, and periorbital edema. **Conclusions:** Pex resulted in significantly improved ORR and clinical benefit in terms of functional outcomes. Serious liver toxicity was observed in some pts. Pex may offer a relevant treatment option for select pts. Clinical trial information: NCT02371369.

11503 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Anlotinib for metastasis soft tissue sarcoma: A randomized, double-blind, placebo-controlled and multi-centered clinical trial. *First Author: Yihebali Chi, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: No standard therapy is available in China for soft tissue sarcoma (STS) patients progressed after first-line chemotherapy. Anlotinib has shown single-agent activity in a phase II study presented orally at 2016 ASCO. This study aimed at confirming anlotinib's efficacy and safety in advanced STS patients after failure of standard chemotherapy. **Methods:** Patients aged 18 years and older with angiogenesis inhibitor naive, histologically proven advanced STS, intolerance or failure to anthracycline-based chemotherapy, at least one measurable lesion according to RECIST 1.1, were eligible. Those patients were randomly assigned (2:1) to receive anlotinib (12 mg per day 2 weeks on and 1 week off) or placebo. The pathologic subtypes enrolled were: synovial sarcoma (SS), alveolar soft part sarcoma (ASPS), leiomyosarcoma (LMS) and others. Different pathologic subtypes were also randomly assigned (2:1) to each arm. The primary endpoint was progression-free survival (PFS). This trial was registered with ClinicalTrials.gov, number NCT02449343. **Results:** 233 patients were randomly assigned to either anlotinib (n = 158) or placebo (n = 75) and included in the final analysis. The median PFS was 6.27 months (95% CI : 4.30-8.40) for anlotinib compared with 1.47 months (95% CI : 1.43-1.57) for placebo (HR = 0.33, $p < 0.0001$); objective response rate was 10.13% versus 1.33% ($p = 0.0145$); disease control rate was 55.7% versus 22.67% ($p < 0.0001$). For SS (n = 57), the median PFS was 5.73 months versus 1.43 months (HR = 0.2, $p < 0.0001$). For ASPS (n = 56), the median PFS was 18.23 months versus 3 months (HR = 0.14, $p < 0.0001$). For LMS (n = 41), the median PFS was 5.83 months versus 1.43 months (HR = 0.19, $p < 0.0001$). The most common grade 3 or higher adverse events were hypertension (18.99% with anlotinib *vs* 0 with placebo, p = 0.00), gamma glutamyl transferase elevation (4.43% *vs* 1.33%, p = 0.44), triglyceride increase (4.43% *vs* 0, p = 0.10), low density lipoprotein elevation (3.16% *vs* 2.67%, p = 1.00), hyponatremia (3.16% *vs* 1.33%, p = 0.67) and neutrophil count reduction (3.16% *vs* 0, p = 0.18). **Conclusions:** Anlotinib is a new treatment option for patients with advanced STS after failure of standard chemotherapy. Clinical trial information: NCT02449343.

11504 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Results of randomized, placebo (PL)-controlled phase II study evaluating efficacy and safety of regorafenib (REG) in patients (pts) with metastatic osteosarcoma (metOS), on behalf of the French Sarcoma Group (FSG) and Unicancer. *First Author: Florence Duffaud, La Timone University Hospital, Marseille, France*

Background: Oral multikinase inhibitor REG has shown activity in GIST and non-adipocytic soft tissue sarcomas. We designed REGOBONE as a non-comparative phase II, double-blind, PL-controlled trial to study the efficacy and safety of REG for pts with metOS and other types of bone sarcomas. This trial consisted of 4 independent cohorts : metOS, Ewing sarcoma, chondrosarcoma, and chordoma. We report here the metOS cohort results. **Methods:** metOS pts were randomized (2:1) to receive either REG (160 mg/d, 21/28d) or PL with optional cross-over at the time of confirmed central review of progressive disease (PD). Key-eligibility criteria were age ≥10 years, histologically confirmed diagnosis of OS, confirmed measurable PD not amenable to curative-intent, 1-2 previous chemotherapy (CT) regimen(s) for metastatic disease, and ECOG 0-1. 24 pts were planned in the REG arm based on A'Hern's single-stage design for phase II trials (1-sided $\alpha = 0.05$, and 80% power) to detect a 27% benefit in the progression-free rate at 8 weeks (P0 = 40%). Major secondary endpoints were PFS (per modified RECIST1.1), OS and safety. **Results:** From June 2014 to April 2017, 43 metOS pts were included. Five pts were not eligible for efficacy analysis. Of 38 efficacy-evaluable pts (12 in PL arm and 26 in REG arm) ; 24 were men, median age was 33 (18-74) years, 28 (74%) had 1 previous CT regimen. 17 pts (65.4% ; one-sided CI95% = [47.4%-]) were non-progressive at 8 weeks in the REG arm vs. 0 in the PL arm. Median PFS was 13.7 (CI95% = 8.0-27.3) vs. 4 (CI95% = 3.0-5.7) weeks for REG and PL arms, respectively. PFS rate at 24 weeks was 35% (CI95% = 17-52) in the REG arm vs. 0 in the PL arm. 1-year OS was 53% (CI95% = 31-71) and 33% (CI95% = 10-59) for REG and PL arms, respectively. Ten pts crossed-over to REG after centrally-confirmed PD on PL. The most common ≥Gr3 REG-related AEs during the double blind period were hypertension (24%), hand-foot skin reaction (17%), asthenia (10%) and diarrhea (7%). **Conclusions:** REG demonstrates very promising activity, with acceptable toxicity, in metOS after failure of conventional chemotherapy, justifying confirmatory trials. Clinical trial information: NCT02389244.

11505 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

A randomized, double-blind, placebo-controlled, phase II study of regorafenib vs placebo in advanced/metastatic, treatment-refractory liposarcoma: results from the SARC024 study. *First Author: Richard F. Riedel, Duke University Medical Center, Durham, NC*

Background: Pazopanib, a multi-targeted tyrosine kinase inhibitor, has shown activity in various soft tissue sarcomas. Activity in liposarcoma, however, is limited. Regorafenib is a multi-kinase inhibitor with anti-angiogenic properties similar to pazopanib. We conducted a randomized, phase II study of regorafenib (R) vs. placebo (P) in refractory liposarcoma patients (pts). **Methods:** Pts with advanced/metastatic, treatment-refractory liposarcoma were randomized 1:1 to receive regorafenib 160 mg daily or placebo (3 weeks on/1 week off). Pts. with well-differentiated liposarcoma only were excluded. Crossover for placebo pts was allowed upon progression. The primary objective was progression-free survival (PFS) for R vs P. Stratification factors included prior lines of therapy (1 vs 2+) and WHO performance status (0-1 vs 2). The study was powered to detect a difference of ≥ 3 months in median PFS. Secondary objectives included AE assessments, overall response rate (ORR), time to tumor progression (TTP), PFS at 8 and 16 weeks, overall survival (OS), and disease–specific survival (DSS). **Results:** Forty-eight subjects were enrolled with 47 (27 M: 20 F) having follow-up information. Median follow-up was 3.8 months (0.2-15.3). More women were randomized to R than men (58% vs. 42%; $p < 0.03$), otherwise baseline characteristics were similar between cohorts. Thirty-three dedifferentiated, 12 myxoid/round cell and 2 pleomorphic liposarcomas were included in the analyses. Most common grade 3-4 AEs observed with R included: grade 3 abdominal pain (13%), hypertension (13%), rash (13%), anemia (8%), anorexia (8%), generalized weakness (8%), and elevated lipase (8%); (grade 4 – none). One grade 5 event occurred in R and 3 in P. Median PFS was 1.9 (0.9-3.7) months for R vs 2.1 (1.6-3.1) months for P; stratified HR 0.87 (0.47, 1.64), p-value = 0.68. No responses were seen in R. One PR was observed in P. Median OS was NR (4.2-NR) for R vs 8.1 (2.9-NR) months for P, stratified p-value = 0.13. **Conclusions:** Regorafenib did not achieve the primary outcome of improved PFS in treatment-refractory liposarcoma. No new safety signals were observed. Clinical trial information: NCT02048371.

11506 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized comparison of pazopanib (PAZ) and doxorubicin (DOX) in the first line treatment of metastatic soft tissue sarcoma (STS) in elderly patients (pts): Results of a phase II study (EPAZ). *First Author: Viktor Grünwald, Clinic for Hematology, Hemostaseology, Oncology and Stem Cell Transplantation, Medical School Hannover, Hannover, Germany*

Background: The systemic treatment standard of advanced, inoperable STS in elderly pts is single agent DOX. We tested the hypothesis whether PAZ has comparable efficacy to DOX in elderly STS pts, while offering better tolerability. **Methods:** Key inclusion criteria: age ³60 years, no prior systemic treatment for STS, progressive disease, ECOG 0-2, adequate organ function. DOX 75 mg/m2 q3wks for a total of 6 cycles or PAZ 800 mg OD continuously were given after 1: 2 randomization. ECOG 2 and liposarcoma histology were used for stratification. The primary endpoint was progression free survival (PFS) in the per protocol (PP) population. A non-inferiority design was applied with an upper limit of the 95% confidence interval (CI) of less than 1.8. Key secondary endpoints were neutropenia and febrile neutropenia in hierarchical order. EORTC QLQ-C30 was utilized to measure quality of life. Cox regression analysis, ANCOVA and Kaplan-Meier curves were applied (NCT01861951). **Results:** Between 10/2012 and 03/2016, 39 pts were randomly assigned to DOX and 81 to PAZ. The median follow-up was 11.8 months (mo). The median age was 71 years (range: 60-88). In the PP population, DOX vs. PAZ achieved a PFS of 5.3 vs. 4.4 mo (HR 1.00; 95%CI 0.65-1.53; P = .993), respectively. The incidence of neutropenia CTC grade 4 and neutropenic fever in patients were 56% and 10% for DOX and 0% and 0% for PAZ, respectively. OS was 14.3 vs. 12.3 mo. (HR 1.083; 95%CI 0.68-1.72; P = .735) for the intention to treat population. Most frequent AEs for DOX were fatigue (64.9%), alopecia (56.8%) and nausea (48.6%), and for PAZ fatigue (58.0%), nausea (43.2%) and diarrhea (43.2%). Similar outcome was reported for global EORTC QLQ-C30 measures. **Conclusions:** This study showed that PAZ was non-inferior compared to DOX, rendering PAZ a putative therapeutic option in the first line treatment of STS of pts above 60 years of age. The distinct AE profile may be used to council pts and tailor therapy to individual needs. Clinical trial information: NCT01861951.

Outcome of primary and key secondary endpoints

	DOX	PAZ	HR	95%CI	P value
PFS	5.3 mo	4.4 mo	0.998	0.650-1.533	0.993
Neutropenia grade 4	56%	0%	-	-	< 0.0001
Febrile neutropenia	10%	0%	-	-	0.003

11507 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Randomized phase II trial of trofosfamide vs. adriamycin in elderly patients with previously untreated metastatic soft tissue sarcoma. *First Author: Joerg Thomas Hartmann, Franziskus Hospital Bielefeld, Catholic Hospital Consortium Estern Westphalia, Bielefeld, Germany*

Background: DOX is still the standard in metastatic STS. We assessed the efficacy and safety of oral TRO. **Methods:** This is a randomized phase 2 trial at 15 german and 1 french centers. We included pts with metastatic high-grade STS, older than 60 yrs of age, with an ECOG of 0-1. They were randomly (1:2) assigned to either (A) DOX (60 or 75 mg/sqm i.v., on day 1, q 22 d for 6 cycles) or arm B (oral TRO, 300 mg, d1-7, then 150mg daily continuously p.o.) as first-line tx. Randomisation was stratified by presence of liver mets, and PS (0 vs 1). Pts were treated until PD or unacceptable toxicity. Primary aim was a 6-months (mos) PFS rate of at least 20 % in Arm B; secondary: safety, ORR, survival. **Results:** Between 8/04 and 10/12 40 pts were randomly assigned to arm A and 80 to Arm B, median age 70 yrs (60-89). Median duration of f/u of surviving patients was 18.4 mos (range, 3.8-94.7). Median treatment duration was 2.8 mos (0-4.6) in A and 2.8 mos (0.4-41.4) in B. No difference in terms of ORR with 7.7% (1.6-20.9) in arm A and 6.7% (2.2-14.9%) in arm B (p = 0.99); disease control rate (including disease stabilization) (53.8% (95%-CI, 37.2-69.9%) vs. 41.3% (95%-CI, 30.1-53.3%), p = 0.23), PFS (4.3 mos; 95%-CI, 2.2-5.9 vs. 2.8 mos; 95%-CI, 1.6-3.5), p = 0.99) and OS (9.6 mos; 95%-CI, 6.4-11.6 vs. 12.1mos; 95%-CI, 9.5-16.0), p = 0.59) were seen, without difference in ITT- and per-protocol populations. Duration of response lasted 5.0 mos in arm A (range, 1.3-8.0) and 4.0 mos (0-46.6) in arm B; however, in pts achieving a CR or PR duration was longer in favor of cohort B (0 vs. 27.7 mos resp. 4.3 vs. 8.2 mos). Primary study endpoint (6-mos PFR) was 27.6% in Arm B (95%-CI, 18.0-39.1). Safety analyses in 115 pts showed at least one side effect in 97.4% vs. 96.1% pts (p = 0.99); of note, side effects G3-4 were lower in favor of Arm B (59% vs. 30.3%; p = 0.005). TRO caused more often dyspnoe, fatigue (but only minor degree); DOX leukocyto- and neutropenia as well as mucositis, G1-4. Discontinuation rate other than PD was 15.4% vs. 7.9%. **Conclusions:** In an elderly population of pts who received either standard Dox or oral TRO for metastatic STS, equal median PFS and OS have been achieved. TRO associated with a more favorable toxicity profile. Clinical trial information: 00204568.

11508 Oral Abstract Session, Mon, 8:00 AM-11:00 AM

Results of a prospective randomized phase III T-SAR trial comparing trabectedin (T) *vs* best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS): A French Sarcoma Group (FSG) trial. *First Author: Axel Le Cesne, Gustave Roussy Cancer Campus, Villejuif, France*

Background: With the exception of a study in translocation-related STS (Kawai, 2015), T has never been compared to BSC in a study including patients (pts) with all sarcoma histotypes. The efficacy, safety and quality of life of T *vs* BSC as second or later treatment line were evaluated in pts with ASTS in a multicenter FSG trial. **Methods:** The study enrolled pts ≥18 years of age with histologically proven ASTS who progressed after at least 1 anthracycline-containing regimen (≤3 previous chemotherapy (CT) lines), stratified by L-STS (lipo-leiomyosarcoma) and non L-STS and with a WHO performance status score 0-1. Pts were randomized 1:1 to receive either T (1.5 mg/m^2 24h every 3 weeks) or BSC until disease progression (PD), unacceptable toxicity, or patient's request. Pts allocated to BSC could cross over to T at PD. The primary endpoint was progression-free survival (PFS). **Results:** Between January to November 2015, 103 pts (median 65 yrs (range 22-84), grade 3 ASTS in 57% of cases, median number of 1 prior CT lines) were enrolled by 16 FSG centers, 52 in the T arm and 51 the BSC arm. Pts with L-STS and non L-STS represented 60% and 40% of pts, respectively. Two pts refused to be allocated in the BSC arm and received other CT. The objective response rate (ORR) in the T arm was 11.8%, all observed in the L-STS group (ORR: 18.8% in L-STS). 23% of pts in the T arm received more than 9 cycles of T. The median PFS were 1.5 months (m) in the BSC arm and 3.1m in the T arm (HR: 0.39, $p < 0.0001$). In the L-STS cohort, the median PFS were 1.4m and 5.1m in the BSC and T arm (HR: 0.29, $p < 0.0001$), respectively, whereas in the non L-STS group they were 1.5m and1.8 m ($p = 0.16$). A cross-over was performed in 92% of pts included in the BSC arm. By After a median follow-up of 25.7 months, the differences on OS were not statistically significant between the two arms, 13.6 m vs 10.8 m in the T and BSC arms respectively ($p = 0.86$). **Conclusions:** This study met its first endpoint as a preplanned PFS analysis showed a significant improvement in median PFS with T over BSC in pts with pretreated ASTS of multiple histologies. L-STS pts benefit the most from T therapy in terms of prolonged tumor control. Clinical trial information: NCT02672527.

11509 Poster Discussion Session; Displayed in Poster Session (Board #254), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of PLX9486 alone and in combination (combo) with the KIT inhibitors pexidartinib (pexi) or sunitinib (su) in patients (Pts) with advanced solid tumors and gastrointestinal stromal tumor (GIST). *First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA*

Background: Most metastatic GISTs have primary (1^0) mut in KIT exons (ex) 9 or 11, which confer sensitivity to imatinib and other agents. Tumors develop clonal secondary (2^y) resistance mut, typically in ex 13, 14, 17, and 18. PLX9486 inhibits KIT 1^0 mut and ex 17 and 18 2^y mut. Pexi (PLX3397) and su inhibit 1^0 mut and ex 13 and 14 2^y mut. Combo of PLX9486 with pexi or su may have activity against a broader spectrum of mutations. **Methods:** 3 + 3 dose escalation study in pts with solid tumors and GIST who had progressed on imatinib and other TKI. Safety, efficacy per RECIST, and PK were assessed. Ct DNA was assessed as a biomarker. Part (P) 1: single agent PLX9486 dose escalation once (QD) and twice daily (BID). P2: combos of PLX9486 500 mg QD with pexi 600 mg QD fed and fasted or su 25 mg QD with food. **Results:** As of January 8, 2018, 36 pts (31 GIST; Part 1-20 pts, part 2-11 pts) were enrolled; median age was 63 years (range 49-82). GIST pts had a median of 4 prior therapies (range 1-7), and all progressed on imatinib. Most pts had tumors with ex 11 and 17 mut. QD dosing of PLX9486 had saturable absorption at steady state with a half-life of 71.4 hrs. No PK advantage to BID dosing and no food effect. One DLT of Grade (G) 3 anemia was reported at the 1000 mg dose level. Escalation stopped due to PK plateau; the RP2D was 1000 mg QD. In P2, no DLTs were observed at the doses studied. PK of PLX9486 was not affected by pexi. Pexi food effect was observed. Adverse events (AEs) in P1 in ≥ 20% pts (N = 24) were diarrhea, nausea, increased AST (29% each) and fatigue (21%). AEs in P2 in ≥ 20% pts (N = 12) were hair color changes (42%), anemia (25%), nausea (25%), and anorexia (25%). Majority were G1-2. No ≥ G3 LFT changes in P1 or P2. In P1, 2 partial responses (PR) were seen with PLX9486 1000 mg and PFS was > 24 weeks. In P2, 1 pt had a PR in the pexi/PLX9486 combo, and the median PFS has not been reached. **Conclusions:** PLX9486 alone and in combo with pexi was generally well tolerated with evidence of activity against resistant GIST. Combos with su and pexi, agents with complementary activity against KIT 2^y resistance mut in GIST, are accruing. Clinical trial information: NCT02401815.

11510 Poster Discussion Session; Displayed in Poster Session (Board #255), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase Ib study of rapid alternation of sunitinib (SU) and regorafenib (RE) in patients (pts) with advanced gastrointestinal stromal tumor (GIST). *First Author: Cesar Serrano, Vall d'Hebron University Hospital Institute of Oncology (VHIO), Barcelona, Spain*

Background: Polyclonal emergence of KIT secondary mutations (muts) is the main mechanism of imatinib (IM) progression in GIST. Although approved KIT inhibitors SU and RE each suppress only a subset of these muts, they have shown complementary activity in GIST models and clinical trial correlates. Preclinical evidence suggests that rapid alternation of SU and RE broadens the spectrum of IM-resistant subclones targeted, compared to either agent as monotherapy. **Methods:** This phase Ib study of rapid alternation of SU and RE was performed in pts with IM-resistant advanced GIST. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose (RP2D). Pts received continuous treatment with cycles of 3 days of SU followed by 4 days of RE. Plasma samples for pharmacokinetics and ctDNA studies (deep next generation sequencing and ddPCR) were collected at several timepoints. **Results:** Fourteen pts were enrolled, and 13 received treatment. Median age 64 (range 42-78), 43% female, median prior therapy 4 (range 3-7, all pts had ≥ 3 prior therapies). SU 37.5mg daily 3 days followed by RE 120mg daily 4 days was established as the RP2D. Two dose limiting toxicities (DLTs) occurred at DL2 (asymptomatic G3 hypophosphatemia). Non-DLT G3/4 toxicities were hypertension (1/13 pts) and hand-food syndrome (2/13 pts). 8/13 patients experienced dose modification, delay, or both. No unexpected toxicities were observed. Of the 13 pts with evaluable CT scans, stable disease (SD) was the best response observed in 4 pts by RECIST. Median progression free survival was 8.4 weeks (95% CI of 6.0-15.7). SU and RE did not reach the steady state, although pts with SD had higher median drug concentration than progressing pts. ctDNA studies show that GIST has low ctDNA shedding and remains KIT-driven even at late stages of disease, with a predominance for activation-loop secondary mutations. **Conclusions:** Rapid alternation of drugs with complementary activity is a well-tolerated treatment strategy. Drug exposure is critical to target effectively specific subpopulations. Although GIST sheds low ctDNA in this heavily pretreated population, identifying KIT muts in plasma is feasible. Clinical trial information: NCT02164240.

11511 Poster Discussion Session; Displayed in Poster Session (Board #256), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Mutation profile of drug resistant gastrointestinal stromal tumor (GIST) patients (pts) enrolled in the phase 1 study of DCC-2618. *First Author: Suzanne George, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: GIST is driven by primary and secondary driver mutations in KIT/PDGFRα and cell-free tumor (ct) DNA may provide the opportunity to assess disease status and response to therapy. The pan-KIT/PDGFRα switch control inhibitor DCC-2618 has demonstrated durable disease control in heavily pre-treated GIST pts in the ongoing Phase 1 study (NCT02571036). **Methods:** Pts with advanced GIST were treated in either the escalation stage or in expansion cohorts of the Phase 1 study with oral DCC-2618. Tissue and liquid biopsies were performed and tested via next generation sequencing (NGS) of tumor tissue and/or plasma ctDNA. **Results:** A total of 136 2nd to 7th line (median of 3 prior therapies) GIST pts (KIT or PDGFRα mutations by local testing) were enrolled as of January 18, 2018 and treated with doses of ≥100 mg per day. 132 patients had a ctDNA sample available for baseline assessment by NGS. To date, activating mutations in KIT or PDGFRα were identified in 71% of baseline ctDNA analyzed from 77 pts. In the 53 confirmed KIT mutant GIST pts, exon 13/14 mutations were detected in 16 patients (30%); while exon 17/18 mutations were detected in 33 patients (62%). Notably, multiple patients had mutations in both exons 13/14 and 17/18. 92 GIST patients had at least one additional ctDNA sample available at first restaging. The correlation between tumor tissue and ctDNA, and the change in KIT/PDGFRA mutant allele frequency for GIST pts following the first 2 cycles of treatment with DCC-2618 will be presented. 76% of 136 pts are still on treatment. In 99 GIST pts with ≥1 on-study tumor assessment, the overall response rate (ORR) was 16%. **Conclusions:** Identification of ctDNA by NGS in the majority of patients in this cohort was feasible. The mutation profile of GIST in both tumor and plasma suggests the need for a pan-KIT inhibitor across various lines of therapy. DCC-2618 is being tested in a pivotal, randomized phase 3 study, INVICTUS, (NCT03353753) in the 4th+ line population with plans to be tested in a second Phase 3 study in 2nd line GIST. ctDNA in this patient population deserves further study as a non-invasive marker of disease heterogeneity and response assessment. Clinical trial information: NCT02571036.

11512 Poster Discussion Session; Displayed in Poster Session (Board #257), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Phase 2 results of selinexor in advanced de-differentiated (DDLS) liposarcoma (SEAL) study: A phase 2/3, randomized, double blind, placebo controlled cross-over study. *First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Locally advanced DDLS is incurable with an overall survival of 11 – 20 mo with palliative therapies. Ideal imaging criteria for efficacy is currently undefined. Selinexor (S) is an oral, selective inhibitor of nuclear export that specifically blocks exportin 1, leading to the nuclear accumulation and reactivation of tumor suppressor proteins. S demonstrated anti-tumor activity against DDLS in preclinical studies and a Ph 1b study in patients (pts) with soft tissue sarcomas. **Methods:** Eligible pts had DDLS and progressive disease (PD) with $\geq$ 1 prior systemic therapy. Pts were randomized 1:1 to receive blinded S (60 mg) or placebo (P) twice weekly; 42 day cycle until PD or intolerability. Pts with PD on P may cross over to S. The primary endpoint was progression-free survival (PFS) by WHO criteria. Pre-specified analyses using RECIST v1.1 (R v1.1) was included. **Results:** Ph 2 enrollment is complete. 56 evaluable pts (33 M, 23 F) were randomized to S or P. Median age: 61 yrs and median prior treatments: 2 (1-9). Treatments for 51 pts were unblinded (24 S, 27 P). The main reason for ending blinded treatment was PD confirmed by Independent Central Radiological Review by WHO Criteria. Common AEs Grade 1/2 (S:P) were: nausea (85% : 31%), anorexia (62% : 14%), and fatigue (58% : 45%). Grade 3/4 AEs were: hyponatremia (15% : 0%), anemia (15% : 7%), and thrombocytopenia (12% : 0%). 12 pts on S had dose reductions due to AEs. There was no difference in median PFS by WHO. By R v1.1, median PFS on S: 5.6 mo; P: 1.8 mo, hazard ratio of 0.64 (p 0.21, not powered in Ph 2). (Table 1). Some pts ended treatment early with small changes in tumor burden due to PD by WHO criteria. **Conclusions:** R v1.1 may be better criteria than WHO to evaluate drug efficacy in DDLS. Improvement of PFS (R v1.1) is promising and supports continuation of the Ph 3 portion of S in DDLS. Clinical trial information: NCT02606461.

Median PFS by R v1.1 and WHO criteria.

Treatment Arm	R v1.1 - PFS (mo)	Hazard Ratio (95% CI)	WHO - PFS (mo)	Hazard Ratio (95% CI)
Selinexor (N = 24)	5.6	0.64 (0.31, 1.32) p = 0.21	1.4	0.92 (0.52, 1.63)
Placebo (N = 27)	1.8		1.4	

11513 Poster Discussion Session; Displayed in Poster Session (Board #258), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Whole exome sequencing (WES) of metastatic leiomyosarcoma (LMS) and liposarcoma (LPS) and correlation of genomic aberrations with clinical outcomes in the phase III randomized trial of trabectedin (T) vs. dacarbazine (D). *First Author: Gurpreet Kapoor, Scientific Operations, LabConnect LLC, Seattle, WA*

Background: This phase 3 study (NCT01343277) showed statistically significant improvement in disease control by T vs. D in patients (pts) with metastatic LMS and LPS (Demetri et al., JCO, 2016). WES was done to explore associations between genomic alterations and clinical outcomes in this prospective database. **Methods:** Of 518 pts enrolled on study, archival tumor samples were collected from 456 (88%) pts: 180 uterine LMS (uLMS), 149 non-uterine LMS (non-uLMS), 66 de-differentiated LPS (ddLPS), 46 myxoid LPS (mLPS) and 15 pleomorphic LPS (pLPS). Peripheral blood samples from a subset of 346 patients were also analyzed as matched normal to filter noise from nonpathogenic variants in WES. **Results:** Consistent with sarcoma TCGA data, these LMS and LPS samples had frequent homozygous gene deletions with relatively low mutational load. TP53 & RB1 alterations were frequent in LMS compared to LPS, and showed no association with clinical outcomes. Analyses of 103 DNA damage response (DDR) genes showed frequent ($>$ 20%) somatic alterations across subtypes, correlating with improved PFS only in uLMS tumors (HR: 0.63, p = 0.03). Genomic alterations in PI3K pathway genes were noted in 30% of mLPS and associated with worse PFS (HR: 3.0, p = 0.045). A trend towards better OS was noted in ddLPS tumors with MDM2 amplification (90%) compared to normal MDM2 copy number. Certain subtype-specific genomic aberrations in immune modulation pathways (uLMS and ddLPS) were associated with worse clinical outcomes, whereas alterations in immune suppressors (non-uLMS) and lipid metabolism (ddLPS) were associated with improved clinical outcomes. **Conclusions:** This detailed genomic analysis of a large cohort of metastatic LMS and LPS pts matched with prospective data on treatment outcomes suggests that aberrations in oncogenic pathways (DDR, PI3K, MDM2-p53) and immune modulation may contribute to response or resistance to treatment with T or D. Further analyses should inform our understanding of sarcomas and may aid clinical decision making for LMS and LPS.

11514 Poster Discussion Session; Displayed in Poster Session (Board #259), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase 1 study of MDM2 inhibitor DS-3032b in patients with well/de-differentiated liposarcoma (WD/DD LPS), solid tumors (ST) and lymphomas (L). *First Author: Todd Michael Bauer, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Inactivation of p53 is the most frequent event in cancer driven by mutations in *TP53* or overexpression of MDM2, a negative regulator of p53. DS-3032b is an oral small molecule that disrupts the MDM2-p53 interaction, resulting in reactivation of wild type p53 and causing growth arrest/apoptosis. We characterized the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK) and pharmacodynamics (PD) and preliminary efficacy of DS-3032b. **Methods:** Patients (pts) received DS-3032b orally in 28 days cycle as per Table. TP53 status was confirmed post-enrollment. **Results:** 94 pts were enrolled with ST (50, 53%), WD/DD LPS (40, 43%), L (4, 4%). Doses, schedules (Sch), MTDs and responses are tabulated below. Median age was 60.5 years, 50% male, 63% had $\geq$ 3 prior therapies. 73/84 (87%) pts tested had WT TP53. The most common ($>$ 10%) TEAEs were nausea 71%, vomiting 31%, diarrhea 40%, decreased appetite 37%, abdominal pain 16%, dry mouth 11%, thrombocytopenia 61%, neutropenia 28%, anemia 43%, fatigue 55%, dysgeusia 18%, headache 19%, cough 19% and peripheral edema 14%. There were 8 dose limiting toxicities (DLT): six Gr 2-4 thrombocytopenia +/- neutropenia; 3 events resolved, 3 unresolved. One Gr 3 nausea, vomiting and anorexia and another Gr 2 fatigue. Sch D (3/14 days) had the best safety profile. In 79 efficacy-evaluable pts, 47 (60 %) achieved stable disease (SD). Median duration of SD was 6.7 (1.6 to 36.4) months. Partial responses (PR) were seen in DDLPS, synovial sarcoma and lung ca (SC).PK parameters AUC0-24h and Cmax were dose proportional with median Tmax 3 hours. PD biomarker MIC-1 correlated with drug exposure. In paired biopsies, MDM2 inhibition resulted in increase of nuclear p53 levels (IHC) in 5/6 pts (83%). **Conclusions:** DS-3032b has acceptable safety profile with intermittent dosing. Objective responses and durable SD were seen in MDM2 amplified ST and DDLPS warranting further studies Clinical trial information: NCT01877382.

Schedule, days	Doses, mg	N = 94 pts	Histology	MTD, mg	Best Response
A – 21/28	15 – 240	40	ST/L	120	SD
A – 21/28	120	20		120	
B – 28/28	90	9		90	
C – 7/28	120, 200	9	Progressing WD/DD LPS and MDM2 amp ST	Not achieved	1 PR DDLPS
D – 3/14 – 3/14	120, 200, 260, 340	16		260	2 PR: synovial sarcoma & SCLC

11515 Poster Discussion Session; Displayed in Poster Session (Board #260), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

IMMUNOSARC: A collaborative Spanish (GEIS) and Italian (ISG) Sarcoma Groups phase I/II trial of sunitinib plus nivolumab in selected bone and soft tissue sarcoma subtypes—Results of the phase I part. *First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/Universidad de Sevilla, Seville, Spain*

Background: Disruption of angiogenesis substantially enhances the efficacy of immune-based cancer therapies. The combination of an antiangiogenic drug (sunitinib or pazopanib) plus anti- PD1 (nivolumab) exhibited both higher activity and toxicity compared with antiangiogenic drug alone in renal cell carcinoma (RCC). We hypothesized that sunitinib (SU) and nivolumab (NI) could be synergistic in some sarcoma subtypes and the toxicity profile could be different from RCC. We present the results of phase I part of the combination of SU-NI in advanced sarcoma patients (pts). **Methods:** Pretreated progressing pts, ECOG 0-1 and diagnosed with UPS, synovial sarcoma (SS), clear cell sarcoma (CCS), angiosarcoma (AS), epithelioid hemangioendothelioma (EH), solitary fibrous tumor (SFT), epithelioid sarcoma (ES), osteosarcoma (OS), Ewing sarcoma (EWS) or dedifferentiated chondrosarcoma (DCh) were eligible. SU 37.5 mg/d as induction was given for the first 14 days. The dose-finding stage (from day 15 to 45) would be completed when 10 dose limiting toxicity (DLT)-evaluated pts had been treated with DLT rate $<$ 0.33. Two level- doses were designed: (0 initial) SU 37.5 mg/d or (-1) SU 25 mg/d along with NI 3 mg/kg/2w for both. SU-NI was maintained up to progression or intolerance. **Results:** From May to October 2017, 16 pts (M/F 10/6), median age 38y (25-78) were enrolled. Diagnosis was: CSS in 4 (25%), ASPS in 3 (19%); AS, OS, SS (2 each, 12.5%); UPS, extraskeletal OS and Ch (1 each, 6%). There were three DLT in the first 6 pts at dose level 0 (G3 fatigue in 2 and G4 septic shock) and 1 DLT in the following 10 pts at level -1 (febrile neutropenia). G3/4 toxicity: fatigue 25%, thrombocytopenia 19%, mucositis 13% and neutropenia 13%. There were 6 RECIST PR (42.8%), 4 SD (2 of them 25% of shrinkage) and 4 PD in 14 evaluable pts. PR occurred in 2 CCS and in one of AS, Ch, SS, ASPS while 2 cases (ASPS and UPS) shrank 25%. **Conclusions:** At the RDP2 (SU 25 mg/d and NI 3 mg/kg/2w), SU-NI is a feasible combination with manageable toxicity. SU-NI has induced objective responses in several sarcoma subtypes. The study is currently on a phase II part. Clinical trial information: NCT03277924.

11516 Poster Discussion Session; Displayed in Poster Session (Board #261), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

A phase II study of talimogene laherparepvec (T-VEC) and pembrolizumab in patients with metastatic sarcoma. *First Author: Ciara Marie Kelly, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: T-VEC is an oncolytic immunotherapy derived from HSV type-1 that is modified to selectively replicate within tumors and produce GM-CSF. Pembrolizumab (P) demonstrated activity in selective sarcoma (SAR) subtypes. The combination of T-VEC and P has shown favorable safety and efficacy in melanoma. We performed an open-label, single-center, phase II study evaluating T-VEC and P in patients (pts) with advanced SAR who failed at least one standard systemic therapy where available. **Methods:** Pts received P (200mg/dose) and ≤4ml of T-VEC injected into palpable tumor site (s). Both drugs were administered on day 1 of a 21-day cycle. The primary endpoint was best objective response rate (RR) (complete response and partial response [PR]) at 24 weeks by RECIST 1.1, with 30% as promising and 5% as not promising. If ≥ 3 responses were observed in 20 pts the combination would be claimed to be positive. Secondary endpoints included adverse events (AEs), RR by irRECIST, progression free and overall survival. Correlative studies included PD-L1 expression by IHC (Qualtek), multiplex IHC, characterization of tumor infiltrating lymphocytes, mutational burden/neoantigen analysis, and T cell receptor clonality. **Results:** 20 pts were enrolled [median age 63.5 yrs (range, 24-90), 60% female]. Represented histological subtypes included: leiomyosarcoma (25%), cutaneous angiosarcoma (15%), SAR not otherwise specified (15%), undifferentiated pleomorphic SAR (10%) and "other" SAR subtype (35%). Pts were refractory to 0 (10%), 1 (20%), and ≥ 2 (70%) prior regimens. Grade (G) 3 treatment related AEs (TRAEs) occurred in 2 pts (10%); fever from TVEC & pneumonitis from P. No G4/5 TRAEs were seen. 1pt stopped P due to G3 TRAE. Among 19 evaluable pts 4 confirmed PRs (21%), 9 stable diseases (SD) (47%) and 6 progressions (32%) were observed by RECIST 1.1. Two of the SDs had decrease in tumor burden of 17% and 28.6% at their first (week8) interval scan. PRs were seen in 3 histologies. The time to PR ranged from 8 to 32 weeks (wks) and all PRs are ongoing (range 1 -36 wks). **Conclusions:** TVEC and P demonstrated acceptable safety and promising anti-tumor activity across a range of SAR histologies. 4 pts maintain a PR. Correlative analyses are ongoing. Clinical trial information: NCT03069378.

11517 Poster Discussion Session; Displayed in Poster Session (Board #262), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Compared descriptive analysis of immunologic landscape in soft tissue sarcoma and GIST. *First Author: Armelle Dufresne, Centre Léon-Bérard, Lyon, France*

Background: Development of immune therapy in sarcoma faces a high heterogeneity of the different histological subtypes, molecular subtypes and immune infiltrate. This is likely to account for the limited response rates in sarcomas of single agent PD1/PDL1 Ab in most series. The objective of this study was to provide a description of immunologic landscape of sarcoma to guide the next clinical trials of immune therapy in these diseases. **Methods:** All patients included in this study had soft tissue sarcoma (STS) and were managed in expert centers of the French Sarcoma Group. Tumor samples were obtained from surgical resection of the primary tumor. Clinical characteristics of patients, tumor and disease evolution were extracted from the Netsarc databases. Gene expression of 90 immune check point (ICP) and membrane markers (MM) of immune cells were performed using Agilent Whole Human Genome Microarrays and correlated to pathological diagnosis and survival. **Results:** This study included 87 STS with complex genetics (SCG), 60 gastrointestinal stromal tumors (GIST), 58 synovial sarcomas (SS) and 50 myxoïd liposarcomas. Overall, there was substantial level of expression of almost all of the ICP/MM across the 4 sarcoma sub types even if important expression heterogeneity was observed across sarcoma subtypes, and across patients within the same tumor type. A strong correlation existed between specific ICP/MM expression profile and the 4 different sarcoma subtypes allowing unsupervised hierarchical clustering to discriminate the histological sub types. Among the 90 genes studied, 40 had a prognostic impact on at least one subgroup. IDO1 seems interesting to target in SCG, NK cells had a strong role in GIST, and SS had an unexpected profile and a T cell-related poor prognosis. **Conclusions:** Sarcomas are heterogenous diseases in terms of histotypes, molecular subtypes, and now as shown here, in terms of MM and ICP expression. To elaborate strong rationale of immune therapy approaches in each sarcoma sub types, present data of ICP and MM expression and prognosis will have to be integrated with mutational load and aneuploidy that appears relevant predictive factors.

11518 Poster Discussion Session; Displayed in Poster Session (Board #263), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Prognostic stratification using the nomogram sarculator and its impact on study results in a randomized controlled trial (RCT) for localized soft tissue sarcomas (STS): A secondary analysis of the EORTC-STBSG 62931. *First Author: Sandro Pasquali, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: To determine whether high-risk STS patients identified using individual patient data and the nomogram Sarculator, benefitted from adjuvant chemotherapy in a RCT which failed to detect any overall survival (OS) differences between chemotherapy and observation. **Methods:** Data from the EORTC 62931 RCT comparing adjuvant doxorubicin plus ifosfamide (Adj) and observation (Obs) for STS (Lancet Oncol 2012;13:1045-1054) were analysed. 10-yr predicted probability of OS (P-OS) was computed using a validated nomogram (Lancet Oncol 2016;17:671-80) for each participant with extremity and trunk wall STS (N = 290/351). Patients were divided in 3 categories of P-OS. OS and disease-free survival (DFS) were calculated at the study median follow-up (8-yr). **Results:** Nomogram P-OS were dispersed (median 72%, IQR 57-83%) and had prognostic value for OS and DFS (Log-Rank test: $P < 0.001$). Patients were grouped in 3 arbitrary P-OS categories: > 66% (high P-OS), > 51≤ 66 (intermediate P-OS), ≤ 51% (low P-OS). Most patients were in the high P-OS category (N = 170 [58.6%], 90 Obs/80 Adj), while 68 (23.5%, 34 Obs/34 Adj) and 52 (17.9%, 24 Obs/28 Adj) fell in the intermediate and low P-OS category, respectively. Adjuvant chemotherapy halved the risk of death in patients with low P-OS (HR = 0.46, 95%CI 0.23-0.94) with a 21.2% 8-yr absolute risk reduction (ARR) of death (8-yr OS: 42% and 21% for Adj and Obs, respectively). This effect was not detected in the intermediate (HR = 1.00, 95%CI 0.53-1.88) and high P-OS categories (HR = 1.08, 95%CI 0.61-1.90). There was a DFS benefit for chemotherapy in low P-OS (HR = 0.46, 95%CI 0.24-0.89) but not in the intermediate (HR = 0.74, 95%CI 0.41-1.34) and high P-OS (HR = 0.90, 95%CI 0.54-1.50) categories, leading to a 21% 8-yr ARR for adjuvant chemotherapy (8-yr DFS: 34% and 13% for Adj and Obs, respectively). **Conclusions:** In this RCT patients with a low predicted P-OS (i.e., high-risk patients) have a statistically significant higher OS and DFS when treated with the study doxorubicin-ifosfamide chemotherapy, although the analysis on all study patients was negative. Clinical trial information: NCT00002641.

11519 Poster Discussion Session; Displayed in Poster Session (Board #264), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Efficacy and safety of lurbinectedin (PM1183) in Ewing sarcoma: Final results from a phase 2 study. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients (pts) with relapsed Ewing sarcoma (ES) have a poor outcome. New therapeutic agents are needed. L is a new anticancer drug that blocks transcription and induces DNA double-strand breaks, leading to apoptosis. Moreover, in sarcomas associated with translocations, such as ES, in which the translocation produces a fusion protein that acts as a deregulated transcription factor, L might interfere with the binding of this protein to specific DNA promoters and thus with the synthesis of downstream proteins. **Methods:** A multicenter phase 2 trial to assess efficacy and safety of L in several types of advanced solid tumors (basket trial), including ES, is ongoing. In the ES cohort, 15 adult pts who had received no more than two prior chemotherapy regimens for advanced disease were recruited. If one confirmed response was observed, recruitment was to be increased to at least 25 evaluable patients. The study treatment was lurbinectedin 3.2 mg/m^2 in a 1-hour infusion every 3 weeks. **Results:** 28 evaluable pts were enrolled. Median age was 33 years (range, 18-74) and 16 (57%) were males. 26 (93%) had an ECOG of 0/1. ES was extraosseous in 15 pts; 7 pts had ≥3 disease sites and 27 had received ≥2 lines of prior chemotherapy. 28 pts received a median of 4 cycles of L (range, 1-12) and a median total dose of 11.9 mg/m^2 (range, 3.2-38.4). Efficacy: 4 pts (14.3%) had a partial response and 12 (42.8%) had disease stabilization, 6 of them for ≥4 months. Median duration of the response was 2.9 months (range, 2.9-5.5) and median progression-free survival was 2.8 months (CI 95% 1.4-4.2). Safety: Most common adverse events were related to myelosuppression: 53.6% neutropenia grade (G) 3/4, 14.3% febrile neutropenia, and 18% thrombocytopenia G 3/4; 6 pts had dose delay due to neutropenia G 2-4 or thrombocytopenia G1, and 6 pts had dose reduced because of neutropenia G2-4. G-CSF was given to 12 pts. There were no withdrawals or deaths due to toxicity. **Conclusions:** L as a single agent has shown activity in pretreated pts with advanced ES, with acceptable safety profile and tolerability. Myelotoxicity was well controlled with dose adjustments and G-CSF. Further and larger studies of L alone or in combination regimens are warranted for pts with advanced ES. Clinical trial information: NCT02454972.

11520 Poster Discussion Session; Displayed in Poster Session (Board #265), Sat, 8:00 AM-11:30 AM, Discussed in Poster Discussion Session, Sat, 3:00 PM-4:15 PM

Apatinib for advanced osteosarcoma after failure of standard multimodal therapy: An open label phase 2 clinical trial. *First Author: Lu Xie, Peking University People's Hospital, Beijing, China*

Background: Anti-angiogenesis Tyrosine kinase inhibitors (TKIs) have been proved to show promising effects on prolonging progression-free survival (PFS) for advanced steosarcoma after failure of standard multimodal Therapy. Methylsulfonic apatinib is one of those TKIs which specifically inhibits VEGFR-2. We aimed to assess the activity of apatinib in patients with locally advanced or multiple metastatic high-grade osteosarcoma progressing after standard treatment. **Methods:** This non-randomised phase 2 trial was done in Peking University People's Hospital. We enrolled participants (≥16 years) with relapsed or unresectable osteosarcoma progressing after standard treatment (methotrexate, cisplatin, doxorubicin, and ifosfamide). Participants received 750 mg or 500mg apatinib according to body surface area (BSA) once daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (CR+PR at least 3 months according to RECIST 1.1) and PFS at 4 months. All analyses were intention-to-treat. **Results:** 37 participant were enrolled between March 17th, 2016 and June 9th, 2017. Until final follow-up, the objective response rate (CR+PR at least 3 m) was 56.76% (21/37). And the 4-m PFS rate was 52% (95% CI 32%–68%). However 9/37 (24.32%) patients was progression free at 6 months. Median PFS and OS were 4.44 (95% CI 3.12–7.08) and 8.77 (95% CI 6.73–16.70) months, respectively. Toxic effects led to dose reductions, or interruptions in a total of 25/37 (67.57%) patients. The most common grade 3–4 adverse events were pneumothorax in 5 (13.51%) patients, wound dehiscence in 4 (10.81%), abdominal cramps in 3 (8.11%), hypokalemia in 2 (5.41%) and bilirubin increase, proteinuria, hypertriglyceridaemia, hand–foot skin reaction and anemia each in one (2.70%). No other serious adverse events were reported during the trial. There were no treatment-related deaths. **Conclusions:** Apatinib was a sensitive drug for advanced osteosarcoma with high response rate after failure of chemotherapy, with almost the same duration of response comparing to other TKIs. Clinical trial information: NCT02711007.

11521 Poster Session (Board #266), Sat, 8:00 AM-11:30 AM

Neoadjuvant denosumab for the treatment of resectable giant cell tumor of bone: First results of Russian multicenter study. *First Author: Alexander A. Fedenko, Federal State Budgetary Institution N.N. Blokhin Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Moscow, Russia*

Background: Giant cell tumor of bone (GCT) is a relatively rare, benign but locally aggressive osteolytic skeletal neoplasm of young adults. This study is non-interventional observational GCT treatment study in the Russian Federation (RF). Designed to detect epidemiology data as well as the clinical efficiency of surgical and/or denosumab (Db) treatment of GCT in the RF. **Methods:** Between August 2016 and October 2017, 112 adult patients (pts) with GCT were enrolled. Ten Russian Cancer Center are included in this study. The primary endpoint was Time-To-Progression (TTP). Adult and skeletally mature adolescent pts with resectable and unresectable GCT (N = 54) received subcutaneous Db 120 mg every 4 weeks with a loading dose of 120 mg SC on study days 8 and 15. Options for surgical treatment (N = 25) include intralesional curettage (InC) (alone or followed by filling of the defect with bone cement), marginal excision (MEx), a wide local excision, or en bloc resection with or without reconstructive surgery. **Results:** 112 pts were enrolled, 71 were evaluable for efficacy evaluation. Median follow-up was 12.5 months. Enrolled subjects were 51.8% women, median age 35 years old. The most commonly affected sites are the epiphyses of the long bones (63%), 44% of all cases affect the distal femur or proximal tibia. Less commonly involved vertebra (3.5%), pelvis (8%), the skull (0.8%) and the small bones of the hands (2.6%). Of 112 pts enrolled, 54 received Db, and 16 with resectable GCT were evaluable for efficacy and underwent surgery - InC and MEx. 6 (37.5%) of 16 pts had disease progression; TTP was 6 months after surgery (11 injection of Db in average). 25 of 71 pts received only surgical treatment, in 4 (16%) of 25 pts InC and MEx were performed, 2 (50%) of 4 pts had disease progression, TTP was 7 months after the surgery. **Conclusions:** In this study, only 37.5% of pts with resectable GCT, who received neoadjuvant Db, had disease progression vs 50% of pts, received only surgical treatment. This study confirms that neoadjuvant Db is a possible treatment option for the resectable GCT to avoid mutilating surgery and decrease the risk of recurrences. Further investigation is awaited.

11522 Poster Session (Board #267), Sat, 8:00 AM-11:30 AM

Genome and transcriptome profiling of relapsed and metastatic osteosarcoma. *First Author: Chia Chin Wu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Osteosarcoma (OS) is characterized by genomic complexity and significant genetic heterogeneity. However, it is unknown whether relapse and metastatic samples incur additional insults to genomic integrity. To examine this, we conducted in-depth genomic profiling in a cohort of 48 pediatric and adult patients with high-grade OS including 42 patients with relapsed/metastatic disease. **Methods:** Whole-genome sequencing, RNA sequencing, and functional proteomic profiling were conducted on primary resection, local relapse, and metastatic OS tumor specimens and matched normal tissue/blood samples. Features including somatic mutations, structural rearrangements, copy number alterations, telomere length, and clonality were characterized. Proteomics analysis is underway. **Results:** Genome doubling (GD) occurred in 58% (22/38) of samples and significantly more rearrangements were found in the samples with GD than those without GD (p =0.01). *TP53* (75% of samples) and *RB1* aberrations (60%) were found in samples both with and without GD, with the majority being losses of heterozygosity. This indicates that *TP53* and *RB1* aberrations are early events and GD further propagates genome instability in OS. Mutational signatures 5 and 8 were most prevalent; mutation signature 8 significantly correlated with mutation burden ($p <$ <0.001) and disease-free survival (p =0.02). There were no significant differences amongst genomic features analyzed when comparing primary tumors and lung metastases or tumors by OS histologic subtype. **Conclusions:** Despite inherent genomic complexity, the genomic landscape of OS at relapse and metastasis is comparable to post-treatment primary tumors. Profiling of primary tumors may be appropriate for guiding therapy at relapse. Introduction of novel therapies in the upfront setting could be considered for poor risk patients.

11523 Poster Session (Board #268), Sat, 8:00 AM-11:30 AM

Rare bone sarcoma: A retrospective analysis of 149 adult patients from the French Sarcoma Group. *First Author: Pascaline Boudou-Rouquette, Department of Medical Oncology, ARIANE, Cochin Hospital, Paris Descartes University, AP-HP, CARPEM, Paris, France*

Background: the benefit of neo-adjuvant/adjuvant chemotherapy (CT) in rare bone sarcoma is poorly documented. **Methods:** retrospective study from the French sarcoma network for bone tumors ResOs: 1) adult patients (pts) from 1976 to 2014, 2) Rare bone sarcoma: leiomyosarcoma, undifferentiated pleomorphic and radiation-associated bone sarcoma 3) with central pathological review. Clinical features, treatment modalities and outcome were recorded and analyzed. **Results:** we identified 149 pts from 14 centers. Of them, 109 (73%) presented with localized disease, the local treatment was associated or not with CT. In localized pts, median age was 53 (range 18-82) years (y), median tumor size was 7cm (range 3-18). Sites of disease were extremities (72%) or axial skeleton (28%). The most common histological subtypes were high-grade leiomyosarcoma (33%) and undifferentiated pleomorphic sarcoma (35%). Surgery was performed in 107 pts, conservative in 76.3%. R0 resection was achieved in 58 (82%) pts. Twenty-eight pts (26%) underwent upfront surgery or exclusive radiotherapy (RT)(> 50 Gy) without CT. Eighty-one pts (74%) received either neo-adjuvant CT (n = 13) or adjuvant CT (n = 23) or both (n = 45). The median duration of neo-adjuvant CT was 2.1 months (mo)(range: 0.1-5.7) and 2.4 mo for adjuvant CT (range: 0.7-6.4). Neo-adjuvant/adjuvant CT was mostly doxorubicin- (95%/85%) and cisplatin- (68%/63%) based, or methotrexate-based in 22%/21% of pts. Adjuvant RT was performed in 23 (22%) pts. An overall disease control rate (CR+PR+SD) of 86% was achieved after neo-adjuvant CT. Median follow-up was 5.6 y (95% CI 4.0-7.8). For patients with localized disease, the 3y and 5y-overall survival (OS) were 74.3% (95% CI: 64.1-82.0) and 62.4% (95% CI: 50.7-72.1). The 3y- and 5y-disease-free survival (DFS) were 52.5% (95% CI: 42.1-61.9) and 38.2% (27.7 and 48.5). In univariate analysis, age≤50y (p = 0.04) and neoadjuvant and adjuvant CT (p = 0.03) were associated with longer DFS, but no association was found with OS. **Conclusions:** in this retrospective study, patients with localized rare bone sarcoma treated according osteosarcoma standard of care, with pre- and post-operative chemotherapy, achieved better DFS.

11524 Poster Session (Board #269), Sat, 8:00 AM-11:30 AM

Drug repurposing as a source of innovative therapies in osteosarcoma. *First Author: Gauthier Bouche, The Anticancer Fund, Strombeek-Bever, Belgium*

Background: Chemotherapy and surgery achieve a 5-year event-free survival of 60-70% in localized osteosarcoma (OS), but little additional progress has been made in recent decades. Clinical research in OS is hampered by a limited pipeline of new agents. Drug repurposing, an alternative development pathway that seeks to reuse existing drugs as the source of new treatment options, represents an interesting opportunity to solve this issue. Repurposing benefits from existing data on safety, dosing and clinical experience. Our goal was to list existing non-cancer drugs active against OS to prioritize future research and trials. **Methods:** We used the Repurposing Drugs in Oncology (ReDO) list of 240 approved non-cancer drugs. We queried PubMed for each drug and screened all abstracts to assess relevance, type of evidence (in vitro, in vivo, human data) and mechanism(s) of action (MoA). **Results:** From the 240 drugs, 65 (27%) have evidence of activity against OS. Of these, 10 (15%) are supported by human data. We found certain MoA patterns and grouped drugs in 7 categories. Drugs affecting coagulation, adhesion and chemotaxis: aspirin, heparin, warfarin, plerixafor, disulfiram. Epigenetic drugs: histone deacetylase inhibitors, DNA methyltransferase inhibitors. Immunomodulators: *all-trans* retinoid acid (ATRA), thalidomide, sirolimus. Differentiating agents: calcitriol, ATRA. Drugs targeting osteosarcoma stem cells: plerixafor, metformin, disulfiram. Chemopotentiating drugs: caffeine, proton pump inhibitors, verapamil, piroxicam. Direct cytotoxicity drugs: simvastatin, glucocorticoids. **Conclusions:** 65 FDA-approved drugs have shown activity against OS. In terms of clinical setting, cytototoxic, epigenetic, differentiating and chemo-potentiating drugs could be tested in the neoadjuvant period to enhance the effect of chemotherapy. Immunomodulators and drugs affecting coagulation and chemotaxis could be tested during the perioperative period to prevent early recurrences. Based on our results, we are exploring the possibility of conducting international collaborative multi-arm trials to accelerate progress in OS.

11525 Poster Session (Board #270), Sat, 8:00 AM-11:30 AM

Can DNA methylation patterns be used as predictive biomarkers for chemotherapy response in osteosarcoma? *First Author: Sarbajit Mukherjee, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Response to neoadjuvant chemotherapy correlates with a positive outcome in localized osteosarcoma patients. However, there are no reliable predictors of chemotherapy response. We investigated the role of DNA methylation patterns as a biomarker to chemotherapy response. **Methods:** We obtained 26 diagnostic biopsy specimens from the Children's Oncology Group tissue biobank: 13 with a good ($\geq$ 90% necrosis in the post-chemotherapy resected tumor specimen) and 13 with a poor chemotherapy response ($<$ 90% necrosis). Patient characteristics were similar between these groups. DNA was isolated from tissue and loaded onto Illumina arrays. Machine learning was used to discriminate responders from non-responders. Samples were randomly split into a development (70%) and a validation (30%) set. A GLMnet model optimized within the development set then tested on previously unseen data within the validation set. The random split, model development, and testing were then repeated for a total of 40 cycles. CpG sites used in at least 3 cycles were selected for further testing (n = 16). An optimized, supervised GLMnet predictive algorithm model was generated using the same procedure (40 cycles) based on these 16 CpG sites, and final performance metrics were recorded. **Results:** During initial algorithm development utilizing all methylation sites, the machine learning algorithms performed with an average 74.7% accuracy on previously-unseen data, corresponding to a receiver operator characteristic (ROC) area-under-the-curve (AUC) value of 0.76. The final optimized algorithms, based on 16 CpG highly discriminant CpG sites, improved to an average 91.87% accuracy to discriminate chemotherapy responders from non-responders, with a corresponding ROC-AUC of 0.97 (2x2 table: Fisher's p = 0.03). **Conclusions:** Based on distinct epigenomic patterns in osteosarcoma patients, we developed an algorithm which accurately differentiates chemotherapy responders from non-responders at the time of initial diagnostic biopsy. These findings have the potential to improve both prognostic accuracy and personalized therapy in osteosarcoma, pending confirmatory studies.

11526 Poster Session (Board #271), Sat, 8:00 AM-11:30 AM

Comprehensive genomic profiling of sarcomas in Chinese population. *First Author: Jie Lin, The Second Affiliated Hospital of Kunming Medical University, Kunming, China*

Background: Sarcomas consist of a broad family of mesenchymal malignancies with remarkable diversity. Currently, there are no targeted drugs approved for sarcomas except for pazopanib and imatinib. In this study, comprehensive genomic profiling of 221 sarcomas by targeted next generation sequencing (NGS) was performed, the clinical relevant genomic alterations (CRGAs) and potential therapeutic targets were explored. **Methods:** 211 sarcomas, including 30 leiomyosarcoma (LMS), 13 osteosarcoma (OS), 13 rhabdomyosarcoma (RMS), 9 synovial sarcoma (SS), 22 liposarcoma (LPS), and 124 other subtypes were sequenced by cancer gene panel (CGP) with all coding exons and splicing sites of 365 cancer-related genes plus selected introns from 25 frequently rearranged genes. Genomic alterations (GAs) including point mutations, short insertions and deletions, copy number variations, and rearrangements were called, and further confirmed manually using IGV. These CRGAs were annotated based on literature review and some of them are actionable. **Results:** There are 1215 GAs for all 211 sarcomas and average 5.5 mutations per sample. Among these subtypes, LPS has the highest number of mutations per sample (average 7.5), SS has the lowest number of mutations per sample (average 2.7). Interestingly, 49% GAs are structure variations (SVs). In addition, the top ranked altered genes were TP53 (36%), RB1 (13%), MDM2 (12%) and CDK4 (11%) in all sarcomas. The genomic alterations across all subtypes of sarcomas are enriched in cell cycle pathway. Furthermore, 88% of patients have at least one CRGA, 10 patients with CRGAs in FGFR1/2/3, VEGFA, KIT, FLT4 or KDR could benefit from pazopanib. 57 patients have at least one actionable mutation. Among them, 24 patients with CRGAs in CDK4, CDKN2A/B could benefit from palbociclib, 22 patients with CRGAs in MTOR , PIK3CA, NF1/2, PTEN, TSC1 or STK11 could benefit from everolimus, and 6 patients with CRGAs in BRCA2, ARD1A or ATM could benefit from olaparib. **Conclusions:** This study demonstrated that sarcomas are characterized predominantly by structure variations, most of sarcomas have at least one actionable mutation. In conclusion, comprehensive genomic profiling in a large cohort highlights the promise of targeted therapies.

11527 Poster Session (Board #272), Sat, 8:00 AM-11:30 AM

Single-agent expansion cohort of lenvatinib (LEN) and combination dose-finding cohort of LEN + etoposide (ETP) + ifosfamide (IFM) in patients (pts) aged 2 to $\leq$25 years with relapsed/refractory osteosarcoma (OS). *First Author: Nathalie Gaspar, Institut Gustave Roussy, Villejuif, France*

Background: LEN is a multikinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRα, KIT, and RET. In human pediatric OS xenograft models, LEN enhanced the antitumor activity of IFM + ETP. In a phase (Ph) 2 study of sorafenib in pts with unresectable high-grade OS, progression-free survival at 4 months (PFS-4) was 46%. We report emerging data from a Ph 2 single-agent LEN expansion cohort and Ph 1b combination dose-finding cohort of LEN + ETP + IFM in pts with relapsed/refractory OS. **Methods:** Pts were age 2 to $\leq$25 years, had relapsed OS, and had $<$ 2 prior VEGF-targeted therapies. The recommended dose (RD; 14 mg/m^2) from Ph 1 was used in Ph 2. In Ph 1b, a 20% reduction of LEN (11 mg/m^2/day) was used as starting dose in combination with IFM 3000 mg/m^2 + ETP 100 mg/m^2 daily/3 days. Ph 2 and Ph 1b primary endpoints were PFS-4 per RECIST 1.1 and RD of the combination. Secondary objectives included best overall response (BOR), objective response rate, PFS, safety, and PK. Data cutoff was October 6, 2017. **Results:** In Ph 2, 16 pts received LEN 14 mg/m^2. Median (min, max) number of cycles received was 3.0 (1, 9). Most common any-grade TEAEs were diarrhea, hypothyroidism, and proteinuria (43.8% each). Most common Grade (G) 3 or 4 TEAEs were back pain and dyspnea (12.5% each). One pt discontinued due to TEAEs (myelodysplastic syndrome); 5 of 15 evaluable pts achieved PFS-4 and BOR was PR (n = 1) and SD (n = 7). In Ph 1b, 7 pts received LEN 11 (LEN 11 mg/m^2 + IFM + ETP) and 6 pts received LEN 14 (LEN 14 mg/m^2 + IFM + ETP). 1 pt had a DLT at LEN 11 (G3 thrombocytopenia) and 2 pts had DLTs at LEN 14 (G4 thrombocytopenia with G3 bleeding in 1 pt; G2 oral dysesthesia, G2 back pain, and G1 muscle spasms in 1 pt). G $\geq$3 TEAEs occurred in 85.7% and 66.7% of LEN 11 and LEN 14 pts, respectively. No pts discontinued due to TEAEs. BOR was PR (n = 1) and SD (n = 5). AUC at steady state of LEN and distributions of interindividual variability of oral clearance were comparable between LEN single agent and the combination. **Conclusions:** In Ph 2, LEN at 14 mg/m^2 achieved PFS-4 in 5 pts; BOR was PR in 1 pt and SD in 7 pts. In Ph 1b, LEN + chemotherapy had a manageable safety profile. The study is ongoing and updated data will be presented. Clinical trial information: NCT02432274.

11528 Poster Session (Board #273), Sat, 8:00 AM-11:30 AM

A comparison of outcomes, presentation, and treatment in pediatric (Ped) versus adult patients (Pts) with Ewing sarcoma. *First Author: Eric B Schwartz, Michigan Medicine, Ann Arbor, MI*

Background: Ewing Sarcoma (ES) afflicts 225 children and 180 adults in the US annually, but the vast majority of research is in ped pts. In multiple series, adults have poorer outcomes. The aim of this study is to evaluate clinical features that correlate with overall survival (OS)/progression-free survival (PFS). **Methods:** ES pts at University of Michigan from 2007-15 were identified using an institutional database. Charts were reviewed for demographic and clinical data. Ped pts were defined as age ≤18 at diagnosis. Two-sample t-tests or Chi-squared tests/Fisher's exact tests were used for comparisons. Survival outcomes were analyzed using Kaplan-Meier methods and Cox proportional hazards regression models. **Results:** Seventy-eight ES pts (26 peds, 52 adult) were included in analysis. Factors evaluated in multivariate analysis model included localized disease, age, surgery, radiation, tumor size, cumulative doxorubicin (DOX), osseous primary and no. of first-line chemo cycles. Localized disease correlated with improved PFS (HR = 0.20, p = < 0.0001) and marginally with OS (HR = 0.386, p = 0.0580). Five-yr OS was higher in ped pts vs adults (81% vs. 49%, p = 0.0218). Ped pts received more cycles of first-line chemo (14.0 vs 11.8, p = 0.003), which positively correlated with OS (HR = 0.78, p = 0.002) and PFS (HR = 0.82, p = 0.024). Other differences included higher cumulative DOX dose and increased incidence of extraosseous ES in adults, but these did not correlate with OS/PFS. **Conclusions:** In our series, younger age correlated with improved OS. Ped pts were more likely to have osseous ES and less DOX, but only increased number of first-line chemo cycles was associated with improved outcomes. Further evaluation of potential tissue biomarkers to differentiate the two groups and early progressors is planned.

Variable	Peds (n = 26)	Adult (n = 52)	p-value
Localized disease, n (%)	17 (65.4)	33 (63.5)	0.867
Mean no. of first-line chemo cycles	14	11.8	0.003
Cumulative DOX (mg/m2)	357.9	445.6	< 0.0001
Osseous primary, n (%)	21 (84)	22 (45.8)	0.002
Mean tumor size, cm (range)	8.2 (3.2 – 19.3)	9.6 (1.8 – 23.5)	0.384
Surgical Resection, n (%)	19 (73.1)	28 (53.8)	0.142
Progression during first line rx, n (%)	1 (4.2)	7 (15.2)	0.249

11530 Poster Session (Board #275), Sat, 8:00 AM-11:30 AM

To compare the efficacy of sunitinib and imatinib following cytoreductive resection in GIST patients with progression on imatinib: A multi-center controlled study. *First Author: Xinhua Zhang, Department of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Imatinib is recommended to treat gastrointestinal stromal tumor (GIST) receiving surgery after localized tumor progression, but the progression free survival (PFS) is not satisfied. The objective of this study is to investigate the optimal therapy after cytoreductive surgery in GIST patients with unifocal or multifocal progression on imatinib. **Methods:** The data of GIST patients who received R0 resection or satisfied cytoreductive surgery after unifocal or multifocal progression followed by different TKIs were collected. The satisfied cytoreductive surgery was defined as the diameter of every residual tumor was less than 1cm, or the proportion of residual tumor was less than 25% after cytoreductive surgery. The primary endpoint is to evaluate the PFS of the patients receiving surgery followed by sunitinib comparing with that of followed by imatinib after tumor progression. PFS curves were constructed according to the Kaplan–Meier method and compared using a log-rank test. **Results:** From January 2006 to June 2017, 97 patients from 13 medical centers were enrolled in this study. Fifty-six patients continued imatinib therapy and 41 patients switched to sunitinib directly after R0 resection or satisfied cytoreductive surgery. The PFS of sunitinib group was longer than that of imatinib group (30.0 months vs 12.0 months, p = 0.009). In subgroup analysis, the PFS of sunitinib group and imatinib group were 25.5 months and 12.0 months in patients with multifocal progression (p = 0.008), 39.0 months and 13.0 months with unifocal progression (p = 0.156), respectively. Patients carrying a primary KIT exon 11 mutation had a PFS of 31 months in sunitinib compared with 11 months in imatinib (p = 0.036), respectively. And those of KIT exon 9 mutation or KIT/PDGFRA wild-type had a PFS of 25.5 months to 13 months (p = 0.06), respectively. The overall survival in sunitinib group and imatinib group were 37.0 months and 33.0 months, respectively (p = 0.794). **Conclusions:** R0 or satisfied cytoreductive surgery followed by sunitinib treatment in GIST patients with progression on imatinib could improve PFS compared with surgery followed by imatinib therapy.

11531 Poster Session (Board #276), Sat, 8:00 AM-11:30 AM

The prognostic value of blood neutrophil-to-lymphocyte ratio (NLR) factor in advanced gastrointestinal stromal tumors (GIST) treated with sunitinib after imatinib failure. *First Author: Piotr Rutkowski, Maria Sklodowska-Curie Institute - Oncology Center, Warsaw, Poland*

Background: Neutrophil-to-lymphocyte ratio (NLR) was shown to be prognostic in several solid malignancies. There are still limited data about predictive/prognostic value of NLR during targeted therapy of patients with advanced gastrointestinal stromal tumors (GIST). The aim of the study was to asses a clinical value of this ratio in patients with unresectable/metastatic GIST treated with sunitinib. **Methods:** Between 2001 and 2016, 146 of 230 patients with metastatic/unresectable GIST and fully available clinicpathologic data who progressed on the imatinib and received sunitinib as second line treatment were included to the analysis. In all patients the NLR was assessed at the baseline, after 3 months of treatment and upon disease progression (or last observation). The cut-off value for NLR was set at median of 2.4. Kaplan-Meier survival probability estimation with in log-rank test, and Cox's proportional hazards model were used for analysis. **Results:** Median Progression-Free Survival (PFS) on sunitinib treatment was 12 months, 2- and 5-year rate were 27% and 5% respectively; median Overall Survival (OS) – 23 months, 2- and 5-year rate 48% and 14% respectively. NLR > 2.4 at baseline was significantly associated with poorer OS: median OS was 30.0 months (95%CI 26.7-40.6) for NLR ratio ≤2.4 vs. 16.4 months (95%CI 14.1-22.8) for NLR > 2.4 (p = 0.002); median PFS was 18.2 (95%CI 10.8-24.2) vs. 9.6 (95%CI 6.9-15.1) respectively, which was close to statistical significance (p = 0.075). In multivariate OS model adjusted for mitotic index, localization of primary tumor (stomach vs. other) and driver oncogenic primary mutation in the tumor (KIT exon 11 mutation versus other) baseline NLR > 2.4 was proven to be statistically significant (HR 1.96 95%; CI 1.31-2.91; p < 0.001). Moreover, NLR value at last observation or disease progression was also prognostic factor for OS (HR 2.37, 95% CI: 1.42-3.96, p < 0.001). **Conclusions:** Our results demonstrate the usefulness of NLR as a prognostic and predictive marker in patients with advanced GIST treated with sunitinib.

11532 Poster Session (Board #277), Sat, 8:00 AM-11:30 AM

Role of resection following focal progression with standard doses of imatinib in patients with advanced gastrointestinal stromal tumor: Results of propensity score analyses. *First Author: Hyungwoo Cho, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, Republic of (South)*

Background: Although the benefits of resection for focally progressive advanced gastrointestinal stromal tumors (GISTs) during imatinib (IM) treatment have been suggested, those benefits over IM alone have not been proven. We compared the clinical outcomes of resection plus IM dose escalation or maintenance (S group) with IM dose escalation alone (NS group) in patients (pts) with advanced GIST following focal progression (FP) with standard doses of IM. **Methods:** Between April 2003 and October 2016, 98 pts with histologically documented initially metastatic or distant recurrent GISTs experienced FP with standard doses of IM in Asan Medical Center, Seoul, Korea. Eight pts who received sunitinib without IM dose escalation after FP were excluded; 90 pts were thus included in this analysis. The primary endpoints were time to IM treatment failure (TTF) and overall survival (OS). TTF was defined as the duration from the date of FP to the date of disease progression on IM dose escalation or intolerance. **Results:** The median age was 61 years (range, 31–78) and 60 pts (66.7%) were male. The small bowel (n = 51, 56.7%) was the most common primary site followed by the stomach (n = 35, 38.9%). Compared to pts in the NS group (n = 52), pts in the S group (n = 38) had a higher proportion of primary tumor site involvement (26.3% vs. 7.7%, $p = 0.02$) and lower tumor burden (median largest tumor size: 34 mm vs. 52 mm, $p = 0.04$) at FP. With a median follow-up duration of 31.0 months, pts in the S group had significantly better TTF and OS than pts in the NS group (median TTF: 24.2 vs. 6.5 months, $p < 0.01$; median OS: 53.2 vs. 35.1 months, $p = 0.009$). Multivariate analysis revealed that along with low initial tumor burden, pts in the S group independently demonstrated better TTF (hazard ratio [HR] 0.29, $p < 0.01$) and OS (HR 0.47, $p = 0.04$). Even after applying inverse probability of treatment-weighting adjustments, pts in the S group demonstrated significantly better TTF (HR 0.36, $p < 0.01$) and OS (HR 0.58, $p = 0.049$). **Conclusions:** Our results strongly suggested that resection following FP with standard doses of IM in pts with advanced GIST may provide additional benefits over IM dose escalation alone.

11533 Poster Session (Board #278), Sat, 8:00 AM-11:30 AM

A retrospective natural history study of patients (pts) with PDGFRα D842V mutant advanced gastrointestinal stromal tumor (GIST) previously treated with a tyrosine kinase inhibitor (TKI). *First Author: Margaret von Mehren, Fox Chase Cancer Center, Philadelphia, PA*

Background: Activating mutations in *KIT* or *PDGFRA* kinases drive the vast majority of GIST in adult pts, making the disease highly amenable to targeted therapy. *KIT*-driven disease is more common (~80% of cases of advanced GIST), while *PDGFRA*-driven GIST is rare (~5-10% of cases of advanced GIST). TKIs have transformed therapy of advanced GIST; however, evidence suggests the benefit of currently approved TKIs has been predominantly in patients with *KIT*-driven GIST. We initiated this study to characterize response and survival of pts with PDGFRα D842 mutant GIST treated with currently approved TKIs. **Methods:** This was a multicenter, retrospective study of adult pts with locally advanced, metastatic, or recurrent PDGFRα D842 mutant GIST diagnosed between Jan 2000 and Jul 2016 who were treated with at least one TKI. Demographic and clinical data were collected through chart review and analyzed to determine overall survival (OS) and best overall response, duration of response, and progression-free survival (PFS) for each line of TKI therapy. **Results:** Twenty-two pts, all with PDGFRα D842V GIST, were identified at 3 US academic institutions: men, n = 15; median age, 57 y [range: 31-72]; median TKI lines of therapy, 4 [range: 1–8]. Ten pts had primary tumor size ≥ 15 cm, and 8 pts had mitotic index > 10/50 HPF at the time of diagnosis. Imatinib was the most common TKI used (n = 21); followed by sunitinib (n = 15), dasatinib (n = 8), sorafenib (n = 6), regorafenib (n = 4), nilotinib (n = 2) and pazopanib (n = 1). Imatinib was the first line TKI in 20 pts (91%). Only 1 (5%) pt responded to first-line TKI therapy (complete response to imatinib in a pt with residual disease following primary resection). Median PFS on first line TKI was 6.4 months. Median OS from initial diagnosis of GIST was 4.2 years. **Conclusions:** These results confirm and extend previous data suggesting that pts with advanced PDGFRα D842V GIST have a low response rate, and poor overall survival with currently available TKIs. To transform therapy for PDGFRa D842V GIST, novel TKIs that potently and selectively inhibit D842V mutant PDGFRα are needed.

11534 Poster Session (Board #279), Sat, 8:00 AM-11:30 AM

Immune microenvironment profiling of gastrointestinal stromal tumors (GIST). *First Author: Maria A. Pantaleo, Interdepartmental Centre of Cancer Research "Giorgio Prodi", University of Bologna, Bologna, Italy*

Background: GIST benefit from TK inhibitors but unfortunately can develop resistance or intolerance. Patients prolonged life expectancy associated with the complex biology involved in progressive disease led to a growing urgency and interest in developing new therapeutic strategies. Recently, few preclinical studies were conducted investigating the immunological profile in GIST. In the present study we analyzed GIST by whole transcriptome sequencing to estimate the gene expression signature, the presence of immune-infiltrate through in silico analysis, and to define the immunological profile of GIST as basis for immunotherapy . **Methods:** 18 fresh frozen GIST tumors (14 primary and 4 metastases) were analyzed. RNA-seq was performed with Illumina technology. Gene expression data was used to estimate the relative and absolute presence of 22 hematopoietic cell types in tumor microenvironment adopting CIBERSORT, an analytical tool suited to perform a deconvolution of neoplastic and tumor-infiltrating cells. The data were further processed to evaluate the enrichment of immune cell types, the correlation between cell subpopulations and to compare GIST microenvironment with other tumors. IHC tests for CD163, CD20, CD8 and TIA1 were performed and scored on FFPE samples. **Results:** A significant presence of immune-infiltrate in all GIST samples was confirmed, with a dominance of macrophages (M2 and M1), immediately followed by CD3+ T cells, both CD4+ and CD8+. Compared to other solid tumors, the immune profile of GIST appears similar to that of melanoma. The most relevant result is the high amount of CD8+ T-cells, suggesting that the adaptive immune response could be an immunotherapeutic target. The presence of CD8+ was confirmed by IHC that also showed the expression of citolytic markers (TIA1). Moreover the abundance of CD8+ T-cells correlated with the expression of IFN-gamma signature genes. Interestingly, the abundance of macrophages negatively correlates with T-cells presence (CD4+ and CD8+) supporting the dynamic balance between the immunosuppressive and active components of the immune-infiltrate. **Conclusions:** These findings represent a potential rationale to plan an immunotherapy approach along with TK inhibitors in GIST.

11535 Poster Session (Board #280), Sat, 8:00 AM-11:30 AM

LMTK3 to regulate the translation of oncogenic KIT in GIST regardless of imatinib sensitivity. *First Author: Lillian Rose Klug, Portland VA Health Care System and OHSU Knight Cancer Institute, Portland, OR*

Background: The majority of gastrointestinal stromal tumors (GIST) have been shown to be caused by somatic activating mutations in the receptor tyrosine kinase KIT. The major cause of death in patients with advanced *KIT*-mutant GIST is due to the development of KIT tyrosine kinase inhibitor-resistant (TKI-resistant) metastatic disease. Drug resistance arises almost exclusively from secondary mutations within KIT, highlighting the importance of KIT in the proliferation and survival of these tumors. **Methods:** We performed a human kinase siRNA screen in multiple *KIT*-mutant cancer cell lines, using viability as a read out. We defined candidate targets as those whose knockdown decreased viability in all cell lines. Validation and mechanistic studies were done using a library of *KIT*-mutant GIST cells. **Results:** We identified lemur tyrosine kinase 3 (LMTK3) as candidate target in three *KIT*-mutant cell lines. *LMTK3* silencing reduced the viability of all *KIT*-mutant GIST cells tested to date, including cell lines with KIT TKI-resistance mutations. Importantly, *LMTK3* silencing decreased the viability of *KIT*-mutant cells specifically, but not that of KIT-independent cells. LMTK3 knockdown also reduced tumor growth *in vivo* in a GIST xenograft model. Further, we found that decreased cell viability after *LMTK3* silencing was due to induction of apoptosis. Because these cells depend so heavily on KIT and the loss of KIT signaling results in cell death, we hypothesized that *LMTK3* silencing may affect this pathway. Indeed, *LMTK3* silencing decreased total KIT protein across all cell lines. The reduction in KIT protein was not the result of changes in KIT transcript or KIT protein stability, but translation rate of KIT was significantly reduced after LMTK3 knockdown. **Conclusions:** The protein kinase LMTK3 is an important translational regulator of oncogenic KIT expression in *KIT*-mutant GIST regardless of drug sensitivity and represents a novel, tractable target, particularly in drug-resistant tumors.

11536 Poster Session (Board #281), Sat, 8:00 AM-11:30 AM

Interrogating the sarcoma immune microenvironment (iME) using multiplex immunohistochemistry (mIHC). *First Author: Andrew Silverman, Columbia University Medical Center, New York, NY*

Background: Soft tissue sarcoma (STS) is a heterogeneous malignancy including more than 50 molecularly distinct subtypes. Undifferentiated pleomorphic sarcoma (UPS) and leiomyosarcoma (LMS) are common subtypes with limited treatment options. LMS can be divided into two distinct subsets: uterine (uLMS) and retroperitoneal (rpLMS). STS subtypes have differing levels of immune infiltration and show variable response to checkpoint blockade. We hypothesize that immune infiltration of cytotoxic T lymphocytes (CTLs) and macrophages will differ among subtypes of STS. **Methods:** 30 patients with sarcoma, naïve to systemic treatment, were identified, 10 cases each: UPS, uLMS and rpLMS. 5μm slides were stained using qmIF protocol for DAPI, CD3 (T cells), CD8 (CTLs), CD68 (macrophages), vimentin (tumor marker), HLA-DR (activation) and PD-L1 (immune suppression). Tumor areas were chosen by a pathologist, multiplex images acquired using Vectra, then processed and analyzed using inForm software. Genomic analysis to be performed using nanoString. **Results:** All cases have been stained and are now being analyzed. Preliminary analysis was performed by qualitative grading of stains (Table 1). We find increased CTL infiltration and HLA-DR expression in UPS as compared to either LMS group. uLMS appears to exhibit higher CTL infiltration and HLA-DR expression than rpLMS. QmIF and genomic analysis is ongoing. **Conclusions:** Qualitative analysis of UPS, uLMS, and rpLMS immune TME finds that UPS appears to have higher levels of CTLs and PD-L1 expression, consistent with results from other studies using conventional immunohistochemistry. Subtypes of LMS harbor distinct immune TME features, as uLMS as higher CTL and HLA-DR expression than rpLMS. These findings could have therapeutic implications. This study is currently ongoing; multiparameter immune phenotyping, spatial localization, and genomic analysis will be reported at the meeting.

Quantitative qmIF analysis.

Group	CD3	CD8	CD68	HLA-DR	PD-L1
rpLMS	+	-	+	++	++
UPS	++	++	++	+++	+++
uLMS	++	+	++	+++	++

- no cells, + few cells, ++ some cells, +++ many cells

11537 Poster Session (Board #282), Sat, 8:00 AM-11:30 AM

Phase II trial of continuous dosing of regorafenib in patients with metastatic or recurrent gastrointestinal stromal tumors (GISTs) after failure of imatinib and sunitinib. *First Author: Yoon-Koo Kang, Department of Oncology, Asan Medical Center, Seoul, Korea, Republic of (South)*

Background: Regorafenib in the standard intermittent dosing schedule (160 mg po per day for 3 weeks followed by 1week rest) was proven effective in the GRID trial in refractory gastrointestinal stromal tumors (GISTs). However, with this dosing schedule, frequent dose reduction was needed and progression of GIST tumors or tumor-related symptoms during the off-treatment period were also noted in some patients (pts).Therefore, we conducted this phase 2 trial to evaluate the efficacy and safety of regorafenib in lower dose continuous dosing schedule (NCT02889328). **Methods:** Pts with measurable, metastatic or recurrent GIST who failed both imatinib and sunitinib were eligible for this study. Regorafenib 100 mg po per day was administered continuously. The primary endpoint was disease control rate [DCR] (CR + PR + SD) lasting for at least 12 weeks by the RECIST v1.1. **Results:** From September 2016 to August 2017, a total of 25 pts were enrolled.The median age was 60 years (range, 42-74), and male was dominant (84%). Small bowel was the most common primary site (n = 15, 60%), followed by stomach (n = 7, 28%). The median treatment duration of imatinib and sunitinib was 40.5 months (range, 7.1–100.5) and 8.3 months (range, 0.7–37.5), respectively. Primary mutation was in kit exon 11 (n = 16, 64%) and 9 (n = 5, 20%), with 3 wild type (12%). The best response was PR in 2 (8%), SD in 16 (64%), and PD in 6 (24%) pts. DCR lasting for at least 12 weeks was 64% (16 of 25). With a median followup of 8.6 months (range, 2.3–14.6), the median PFS was 7.3 months (95% CI, 5.9–8.6), and the median OS was not reached with 1-year survival rate of 64.5%. Treatment was well tolerated. Ten pts (40%) experienced grade 3-4 toxicities including hand-foot skin reaction (n = 4, 16%), and elevation of alanine aminotransferase (n = 2, 8%). Only 5 pts (20%) needed dose modification with relative dose intensity of 91.8% for 8 cycles in all pts. **Conclusions:** With comparable efficacy and better safety profile compared to standard intermittent dosing schedule, regorafenib in this trial with lower dose continuous schedule might be an alternative treatment in GIST pts after failure of imatinib and sunitinib. Clinical trial information: NCT02889328.

11538 Poster Session (Board #283), Sat, 8:00 AM-11:30 AM

Impact of proton pump inhibitors (PPIs) on sunitinib (SU) pharmacokinetics (PK) and activity in GIST patients (pts). *First Author: Olivier Mir, Gustave Roussy Cancer Campus, Villejuif, France*

Background: PPIs alter the PK of several oral drugs, either through a decrease in absorption due to higher GI tract pH, or the induction of efflux pumps such as ABCB1. The PK of SU is well correlated with its activity in GIST. Previous works have suggested a deleterious impact of PPI intake on SU activity in mRCC, but sunitinib PK was unchanged in pts with previous gastrectomy. Overall, the impact of PPI intake on SU PK and activity in GIST remains to define. **Methods:** Steady-state plasma concentrations of SU were determined in 57 GIST pts treated in the 2nd line setting over 10 years (2008-2017), at the dose of 50 mg/day 4 weeks/6, or 37.5 mg daily, according to their performance status (PS) and co-morbidities, at the discretion of the treating physician. PK data were analyzed with a nonlinear mixed-effect modeling approach, using the Monolix software. For the population PK model, covariates included lean body mass (LBM, estimated using CT-scan) and PPI intake. PFS was analyzed using the Kaplan-Meier method. **Results:** 18 pts (32%) received PPIs troughout SU treatment. SU PK was satisfactorily described by a one-compartment model with a zero-order absorption. SU CL/F and V/F were increased by a 1.55 factor when co-administered with PPI, resulting from a decreased relative bioavailability. Covariate modeling showed that PPI intake decreased the fraction of dose absorbed by ~40%, and LBM was better related to the CL and V inter-subject variations than weight, supporting a major role of the non-fat mass in the elimination and distribution parameters. Overall, the covariate effects explained approximately half of the CL/F between subject variability. Median PFS was 3.0 months (95%CI: 2.5-3.2) vs. 7.7 months (95%CI : 6.1-11.2) in pts receiving PPIs, or not, respectively. Mutational status had no impact on PFS. **Conclusions:** Our results suggest that SU plasma concentrations in pts receving PPis could be sub-optimal, leading to early anti-tumor treatment failure. In this setting, either PPI discontinuation or SU dose escalation (up to 75 mg daily, in lack of limiting toxicity) should be considered.

11539 Poster Session (Board #284), Sat, 8:00 AM-11:30 AM

Utility of circulating tumor DNA (ctDNA) in the management of patients with gastrointestinal stromal tumor (GIST): Analysis of 152 patients. *First Author: Junaid Arshad, Jackson Memorial Hospital, Miami, FL*

Background: GIST is the most common sarcoma of the GI tract. Management of GIST is determined by KIT, PDGFR, or other genomic alterations. Tissue diagnosis has been the mainstay of the biomarker assessment but next generation sequencing (NGS) - based analysis of ctDNA is a novel, effective and non-invasive alternative. **Methods:** DNA sequencing of the circulating tumor DNA (ctDNA) was perfomed on blood samples from 152 patients. Samples were collected, shipped at room temperature and centrifuged to isolate plasma. DNA was extracted, concentrated, and quantified. **Results:** Of 152 unique patients, 72 (47%) females and 80 (52%) males with a median age of 59. 41 (27%) patients did not test positive for either KIT or PDGFRA while 111 (73%) had either KIT or PDGFRA mutation. 6 patients were positive for both KIT and PDGFRA mutations. Of these 6, 1 had KIT amp plus PDGFRA amp, then only a KIT point mutation 6 months later. 2 had KIT plus PDGFRA point mutations. Most of the imatinib resistance mutations were missense mutations and were found in males (p = .005). There were 3 (2%) patients positive for PDGFRA D842V with resistance to imatinib. Mutations other than KIT or PDGFRA included EGFR 8(7%), ERBB2 8 (7%), NF1 7 (6%), PIK3CA 7(6%), ARID1A 6(5%), FGFR2 6(5%), KRAS 6(5%), BRCA2 5 4%), MET 5 (4%), PTEN 5(4%), MYC 4(3%), NTRK1 4(3%). Overall, the average number of mutations at first test: 3 (range 1-11). The average highest MAF: 4.74% (RANGE 0-52.98%), MEDIAN 0.72%. Of the the 25 patients with clinical annotation 15 (10%) had treatment impacted, 20 (13%) identified resistance mutations, and and 30 (20%) of patients were found to harbor additional mutations. **Conclusions:** Digital DNA sequencing from ctDNA provides a reliable picture of the genomic profile in GIST. However, there is limited information related to resistance, prognosis or predictive role along with the effect of chemotherapy. Further validation and evaluation of clinical utility is warranted.

11540 Poster Session (Board #285), Sat, 8:00 AM-11:30 AM

Activity and safety of crizotinib in patients with advanced, metastatic alveolar soft part sarcoma (ASPS) with rearrangement of *TFE3:* European Organization for Research and Treatment of Cancer (EORTC) phase 2 trial 90101 CREATE. *First Author: Patrick Schoffski, Department of General Medical Oncology Leuven Cancer Institute, University Hospitals Leuven, KU Leuven, Leuven, Belgium*

Background: ASPS is an orphan disease associated with rearrangement of transcription factor E3 (*TFE3*), leading to abnormal *MET* expression. We assessed crizotinib in pts with ASPS (NCT01524926). **Methods:** Eligible pts with reference pathology-confirmed ASPS received crizotinib 250 mg bid. By central FISH assessment of *TFE3* rearrangement , pts were attributed to *MET*+ or *MET*- sub-cohorts. Primary endpoint was objective response rate (ORR; RECIST 1.1) according to local investigator. Secondary endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), progression-free rate (PFR), overall survival rate (OSR), overall survival (OS) and safety. **Results:** Among 53 consenting pts with confirmed diagnosis of ASPS, 48 were treated and 45 were evaluable. Among 40 *MET*+ pts, 1 achieved a confirmed partial response (PR) lasting 215 d and 35 had stable disease (SD) (ORR: 2.5%, 95%CI: 0.6-80.6%). Further efficacy endpoints in *MET*+ cases were: DCR 90.0% (76.3-97.2%); 1-year PFR 37.5% (22.9-52.1%); 1-year OSR 97.4% (82.8-99.6%). Among 4 *MET*- pts, 1 achieved a PR lasting 801 d and 3 had SD (ORR: 25.0%, 0.6-80.6%) for a DCR of 100% (39.8-100.0%). The 1-year PFR in *MET*- cases was 50% (5.8-84.5%); 1-year OSR was 75% (12.8-96.1%). One pat with unknown *MET* status (technical failure) achieved SD but progressed after 17 cycles. Shrinkage of target lesions was seen in 17 pts, both in *MET*+ and - cases. The most common related AEs were nausea (34/48 [70.8%]), vomiting (22/48 [45.8%]), blurred vision (22/48 [45.8%]), diarrhea (20/48 [41.7%]) and fatigue (19/48 [39.6%]). **Conclusions:** According to EORTC efficacy criteria for sarcoma, our data suggest that crizotinib has activity in *TFE3* rearranged ASPS. While objective responses were infrequent, we observed tumor shrinkage in a significant proportion of pts, excellent DCR and good survival. We present very mature and reliable prospective PFS and OS estimates as reference for future research in pts with ASPS. Clinical trial information: NCT01524926.

11541 Poster Session (Board #286), Sat, 8:00 AM-11:30 AM

Anti CXCR4 antibody combined with activated and expanded natural killer cells for sarcoma immunotherapy. *First Author: Maria Vela, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain*

Background: Metastasis occurs in 20-55% of sarcoma patients and remains the main cause of death. We propose a novel immunotherapeutic approach based in anti CXCR4 antibody MDX1338 (Bristol Myers Squibb) in combination with Activated and Expanded Natural Killer (NKAE) cells therapy. CXCR4 is upregulated in 33.3-73.3% sarcomas. Its signaling blockade by MDX1338 may reduce tumor growth and metastatic burden. NKAE cells have shown cytotoxicity against osteosarcoma and Ewing sarcoma. **Methods:** Expression of CXCR4 by different sarcoma cell lines was analyzed by flow cytometry. Its migration and invasion capacity towards CXCL12 was tested using Transwell plates and Matrigel. NKAE cells were obtained coculturing healthy donors' peripheral blood mononuclear cells with K562-mb15-41BBL cells and IL-2. Rhabdomyosarcoma cells were inoculated intravenously in immunodeficient NSG mice to generate an *in vivo* model of metastatic sarcoma. Four treatment arms were established: MDX1338; NKAE; MDX1338+NKAE; vehicle. Luminiscent tumors were monitored and subsequently micrometastasis were identified and quantified: by qRT-PCR; by immunohistochemistry; and by fluorescence *in situ* hybridization. **Results:** Alveolar rhabdomyosarcoma RH30 cell line showed the highest CXCR4 expression, concomitant with highest migration and invasion index. Both MDX1338 and NKAE efficiently reduced *in vitro* RH30 cells migration and invasion, but only the combination of both agents completely abrogated it. In *in vivo* assays, NKAE treatment was enough to completely prevent RH30 tumor implant. Nontheless, qRT-PCR analysis found RH30 lung micrometastasis in NKAE-treated mice group. Again, the combination of both MDX1338 and NKAE was necessary to completely eliminate it. Immunohistochemical and *in situ* hybridization analysis further confirmed these results. **Conclusions:** Our *in vitro* and *in vivo* studies show a complementary role of anti CXCR4 antibody MDX1338 and NKAE cell therapy to prevent rhabdomyosarcoma cells migration, invasion, tumor implant and lung metastasis formation. These preclinical results constitute a first evidence of the efficacy of this combined immunotherapy to prevent sarcoma disease dissemination.

11542 Poster Session (Board #287), Sat, 8:00 AM-11:30 AM

Phase 1b/2 study of olaratumab plus gemcitabine and docetaxel for the treatment of advanced soft tissue sarcoma (STS) (ANNOUNCE 2): Phase 1b results. *First Author: Victor Manuel Villalobos, University of Colorado, Denver, CO*

Background: Olaratumab (O) is an antibody against platelet-derived growth factor receptor alpha. In a randomized phase 2 study, O in combination with doxorubicin (dox) demonstrated a significant improvement of overall survival (OS) over dox alone in patients (pts) with advanced STS. Here we report the safety, tolerability and recommended phase 2 dose (RPTD) of O plus gemcitabine (G) and docetaxel (D) (O + G/D). **Methods:** This dose-escalation study enrolled pts with advanced/metastatic STS, $\leq$2 prior lines of systemic therapy, no prior G, D or O, and ECOG PS 0-1. Pts received O on Days 1 and 8 at 15 mg/kg (cohort 1) or 20 mg/kg (cohort 2) with G (900 mg/m^2 Days 1 and 8) and D (75 mg/m^2 Day 8) on a 21-day cycle. The primary objective was to determine the RPTD of O + G/D, with a dose-limiting toxicity (DLT) occurring in Cycle 1 at a rate below 33%. Secondary objectives included safety and pharmacokinetics (PK). **Results:** 54 pts (cohort 1/2 = 21/33) received at least one dose of treatment. No DLT occurred in cohort 1. In cohort 2, 5 pts (15.2%) experienced 6 DLTs (ALT increase, bacteremia, neutropenia [2 pts], and thrombocytopenia [2pts]). Treatment-related adverse events (TRAEs) reported for cohorts 1 and 2 included all grades (90.5% and 93.9%), Gr 3 (14.3% and 42.4%), Gr 4 (0 and 18.2%), and serious AEs (9.5% and 15.2%), respectively. Common TRAEs (all grades, Gr $\geq$3) occurring in $\geq$ 25% of pts were fatigue (66.7%, 11.1%), anemia (61.1%, 18.5%), thrombocytopenia (35.2%, 18.5%), nausea (29.6%, 0%) and diarrhea (27.8%, 3.7%). 1 pt discontinued due to a study-related AE of fatigue (cohort 1). Following 2 deaths unrelated to study treatment, cohort 2 was expanded to 33 pts. The PK profile of O + G/D was similar to that of O in combination with other chemotherapies. **Conclusions:** Both dose levels were tolerated with a higher incidence for known toxicities of G/D in cohort 2. Based on safety and exposure-response analyses across O studies, the RPTD for O + G/D is 20 mg/kg at Days 1 and 8 in Cycle 1, followed by 15 mg/kg at Days 1 and 8 thereafter. The randomized, double-blinded phase 2 part of the study is enrolling and will compare OS of pts with STS receiving G/D + O vs G/D + placebo (ANNOUNCE 2). Clinical trial information: NCT02659020.

11543 Poster Session (Board #288), Sat, 8:00 AM-11:30 AM

CDKN2A deletion as a prognostic marker: A clinico-genomic analysis of sarcoma patients. *First Author: Nam Bui, Stanford Cancer Institute, Palo Alto, CA*

Background: Sarcomas are a heterogeneous group of tumors with variable tendencies for aggressive behavior. Molecular markers for prognosis are needed to help risk stratify patients and potentially identify those who may benefit from more intensive therapeutic strategies. **Methods:** We analyzed somatic tumor genomic profiles in 152 soft tissue (STS) and bone sarcoma (BS) patients as part of 1,282 oncologic patients sequenced at Stanford Cancer Institute. We also examined 206 STS patients with whole exome and RNAseq from The Cancer Genome Atlas (TCGA). **Results:** Compared to all other histologies, sarcomas were found to be driven by copy number and fusion alterations with the highest relative percentage of amplifications/deletions/fusions (BS 53%, STS 57%, lung cancer 34%, melanoma 26%) and the lowest average SNV count (BS 1.7, STS 1.8, lung cancer 3.4, melanoma 6.1) The most common genomic alterations were TP53 mutation (34%), CDKN2A deletion (21%), RB1 deletion (11%), TP53 deletion (8%), MDM2 amplification (8%), and PIK3CA mutation (6%). When all genomic alterations were tested for prognostic significance in the cohort of localized STS (n = 96), only CDKN2A alterations (n = 22) correlated significantly with prognosis with a hazard ratio (HR) of 2.83 for overall survival (p = 0.01). There was a trend towards earlier recurrence for CDKN2A patients (p = 0.08) and no difference in chemotherapy time to treatment failure (p = 0.26), suggesting that CDKN2A alterations portend a more aggressive course but not necessarily any additional chemo resistance. These findings were validated in the TCGA dataset where CDKN2A altered patients (n = 24) had significantly worse overall survival with a HR of 2.55 (p = 0.004). Gene Ontology enrichment analysis revealed upregulation of pathways involved in RNA processing, protein translation, and catabolic processes. **Conclusions:** This is the first study to suggest that CDKN2A deletion is a poor prognostic marker in STS. Further research is warranted towards novel agents that affect the CDKN2A pathway and whether aggressive adjuvant therapy can attentuate the poor prognosis. We are undertaking further study towards the correlation of loss of p16 expression as an IHC biomarker for CDKN2A deletion.

11544 Poster Session (Board #289), Sat, 8:00 AM-11:30 AM

Multi-institutional European phase I/II trial of trabectedin plus radiotherapy in metastaticsoft tissue sarcoma (STS) patients. A Collaborative Spanish (GEIS), Italian (ISG) and French (FSG) Sarcoma Groups study. *First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/Universidad de Sevilla, Seville, Spain*

Background: Patients (pts) with advanced STS who require tumor shrinkage beyond first line, have very limited options since the approved drugs exhibit less than 10% of RECIST response. Trabectedin (T) had shown preclinical synergy with radiotherapy (RT). Low-dose RT concurrent with T was conducted in a phase I/II trial as a proof-of-concept of synergy. We present here data from the phase I (pulmonary metastatic cohort) **Methods:** Pts received T along with RT (30 Gy) in 10 fractions (3Gy/fr). Dose Levels for T were: -1 (1.1 mg/m^2), 1 (1.3 mg/m^2) and 2 (1.5 mg/m^2). Dose level 1 was expanded for a better cardiotoxicity assessment. Dose-limiting toxicity (DLT) were defined as grade $\geq$3 events excluding G3/4 neutropenia lasting $<$ 5 days, G3 transaminitis if not led to T delay and G3-4 nausea/vomiting due to inadequate prophylaxis. Primary endpoint was response rate according to RECIST **Results:** From 04/2015 to 06/2017, 18 pts were enrolled. Histologies were: synovial sarcoma in 10 (56%) pts, UPS in 3 (17%), myxoid liposarcoma, dedifferentiated liposarcoma, G3 NOS sarcoma, leiomyosarcoma and MPNST in 1 pts each. Median previous lines 1 (0-3). Twelve pts received T at dose level 1 and 6 pts at level 2. Overall, G 3/4 AEs were: neutropenia (8), ALT elevation (2), GGT elevation (2), anemia (2), febrile neutropenia and pneumonitis (1 each). There were two DLTs: Transient G4 ALT elevation in level 1 and G4 neutropenia ($>$ 5 days) in level 2. Based on central radiological review and 17 evaluable pts, 2 pts achieved CR (12%), 3 PR (18%), 6 SD (35%), 6 PD (35%). On local review, we found 2 CR (12%), 5 PR (29%), 4 SD (24%), 6 PD (35%). On the irradiated lesions, 4 CR (24%), 8 PR (47%), 4 SD (24%) and 1 PD (5%) were found. With a median FU of 18 m, median PFS was 2.83 (2.3-3.3). Thirteen pts (72%) have died, with a median OS of 8.77 m (3.6-13.9) and 12-month OS rate of 48% **Conclusions:** T concurrent with RT was feasible in pts with pulmonary metastatic STS regardless of histologic subtype. T at 1.5 mg/m^2 is the recommended dose for phase II part. We confirmed the synergy of T+RT, with 71% of the irradiated lesions showing long-lasting dimensional responses. Clinical trial information: NCT02275286.

11545 Poster Session (Board #290), Sat, 8:00 AM-11:30 AM

Clinical and pathological analysis of eleven adult patients with inflammatory myofibroblastic tumor. *First Author: Xin Liu, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal malignancy which occurs primarily in children and adolescents. Complete surgical resection is the major treatment, and conventional chemotherapy and radiotherapy are usually invalid. In this study, we retrospectively analyzed the clinical and pathological features of eleven patients with adult IMT. **Methods:** A total of eleven patients with adult IMT were enrolled into this study between February 2013 and November 2017. The clinical, pathological data, treatment and prognosis were analyzed. **Results:** Among the eleven patients with adult IMT, five patients were male (45%), six patients were female (55%), and the median age was 39 (24-74 years). The primary tumor was located in two patients (18%) in the lung and two cases (18%) in the retroperitoneum, and seven cases (64%) in the abdominopelvic region. Four cases were abdominal epithelioid inflammatory myofibroblastic sarcoma. The positive rate of anaplastic lymphoma kinase (ALK) immunohistochemical expression was 82% (9/11), and the positive rate of ALK translocation was 86% (6/7). Seven patients with ALK-positive advanced disease received the treatment of ALK inhibitor crizotinib, the response rate was 86%, and the median progression free survival (PFS) was 20.8 months (95% confidence interval: 7.6 months-34.0 months). Two patients were treated with the more potent ALK inhibitor ceritinib after progression of disease on crizotinib and both of them showed significant and durable partial responses. **Conclusions:** The treatment of crizotinib in adult patients with ALK-positive advanced IMT resulted in a very high response rate and a long-term PFS, and the patients still responded to the next generation of ALK inhibitor after the failure of crizotinib in our study, which suggested that ALK signaling pathway may play an important role in the development of adult IMT. Further studies are warranted to clarify the effects of ALK signaling pathway and the mechanism of ALK inhibitor resistance in adult patients with IMT.

11546 Poster Session (Board #291), Sat, 8:00 AM-11:30 AM

Efficacy and safety of apatinib in advanced soft tissue sarcoma: A multi-center, open-label phase II clinical trial. *First Author: Wenxi Yu, Affiliated Sixth People's Hospital, Shanghai Jiaotong University, Shanghai, China*

Background: Soft tissue sarcomas (STSs) are a heterogeneous group of mesenchymal tumors, accounting for $<$ 1% of all adult malignancies. Although surgery combined with radiation results in high local control rates in localized STSs, high-risk patients (pts) have only 50% 5-year survival. Moreover, chemotherapy has been shown to be lack of consistent overall survival benefit in clinical trials. The vascular endothelial growth factor (VEGF) signaling mediated tumor growth plays an important role in the pathogenesis of several STSs subgroups. This study aimed to explore the efficacy and safety of apatinib, an oral tyrosine kinase inhibitor targeting VEFGR-2, in pts with advanced STS after failure of prior chemotherapy preliminarily. **Methods:** This is a prospective, open-label, single-arm, multi-center phase II study, with planned sample size of 53. All pts with histologically confirmed STSs experienced failure of prior chemotherapy in the last 6 months. Oral apatinib (500 mg) was given to pts daily in cycles of 28 days until disease progression, death or unacceptable toxicity. The primary outcome was 6-month progression-free survival (PFS) rate. **Results:** 35 pts were enrolled as of January 16, 2018. The top 3 subtypes of STSs were alveolar soft tissue sarcoma (20%), leiomyosarcoma (17%) and liposarcoma (12%). The 6-month PFS rate was not reached. Of 35 pts, 23 were available for response evaluation: 6 achieved partial response, 15 had stable disease, and 2 had progressive disease, resulting in an overall response rate of 26.1% and a disease control rate of 91.3%, at primary response. 33 pts were eligible for safety evaluation. The incidence of adverse events (AEs) was 93.9%. The most common AEs were hypertension (63.6%), proteinuria (60.6%), and hand-foot syndrome (54.6%). The incidence of Grade 3-4 AEs was 42.2%, and hypertension (30.0%) was the most common Grade 3-4 AEs. **Conclusions:** Current results demonstrated encouraging signs of anti-tumor activity, and well-tolerated toxicity of apatinib in previously treated advanced STSs. Clinical trial information: NCT03064243.

11547 Poster Session (Board #292), Sat, 8:00 AM-11:30 AM

A phase II trial of axitinib plus pembrolizumab for patients with advanced alveolar soft part sarcoma (ASPS) and other soft tissue sarcomas (STS). *First Author: Breelyn A. Wilky, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Inhibition of programmed-death 1 (PD1) by pembrolizumab (P) produced overall response rates (ORR) of 19% in advanced STS [SARC028]. Vascular endothelial growth factor (VEGF) suppresses the immune microenvironment and may contribute to checkpoint inhibitor resistance. Axitinib (Ax) is a pan-VEGFR inhibitor that prolongs progression-free survival (PFS) in advanced STS [Axi-STS], with striking antitumor activity in combination with P in renal cell carcinoma. We report toxicity, efficacy, and correlative endpoints of combination Ax/P for patients (pts) with advanced STS. **Methods:** NCT02301039 is an open-label Phase II trial of Ax/P in 30 pts with advanced or metastatic STS, requiring RECIST 1.1 progressing disease, adequate end-organ function and performance status. Pts received Ax 5 mg PO twice daily with concurrent P 200mg IV q21 days. Primary endpoint: 3-month PFS rate (PFS_{3mo}); secondary endpoints: toxicity, ORR and clinical benefit rate (CBR) by RECIST 1.1, and overall survival. Tumor biopsies and peripheral blood samples were obtained for correlative studies of TIL and PBMC at baseline, 3 months on treatment, and at progression. **Results:** 33 pts received at least one dose of study drugs, with 30 pts evaluable for primary endpoint. Enrolled subtypes: ASPS (36%), UPS (15%), LMS (18%), other (30%). PFS_{3mo} was 70.3% [95% CI 50.7-83.3], with median PFS of 5.4 months [95% CI 3.02-11.6]. Best ORR was 21.9% [95% CI 5.9-33.5]. PFS_{3mo} in ASPS pts was 90.9% [95% CI 50.8-98.7], with best ORR of 45.5% [95% CI 18.1-75.4] and CBR of 72.7% [95% CI 39.3-92.7]. Ax/P was well-tolerated, with similar immune-related toxicity rates to prior studies. Correlative markers were analyzed by a penalized logistic regression model with bootstrapping to predict PFS_{3mo}. Baseline high plasma angiogenic activity, circulating neutrophil:lymphocyte ratio $<$ 4.1, low naïve fraction $CD4^+$ TIL, and low $PD1^+CD8^+$ PBMC were associated with lack of progression (AUC 0.878 [95% CI 0.743-1, p = 0.0002]). **Conclusions:** Combination Ax/P is well-tolerated with promising activity in ASPS pts. Identified immune correlates associated with PFS should be validated in prospective immunotherapy trials. Clinical trial information: NCT02301039.

11548 Poster Session (Board #293), Sat, 8:00 AM-11:30 AM

Characteristics and clinical outcomes of French patients diagnosed with advanced soft tissue sarcoma (aSTS) in real-life setting: Data from the European sarcoma biological and clinical data banking (ESBCB). *First Author: Jean-Yves Blay, Centre Léon Bérard, Lyon, France*

Background: This study describes clinical characteristics of a large cohort of aSTS patients (pts) and effectiveness of chemotherapy (CT) based on real world data. **Methods:** Multicenter retrospective cohort analysis using data from the French centers of the ESBCB (Conticabase.org) with an extraction in 2017. This study included adult pts with a diagnosis of sarcoma (WHO2013) between 2010 and 2013 in soft tissue or viscera, excluding GIST and Kaposi's sarcoma. **Results:** 2747 pts were included with a diagnosis of STS. 34.6 % of them had an aSTS and were described in this study. Among them were 608 with secondary (metachronous) metastasis, 299 metastatic at diagnosis (synchronous) and 61 pts with locally aSTS, not amendable to surgery. The mean age at diagnosis was 59.3 years (+/- SD 16.9), 52.3% of pts were female and 21.2% had cancer of viscera. Most frequent sarcoma subtypes were undifferentiated sarcoma (24.9 %), leiomyosarcoma (23.8%) and miscellaneous sarcoma (14.7%). Sarcoma were grade 1 for 4.4%, 2 for 27.3% and 3 for 55.0 %, missing for 13.3%. Surgery for primary tumor was more frequent in the metachronous metastasis group than in the synchronous metastatic one (89.6% vs 41.5% respectively). At least one line of CT was administered to 56.9% and 61.2% pts with synchronous and metachronous metastasis, respectively. Anthracyclin-containing CT regimen were delivered in 63.6% of pts treated by first-line chemotherapy. Responses rates to first line chemotherapy were 30.6 % for pts with synchronous metastasis and 19.1 % for those with metachronous metastasis. For the entire aSTS population, the median overall survival was 1.45 years (95% CI : [1.23; 1.63]). The rates of overall survival (OS) at 3 years were 35.7% [22.2%; 49.3%] for pts with locally advanced disease, 29.4% [23.8%; 35.2%] for the pts with metachronous metastasis and 21.1 % [15.2%; 27.7%] for pts with synchronous metastasis. **Conclusions:** In this large nationwide database, therapeutic strategies and OS differed across groups of cancer diagnosis dates. These data are useful to provide real world treatment patterns and outcomes in a hard to study disease.

11549 Poster Session (Board #294), Sat, 8:00 AM-11:30 AM

Genomic alterations in the homologous recombination pathway in soft-tissue sarcomas. *First Author: Nathan David Seligson, Division of Pharmacy Practice and Science, College of Pharmacy, The Ohio State University, Columbus, OH*

Background: Soft-tissue sarcomas (STS) describe a heterogeneous group of tumors with limited treatment options available to patients. Targeted therapy exists for tumors with alterations in *BRCA1/2* as well as other homologous recombination (HR) pathway genes; however, their prevalence has yet to be fully described in STS. We hypothesized that tumors with these alterations may represent a targetable cohort with the advent of poly (ADP-ribose) polymerase (PARP) inhibitors. Here we assess the frequency of *BRCA1/2* and HR alterations in STS. **Methods:** DNA sequencing data was aggregated from The Cancer Genome Atlas (n = 255), Genomics Evidence Neoplasia Information Exchange (n = 583), and The Ohio State Sarcoma Registry (n = 398). Deleterious genomic alterations were defined as in ClinGen. Clinical data from three patients with somatic *BRCA2* loss who were treated with PARP inhibitors were collected for analysis. **Results:** *BRCA1* and HR somatic alterations were more common in leiomyosarcoma (LMS) subtype compared to other STS (LMS 17%, liposarcoma 9.8%, other 8.9%, p = 0.001). A disproportionate number of *BRCA2* losses were detected in uterine LMS (uLMS) with 85.7% of tumors harboring *BRCA2* loss identified in this STS subtype ($p < 0.001$). When considering uLMS, 9.8% of tumors had a loss of *BRCA2* (0.9% in non-uterine LMS, 0.5% in all other STS). Tumors with *BRCA2* loss often exhibited a poor differentiated histology (57.1% of *BRCA2* loss *vs* 38.8% BRCA2 intact; p = 0.59) and tended to have a higher mitotic count (10.7 count/HPF *BRCA2* loss *vs* 3.3 count/HPF *BRCA2* intact; p = 0.10). Retrospective evaluation of three uLMS patients with somatic *BRCA2* loss treated with PARP inhibitors demonstrated a median progression-free survival of nine months highlighting the potential targetability of *BRCA2* loss in uLMS. **Conclusions:** Here we assess the frequency of *BRCA1/2* and HR alterations and their clinical phenotype in STS. We identify somatic *BRCA2* loss in a subset of patients with uLMS and describe three patients with uLMS harboring *BRCA2* loss who were treated with PARP inhibitors. Our data suggests that patients with uLMS should be screened for *BRCA2* alterations. Prospective trials are needed to confirm the efficacy of PARP inhibition in this cohort of patients.

11550 Poster Session (Board #295), Sat, 8:00 AM-11:30 AM

A phase II study of pazopanib with oral topotecan in patients with metastatic and non-resectable soft tissue and bone sarcomas. *First Author: Mark Agulnik, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Topotecan and pazopanib (PAZ) individually have clinical benefit in patients (pts) with sarcomas. PAZ is a multi-tyrosine kinase inhibitor and topotecan affects endothelial cells, and inhibits HIF-1, an upstream regulator of VEGF expression. The utilization of PAZ with topotecan is anticipated to produce anti-tumor synergism in pts with sarcomas. **Methods:** A phase II study of PAZ/topotecan in pts with metastatic and non-resectable bone and soft tissue sarcomas (STS) was conducted by the Midwest Sarcoma Trials Partnership. Age > 18, ECOG ≤ 1, adequate organ function, measurable disease and 1 prior therapy were required. Pts were treated with PAZ 800mg oral daily, Topotecan 8mg orally day 1, 8, 15 on a 28-day cycle until disease progression or unacceptable toxicity. Pts enrolled in 3 cohorts: 1. STS non-liposarcoma 2. osteosarcoma 3. liposarcoma. Primary endpoint: progression-free rate (PFR) at 12 weeks in cohort 1. Secondary endpoints: overall response rate (ORR), clinical benefit rate (CBR), OS, median progression free survival (PFS), PFR at 12 weeks in cohort 2 and 3, and safety and tolerability. Lab correlates evaluated PFR and OS to levels of VEGFR2 and PDGF. Simon 2-stage design was used for cohort 1. **Results:** A total of 139 pts were enrolled at 6 sites, with 121 evaluable for response. Data per cohorts 1,2, and 3: # of pts- 103, 17 and 19; mean age- 56, 41, 57; % female- 63, 53, 32%; 1-2 prior therapies- 75, 65, 84%. PFR at 12 weeks is 57.5%, 62.5%, 31.3% with a median PFS of 4.4, 4.5, 1.4 months and OS of 9.8, 11.1, 12.3 months. ORR is 8,6,0 % and CBR is 74, 88, 38%. Grade 3-4 adverse events (%): neutropenia (42), thrombocytopenia (29), hypertension (16) and anemia (12). Pts in cohort 1 who progressed within 6 weeks received 61% of prescribed PAZ dose vs. 67% for those with did not progress. Histologies in cohort 1- LMS (49%), UPS (15%), synovial (10%). Correlative data will be presented. **Conclusions:** The combination of PAZ/topotecan produced identical results to historical data for PAZ alone in pts with STS, except with a worse toxicity profile. For pts with osteosarcoma, the combination proved extremely promising and cohort 2 will be expanded. The combination was ineffective in liposarcoma. Clinical trial information: NCT02357810.

11551 Poster Session (Board #296), Sat, 8:00 AM-11:30 AM

Targeted tumor profiling and actionable somatic variants in sarcoma. *First Author: Eytan Ben Ami, Dana-Farber Cancer Institute, Boston, MA*

Background: The impact of next generation sequencing data on treatment decision and clinical outcome in sarcoma remains under investigation. **Methods:** We queried the Dana Farber Cancer Institute database to identify soft-tissue and bone-sarcoma patients (pts) who underwent targeted sequencing under a research protocol. We searched for mutations and somatic copy number alterations (SCNA) and evaluated clinical outcomes in cases bearing actionable genetic abnormalities (eligible for NCI-MATCH/ASCO-TAPUR studies). **Results:** 613 pts with 38 sarcoma histologies were evaluated. Leiomyosarcoma (LMS, 23.8%), liposarcoma (LPS, 13.2%), undifferentiated pleomorphic sarcoma (9.4%) and solitary fibrous tumor (4.7%) were the common histologies. Frequent mutations were observed in *TP53* (30.1%), *ATRX* (12.1%) *KMT2D* (11.1%), *NF1* (8%) and *ATM* (7.3%) genes. Common SCNA included homozygous deletions in *RB1* (10%) and *CDKN2A* (8.1%), and high copy number gains in *MDM2* (13.6%), *CDK4* (11.5%), *GLI1* and *MYC* (3%). 123 pts (20%) had 145 actionable somatic variants (59 mutations, 86 SCNA). Actionable mutations, observed in 52 pts, frequently involved the *PI3K/Akt/mTOR* pathway (*PI3K3CA*, *TSC1/2* and *AKT1* genes; 25% of actionable mutations), *BRCA1/2* (15.2%), and *IDH1/2* (17%, exclusively in chondrosarcoma) genes. Actionable SCNA, observed in 82 pts, comprised mostly of homozygous deletions in *CDKN2A* (51% of actionable SCNA) and *PTEN* (15.1%), and high copy number gain, not associated with LPS, in *CDK4* (12.8%). Of 72 metastatic pts with actionable alterations and clinical data, 12.5% (9 pts) received matched therapies. Tumor responses were observed in 6 pts, including durable responses (6-28 months) in dedifferentiated chondrosarcoma (*IDH2* mutation), inflammatory myofibroblastic tumor (ALK rearrangement), LMS (*TSC2* mutation), spindle cell sarcoma (*NTRK1* rearrangement), and chordoma (*CDKN2A* deletion). **Conclusions:** As many as 20% of sarcoma pts may harbor actionable genetic alterations. We observed durable tumor responses with matched therapies in several sarcoma histologies and further research is needed to understand the proportion of patients who may benefit from this approach. Mutations and SCNA incidence by histology will be presented at the meeting.

11552 Poster Session (Board #297), Sat, 8:00 AM-11:30 AM

Outcome of 91 clear cell sarcoma tumor patients: A retrospective study from the French Sarcoma Group (GSF-GETO). *First Author: Nelly Firmin, Institut du Cancer de Montpellier, Montpellier, France*

Background: Clear-Cell Sarcoma (CCS) is a rare soft tissue sarcoma poorly documented, with poor prognosis. Primary objective was to study the characteristics and outcomes of CCS patients (pts). **Methods:** Retrospective study from the nation-wide French sarcoma network (NetSarc) from 1991 to 2017. Inclusion criterion was CCS central pathological review. Endpoints were local recurrence-free survival (LRFS), metastatic-free survival (MFS), disease-free survival (DFS) and overall survival (OS). **Results:** 91 pts from 16 centers were included (molecular biology confirmed in 53% pts). Pts were aged 41 years (18-73), 57.1% men. The median tumor size was 4 cm (3-17). Patients were divided in 3 groups: localized (L) (61.5%), locally-advanced (LA) (15.4%), metastatic (M) (23.1%). Presurgical biopsy was performed in 50.7% of pts. All L and LA CCS pts underwent surgery, which was conservative in 70.6% pts. R0 resection was achieved in 71.9% of pts with 42.4% surgical revision to obtain clear margins. After a median follow-up of 6.5 years (95% CI: 4.5-9), 16 (22.9%), 37 (52.9%), 45 (64.3%), 29 (41.4%) events for LRFS, MFS, DFS and OS, were reported. Prognostic factors of the univariate analysis in L and LA pts are presented in Table 1. (Neo)Adjuvant radiotherapy and chemotherapy were performed in 54.4% and 30.9% pts, respectively, with no impact on OS or DFS. The 5-year OS rate for the 91 pts was 53.8% (95% CI: 41.70-64.22). For M pts, median OS was 12.7 months (95% CI: 10.4-21.5). Poor prognostic factors found in univariate analysis were male gender, delay between diagnosis and metastatic stage < 24 months, metastases other than pulmonary, and no surgery for metastatic disease. **Conclusions:** It's the largest study on CCS since the 1990s, with a large proportion of molecular biology confirmation. Stage, tumor necrosis, tumor size and localization are poor prognosis factors.

Endpoint	Variable		Hazard Ratio (95% CI)	p
OS	Stage	Localized	1	**0.0128**
		Locally Advanced	2.76 [1.2 ; 6.37]	
	Tumor Size (mm)	< 50	1	**0.0171**
		≥50	2.82 [1.16 ; 6.85]	
DFS	Stage	L	1	**0.0253**
		LA	2.21 [1.08 ; 4.53]	
	Tumor necrosis	Yes	1	**0.0473**
		No	2.30 [1.00 ; 5.36]	
	Tumor Size (mm)	< 50	1	**0.0304**
		≥50	2.18 [1.06 ; 4.49]	
	Localization	Members	1	**0.0335**
		Other	2.08 [1.04 ; 4.13]	

11553 Poster Session (Board #298), Sat, 8:00 AM-11:30 AM

Primary pulmonary sarcomas (PSRC): A comprehensive genomic profiling (CGP) study. *First Author: Sophie Beaucaire-Danel, Institut Curie, Paris, France*

Background: In an exploratory study to find biomarkers for both targeted and immunotherapy treatments, we performed CGP on a series of PSRC to search for novel therapy options for patients with clinically advanced disease. **Methods:** Hybrid capture-based CGP was performed on 21 cases of PSRC, with 17 PSRC also undergoing RNA sequencing to enable expanded gene fusion detection. Tumor mutational burden (TMB) was determined on 1.1 Mbp of sequenced DNA and microsatellite instability (MSI) was determined by principal components analysis of optimal homopolymer loci. **Results:** There were 10 sarcoma NOS, 5 pulmonary artery intimal sarcomas, 4 pleomorphic/MFH sarcomas, 1 primary inflammatory myofibroblastic tumor (IMT) and 1 primary solitary fibrous tumor (SFT) cases. There was 1 stage I, 1 stage II, 9 stage III and 10 Stage IV tumors. The patients had a median age of 58 years (range 33 to 81 years). There were 7 female and 14 male patients. The mean number of genomic alterations (GA) per sarcoma was 5.8. Notable alterations not considered presently actionable included *TP53* (47%), *CDKN2A* (36%), *CDKN2B* (25%) and *RB1* (13%). Clinically relevant GA (CRGA) affected *PDGFRA*, *RICTOR*, *CDK4* and *KIT,* all at 11%. When considering additional CRGA in *EGFR*, *TSC2, ALK* and *BRAF* (each at 5%), a total of 10 (48%) PSRC featured ≥1 CRGA. The case with an *ALK* fusion represents an IMT initially localized to the lung and diagnosed as a primary lesion. The mean TMB in the PSRC was 8.3 mutations per Mb with 14% having TMB of > 10 mut/Mb and 10% having TMB > 20 mut/Mb. MSI status was available for 9 (43%) of the PSRC cases, and the remainder were all microsatellite stable. Assessment of therapeutic intervention and responses to targeted and immunotherapies is ongoing. **Conclusions:** PSRC is characterized by a relative high frequency of GA, including driver mutations or fusions in tyrosine kinases and cell cycle regulatory genes. In addition, this study identified a significant proportion of PSRC that feature an intermediate or high TMB, indicating the potential for use of immunotherapies for these patients. Further study of CGP to assist in management of patients suffering from this rare form of pulmonary malignancy appears warranted.

11554 Poster Session (Board #299), Sat, 8:00 AM-11:30 AM

Systemic therapy regimen outcomes in metastatic phyllodes tumors of the breast. *First Author: Amanda Marie Parkes, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Phyllodes tumors of the breast (PT) account for < 1% of all primary breast neoplasms. Metastatic PT (MPT) are less common, limiting development of standardized treatment approaches. We sought to characterize the largest group of MPT thus far reported, evaluating outcomes with systemic therapy regimens. **Methods:** Adult MPT patients followed at MD Anderson Cancer Center from 1954-2015 were selected for retrospective chart review. Systemic therapy was sorted into five categories: Adriamycin/Ifosfamide (AI), other anthracycline regimens (A), other ifosfamide regimens (I), gemcitabine regimens (G), and other (O). Given one patient may have received > 1 regimen, we assumed that the effects of each regimen were independent. Descriptive statistics, response to treatment, and survival analyses were performed. **Results:** We identified 50 MPT patients. Most patients had metachronous metastases (47/50, 94%) and lung was the most common site of metastasis at time of MPT diagnosis (35/50 patients, 70%). Thirty-one of 50 MPT patients received 61 systemic regimens (range: 1-4 regimens per patient, median: 1). Overall response rate (ORR) was highest in AI (10/19 patients, 53%), followed by A (5/13, 38%), I (2/8, 25%), G (3/13, 23%), and O (1/8, 13%). Median overall survival (OS) was 10.7 months (95% CI: 8.67, 16.5). Sixty regimens had complete information available for progression free survival (PFS) analyses. Table 1 details median PFS by regimen. After adjusting for tumor size, comparing other therapies to AI, risk of progression/mortality was significantly higher with G, A, and O (Table 1). There was no statistically significant difference between AI and I. **Conclusions:** MPT patients are a unique population with limited characterization. Our study demonstrates superiority of AI, with I showing similar risk of progression/mortality, but lower ORR.

Median PFS and risk of progression/mortality using multivariate cox regression.

Systemic regimen	Cases	Total	Median PFS (95% CI) (months)	HR (95% CI)	P-value
AI	16	19	9.10 (5.03, 14.2)	Ref	
I	8	8	5.10 (0.67, 12.1)	2.29 (0.88, 5.96)	0.090
A	12	12	3.65 (1.17, 7.90)	3.19 (1.38, 7.40)	0.007
G	12	13	2.80 (1.83, 4.60)	3.09 (1.31, 7.25)	0.010
O	6	8	1.67 (1.13, 7.77)	7.74 (2.42, 24.8)	< .001

11555 Poster Session (Board #300), Sat, 8:00 AM-11:30 AM

Early metabolic response as predictor for treatment outcome of pazopanib in patients with metastatic soft tissue sarcomas (the PREDICT study). *First Author: Winette T.A. Van Der Graaf, Institute of Cancer Research and The Royal Marsden NHS Trust Foundation, London, United Kingdom*

Background: Pazopanib is the first approved targeted treatment for non-GIST soft tissue sarcoma (STS) pts. In the PALETTE study 23% of pts had progressive disease as best response. This study correlates early metabolic response evaluated by FDG-PET/CT to treatment outcome assessed by RECIST and investigates the relation between metabolic response and pazopanib pharmacokinetics. **Methods:** Twenty STS pts recruited from sarcoma clinics in Radboud University Medical Centre Nijmegen and the Netherlands Cancer Institute Amsterdam, underwent FDG-PET scans at baseline, and 2 and 8 weeks after start of pazopanib. Blood samples were collected for pharmacokinetic (PK) assessment (C_{trough} levels and $AUC_{0\text{-}24h}$). We investigated the relation between early metabolic response after 2 weeks of therapy and pazopanib exposure at 2 weeks, and the relation between early metabolic response and treatment response assessed by RECIST1.1 at 8 weeks. The study was registered at ClinicalTrials.gov (NCT01995981) and approved by the regional medical ethics committee. All patients gave written informed consent. **Results:** After 8 weeks of therapy, 14 out of 20 pts had discontinued pazopanib due to radiological tumor progression ('non-responders' n = 12) or toxicity (n = 2). Quantitative FDG-PET scoring according to PERCIST guidelines at 2 weeks identified 25% (3 of 12) of all non-responders versus 42% (5 of 12) with visual response analysis by an independent evaluation from a nuclear medicine physician. No patient was incorrectly labeled as non-responder. PK results were not related to metabolic response. **Conclusions:** In this heterogeneous STS patients' cohort we did not see a relation between pharmacokinetics and pharmacodynamics of pazopanib, but we did show that FDG-PET/CT identified a substantial part of pazopanib non-responders. The results of this study warrant a larger study, to enable future early and cost-effective decision making in STS pts treated with pazopanib. Funding: This academic investigator-initiated study was supported by a grant from GlaxoSmithKline/ Novartis to the institute. Clinical trial information: NCT01995981.

11556 Poster Session (Board #301), Sat, 8:00 AM-11:30 AM

FAP-related desmoid tumours treated with low dose chemotherapy: Results from a multicentre retrospective analysis. *First Author: Bruno Vincenzi, Department of Medical Oncology, University Campus Bio-Medico of Rome, Rome, Italy*

Background: Desmoid tumours (DTs) are monoclonal neoplasms with fibroblastic-myofibroblastic differentiation and they represent the most common extra-intestinal manifestation of familial adenomatosis polyposis (FAP). DTs are often multifocal and, even in the absence of a metastatic potential, they represent the first cause of death in FAP patients after colectomy. Data on the activity of chemotherapy in FAP-associated DTs are limited. We specifically examined the activity of chemotherapy with low-dose methotrexate (MTX) + vinca alkaloids. **Methods:** We retrospectively reviewed data from all patients treated with MTX + vinca alkaloids for FAP-associated DTs in 5 reference centres and cases included into the National rare cancer network were also reviewed and included if sufficiently informative for the study purposes. Radiological responses were assessed using both RECIST and CHOI criteria. **Results:** We identified 28 patients treated with MTX + vinca alkaloids. All patients had progressive disease before chemotherapy; 17 patients and 9 patients had previously received respectively surgery and/or systemic treatments (i.e. hormone therapy, NSAIDs). Chemotherapy was administered for a median duration of 11 months. According to RECIST criteria (CHOI evaluation is ongoing) complete response, partial response, stable disease, and progressive disease were observed in 1, 17, 10, and 0 patients, respectively. The median progression-free survival (PFS) was 78 months; it was 124 months in responding patients. After chemotherapy withdrawal, MTX + vinca alkaloids rechallenge was offered to 11 patients with progressive disease. In these patients, we obtained a control rate of 100%, resulting in a median second PFS of 64 months. **Conclusions:** To the best of our knowledge, this is the largest series on the activity of low dose chemotherapy in FAP-related DTs. Our data suggest a tremendous activity of low dose chemotherapy in this very rare subset of patients.

11557 Poster Session (Board #302), Sat, 8:00 AM-11:30 AM

A multicenter phase II study of pazopanib in patients with unresectable or recurrent dermatofibrosarcoma protuberans (DFSP). *First Author: Julie Delyon, AP-HP Hôpital Saint-Louis, Paris, France*

Background: DFSP is a tumor accounting for 6% of soft-tissue sarcoma, with a high risk of local infiltrative dissemination. Wide local excision is the standard treatment. The identification of the *COL1A1-PDGFB* translocation activating the PDGF pathway in > 90% of DFSP had led to the use of the kinase inhibitor imatinib in locally advanced or metastatic DFSP, with a response rate of 36-57%. Pazopanib (pazo) is a multitargeted tyrosine kinase inhibitor (VEGF, PDGF, KIT) approved in severe pretreated soft-tissue sarcomas. We sought to evaluate the efficacy and safety of pazo in the treatment of DFSP. **Methods:** We conducted an open-label phase II trial in patients with histologically proven unresectable primary, recurrent or metastatic DFSP. Patients received pazo 800 mg qd. The primary study endpoint was the objective response rate defined as the reduction of the biggest diameter of the tumor ≥ 30%(RECIST) at 6 months(mo) or at surgery if performed before 6 mo. Pharmacodynamics analyses were performed on tumor biopsies and blood samples at baseline, month 1-3-6 and progression (*PDGF*, *PDGFR*, *VEGF*, *VEGFR* mRNA and downstream signaling pathway components). **Results:** 23 patients were included from Jul 2010 to Feb 2014 (9 centers, France). 18 had primary, 4 recurrent and 1 metastatic DFSP. The median follow up was 6.2 mo (interquartile range 5.6-7.8). 5 patients (22%, 95% CI: 7-22%) among 23 evaluable had response according to the primary endpoint. The best objective response rate was 30% (7/23, 95%CI 13-53%). 18 patients had surgery, including 12 with free margins. One patient with metastatic DFSP died. Median treatment duration was 3.8 mo (2.1-6.0); 9/23 patients discontinued for AEs; 11(48%) patients had dose reduction. Grade 3-4 AEs were transaminitis(5), cholestasis(3), hemolytic and uremic syndrome(1), nephrotic syndrome(1). No drug-related death occurred. Using FISH the *COL1A1-PDGFB* translocation was identified in 18 patients(5 not evaluable). High plasma level of soluble VEGFR2 was associated with tumor response (p = 0.01). **Conclusions:** Our results suggest that pazo is a therapeutic option in DFSP. As compared to previous studies with imatinib, we did not observe an improved response rate. Clinical trial information: NCT01059656.

11558 Poster Session (Board #303), Sat, 8:00 AM-11:30 AM

Short, full-dose neoadjuvant chemotherapy in localized high-risk adult soft tissue sarcomas (STS): An exploratory subgroup analysis on responding patients in a randomized controlled trial comparing 3 neoadjuvant versus 3 neoadjuvant + 2 adjuvant cycles of full dose anthracycline and ifosfamide chemotherapy at a 10yr median FU. *First Author: Silvia Stacchiotti, Department of Cancer Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: We already reported (*Cancer 2012;118:5857*) the correlation of Choi criteria (Choi) and RECIST with outcome of pts affected by high-risk STS entering a multicentric Italian/Spanish Phase 3 trial comparing 3 vs 5 cycles of (neo)adjuvant CT with full-dose epirubicin + ifosfamide (*JCO 2012; 30:850; Ann Oncol 2016; 27:2283*). We investigated whether the non inferiority of 3 vs 5 cycles held also in the subgroup of patients responsive to preoperative treatment. **Methods:** Patients were randomized to receive 3 cycles of preoperative CT with epirubicin 120 mg/m2 and ifosfamide 9 g/m2 (Arm A) or to receive the same 3 cycles of preoperative CT followed by 2 further cycles of post-operative CT (Arm B). Radiotherapy could be delivered in the preoperative or in the post-operative setting. Non-inferiority of the primary end-point, overall survival (OS), was assessed by the confidence interval of the hazard ratio (HR; Arm A/Arm B) derived from Cox model. Response was assessed by RECIST and Choi. **Results:** Between January 2002 and April 2007, 160 pts were assigned to Arm A and 161 to Arm B, 158 patients received preoperative RT (Arm A = 77; Arm B = 81). At a median FU of 117 months (IQR 103-135 months), 123 deaths were recorded, 58 in Arm A and 65 in Arm B. Ten-year OS was 61% for the entire group of patients, 64% in Arm A and 59% in Arm B (HR 0.92, 90% confidence interval [CI] :0.68–1.23). Of 243 patients evaluable for RECIST, 208 achieved a partial response (PR) or stable disease (SD), 93 in Arm A and 115 in Arm B. Ten year OS was 62% in Arm A and 59% in Arm B (HR 1.02; 90% CI 0.70-1.48). Of 166 pts evaluable for Choi, 135 achieved a PR, 60 in Arm A and 75 in Arm B. Ten-year OS was 60% in Arm A and 66% in Arm B (HR 1.29; 90% CI 0.80-2.07). **Conclusions:** In this (neo)adjuvant trial, the non inferiority of 3 vs 5 cycles of full dose anthracycline and ifosfamide /neo) adjuvant chemotherapy was confirmed also in the subgroup of patients with evidence of radiologic response to the preoperative treatment Clinical trial information: 2004-003979-36.

11559 Poster Session (Board #304), Sat, 8:00 AM-11:30 AM

Gemcitabine re-challenge in metastatic soft tissue sarcoma: A therapeutic option for selected patients. *First Author: Ana Sebio, Hospital de la Santa Creu i Sant Pau, Medical Oncology Department, Barcelona, Spain*

Background: Treatment options for patients with metastatic sarcoma are limited. Gemcitabine-based schedules have shown activity and in selected patients, re-challenge with a previously successful gemcitabine-based regimen is common practice. There are no published data to support this practice. This study evaluates the efficacy and safety of gemcitabine re-challenge in advanced soft tissue sarcoma. **Methods:** A retrospective search of a prospectively maintained database was performed to identify patients re-challenged with gemcitabine-based chemotherapy (GBC) from 2003 to 2015. Baseline clinical characteristics, progression-free and overall survival were obtained from clinical records and response evaluation was performed by RECIST 1.1 criteria. **Results:** 29 patients were identified. The most frequent histology was leiomyosarcoma (n = 25, 86%). In the first GBC treatment, 86% (n = 25) of patients received gemcitabine-docetaxel and the others gemcitabine monotherapy. 38% (n = 11) of the patients received the first GBC as 1st treatment line, 45% (n = 13) as 2nd line and 17% (n = 5) as 3rd or further. The re-challenge GBC consisted of gemcitabine-docetaxel in 66% (n = 19) of the patients, gemcitabine monotherapy in 31% (n = 9) and gemcitabine-DTIC in 3% (n = 1) of the cases. Re-challenge GBC was administered as 2nd treatment line in 21% (n = 6) of the patients, as 3rd line in 34% (n = 10) and 45% (n = 13) of the patients received it in 4th or further line. In the evaluable patients (n = 28) the first GBC yielded a 55% response rate and after re-challenge GBC 26% (n = 6) of the evaluable patients (n = 23) responded. Progression-free survival was 11.1 months (95% CI, 7.2-11.9) for the first GBC and 5.3 months (95% CI, 2.0-7.5) in the re-challenge setting. Overall survival following gemcitabine re-challenge was 12.2 months (95% CI, 7.0-18.2). Regarding toxicity, 46 % of the patients (n = 12 of 26 evaluable) treated with re-challenge GBC presented grade 3-4 adverse events (CTCAE 4.03) and 31% of the patients needed a dose reduction. **Conclusions:** In selected sarcoma patients, re-challenge with a gemcitabine-based regimen can be considered as a treatment option in advanced disease at the expense of increased toxicity.

11560 Poster Session (Board #305), Sat, 8:00 AM-11:30 AM

First prospective observational study in diffuse-type tenosynovial giant cell tumors. *First Author: Monique Mastboom, Leiden University Medical Center, Leiden, Netherlands*

Background: Tenosynovial giant cell tumor (TGCT) is a rare, benign, but potentially locally aggressive and often recurrent disease. Its impact on patient quality of life and ability to work is not well defined. This is the first prospective registry detailing economic impact, management and burden of TGCT. **Methods:** This international, multicenter, prospective, non-interventional observational registry enrolled patients with histologically proven diffuse-TGCT. Patient data was collected at baseline (time of patient enrolment) and at follow up data collection points, performed at 12 and 24 months. **Results:** This snapshot analysis included 88 TGCT patients with complete baseline data from six active international sites between November 2016 and September 2017: 58% female; mean age at enrolment 45 years (standard deviation [SD] 14 years). Most (73%) patients had tumors located in the knee. Fifty six (64%) patients with a primary diagnosis of TGCT were included, 32 (36%) with recurrent disease. Mean time from first symptoms until diagnosis was 42 months (median 21 months) and the most commonly reported symptom was pain (78%). A total of 63 (72%) patients had surgery, primarily open synovectomy (54%). Thirty eight (43%) patients received systemic therapy, pexidartinib [55%] and imatinib [42%]. Over 12 months, 44 (50%) patients reported that TGCT compromised their ability to work with a mean of 51 days of work (median 21 days) missed due to TGCT. Eight (9%) patients were fully unemployed due to TGCT, 2 (2%) were partially unemployed and 1 (1%) patient had retired prematurely. On average, a clinically significant impairment of physical function at baseline was observed as compared with the reference population based on PROMIS Physical Function score (42 [SD 7] vs 50 [SD 10]). Mean EQ-5D-5L at baseline was 0.75 (SD 0.19). **Conclusions:** This disease-registry in six sites, with a two-year recruitment period and two-year follow-up per patient, showed that TGCT has a major impact on daily living in a relatively young and working population. Clinical trial information: NCT02948088.

11561 Poster Session (Board #306), Sat, 8:00 AM-11:30 AM

Characterization of tumor microenvironment in extraskeletal myxoid chondrosarcoma (EMC). *First Author: Valentina Indio, Interdepartmental Centre of Cancer Research "Giorgio Prodi", University of Bologna, Bologna, Italy*

Background: EMC is a rare sarcoma mostly originating from soft tissues. EMC carries a specific translocation, involving NR4A3, which is fused more often with EWSR1 and less frequently with other partners, including TAF15. We investigated EMC tumor microenvironment to define the differential immune-profile of NR4A3-EWSR1 and NR4A3-TAF15 EMC subtypes and to evaluate if EMC could be good candidate to immunotherapy. **Methods:** RNA-seq was performed on 12 naïve tumors with Illumina technology. The gene expression was quantified and, after normalization, the tool CIBERSORT was adopted to evaluate the presence of 22 hematopoietic population within the tumor-infiltrating environment. Absolute and relative abundance were used to estimate the correlation between infiltrating cell types. Moreover, the EMC immune-profile was comparatively evaluated between two subgroups of EMC based on the rearrangement type EWSR1-NR4A3 (7/12) and TAF15-NR4A3 (5/12). Immunohistochemistry, for CD3, CD20, CD14, CD163, CD56, HLA ABC, PDL1(22C3), and CD1a was performed and scored on available FFPE specimens (3/12). **Results:** The analysis showed in all cases the existence of gene signatures related to the presence of immune-infiltrate. Globally, M2 macrophages were the most enriched cell type, followed by CD4+ memory resting, and M0 macrophages; B-cell and mast cell were also moderately observed. The correlation analysis showed that the abundance of M2 macrophages negatively correlated with the presence of CD3+ T-cells. Comparative analysis showed that the EMC with TAF15 fusion had a significantly lower level of CD4+ memory resting cells ($p = 0.042$), lower NK cells and a trend to a higher enrichment of mast cells compared to EWSR1+ EMC. IHC analysis confirmed the presence of an immune-infiltrate, with both a macrophagic and a lymphocytic component. **Conclusions:** Our results showed that EMC is marked by the presence of a macrophagic and, to a less extent, a CD4+ T cells immuno-infiltrate. Interestingly, the immune-profile differed between the 2 molecular subtypes, highlighting that the high degree of diversity that marks sarcomas is reflected also in their immune-profile. EMC looks to be a potential interesting candidate for immune-therapy.

11562 Poster Session (Board #307), Sat, 8:00 AM-11:30 AM

Phase 1b study of selinexor, a first in class selective inhibitor of nuclear export (SINE) compound, in combination with doxorubicin in patients (pts) with locally advanced or metastatic soft tissue sarcoma (STS). *First Author: Eoghan Ruadh Malone, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Selinexor is a first-in-class SINE compound with single-agent activity in STS. We undertook this study to determine the safety, tolerability and efficacy of selinexor when combined with doxorubicin in pts with locally advanced or metastatic STS. **Methods:** This phase 1b study was conducted using a modified toxicity probability index (mTPI) design. Patients with locally advanced or metastatic STS received selinexor at two dose levels (60 or 80mg weekly PO) plus doxorubicin (75mg/m^2 IV q21 days, max 6 cycles). Pts with stable disease or better (per RECIST 1.1 criteria) after 6 cycles of combination treatment received selinexor monotherapy until disease progression or unacceptable toxicity. Disease assessments were made with standard imaging after every 2 cycles. Limited pharmacokinetic (PK) data was collected for the first 3 pts at each dose level. **Results:** 13 pts (11F/2M, ECOG 0/1: 5/8, median age 63 years [range 51-73]) were enrolled. Disease subtypes included leiomyosarcoma (n = 6), undifferentiated pleomorphic sarcoma (n = 2; UPS), liposarcoma (n = 2) and other sarcomas (n = 3). Three pts at 60mg selinexor and 10 pts at 80mg selinexor have been treated. The most common G3 drug related adverse events (AEs) were hematological, including neutropenia n = 6 (46%), anemia n = 3 (23%). There were two dose-limiting toxicities (febrile neutropenia and unresolved fatigue lasting more than 7 days), both at the 80mg dose level. Of the 13 evaluable pts (median follow-up of 15 weeks [range 5-31]), partial response was seen in 3 pts (23%, n = 1 for UPS, malignant peripheral nerve sheath tumor and myxofibrosarcoma) and stable disease was seen in 7 (54%). PK analysis of selinexor did not demonstrate changes compared to single agent profile. **Conclusions:** Our initial data demonstrate that the combination of selinexor and doxorubicin appears to be tolerable and safe. There was no exposure changes oberserved for selinexor in this combination regimen. Updated toxicity, safety and efficacy data will be presented at the meeting. Clinical trial information: NCT03042819.

11563 Poster Session (Board #308), Sat, 8:00 AM-11:30 AM

Discovery and characterization of novel, recurrent, targetable ALK fusions in leiomyosarcoma. *First Author: Lara Emily Davis, Oregon Health & Science University, Portland, OR*

Background: Leiomyosarcoma (LMS), a type of soft tissue tumor that originates from smooth muscle, is the second most common type of sarcoma. Despite multimodal treatment including surgery, chemotherapy and radiation, locally advanced or metastatic LMS portends poor prognosis. We hypothesize that discovery and validation of oncogenic drivers and cognate targeted therapies holds the potential to dramatically impact LMS patient outcomes. **Methods:** To discover putative kinase fusions, we analyzed existing genomic or transcriptomic data from LMS clinical samples. We functionally validated the oncogenic potential and targetability of discovered kinase fusions through biochemical, cell-based and *in vivo* tumor modelling approaches. Multiple independent cell-based (Ba/F3, NIH3T3 and murine smooth muscle cell) model systems were utilized. **Results:** We identified ALK rearrangements in 7 of 280 (2.5%) LMS patients, including a novel KANK2-ALK fusion and a recurrent ACTG2-ALK fusion. KANK2-ALK and ACTG2-ALK operate as dominant oncogenes in Ba/F3 or NIH3T3 model systems, and KANK2-ALK is tumorigenic when introduced in smooth muscle cells, the cell of origin for leiomyosarcoma. Oral monotherapy with the targeted ALK kinase inhibitor lorlatinib significantly inhibited tumor growth and prolonged survival in a murine model of KANK2-ALK leiomyosarcoma. **Conclusions:** These results provide the first validation of a targetable oncogenic kinase fusion as a driver in a subset of leiomyosarcomas. Overall, these findings suggest that some soft tissue sarcomas may harbor previously unknown kinase gene translocations, and their discovery may propel new therapeutic strategies in this treatment-refractory cancer.

11564 Poster Session (Board #309), Sat, 8:00 AM-11:30 AM

Sarcomas in patients over 90: Natural history and treatment—A nationwide study over 6 years. *First Author: Clemence Basse, Centre Léon Bérard & University Claude Bernard Lyon I, Lyon, Lyon, France*

Background: Soft tissue sarcomas (STS) are rare tumors accounting for less than 1% of human cancers. While the highest incidence of sarcomas is observed in elderly, this population is often excluded or very poorly represented in clinical trials. The present study reports on clinicopathological presentation, and outcome of sarcoma patients over 90 recorded in the Netsarc French national database. **Methods:** Information of soft tissue and visceral sarcoma patients registered from January 1st 2010 to December 31st 2016 in Netsarc were collected, analyzed and compared with younger ($<$ 90-years old) patient population. **Results:** Patients with sarcomas aged $>$ 90 have almost exclusively sarcomas with complex genomics (92·0% vs 66·3%), are less frequently metastatic (5·3% vs 14·7%) at diagnosis, have more often superficial tumours (39·8% vs 14·7%), as well as limbs and head and neck sites (75·2% vs 38·7%) (all $p < 0·001$). Optimal diagnostic procedures and surgery were less frequently performed in patients over 90 (all $p < 0·001$). However, local relapse free, metastatic relapse free, and relapse-free survival were not significantly different from those of younger patients, in the whole cohort, as well as in the subgroup of operated patients. As expected overall survival was worse in patients over 90 ($p < 0·001$). Patients over 90 who were not operated had a worse overall survival than younger patients (9·9 vs 27·3 months, $p < 0·001$). **Conclusions:** Patients with STS diagnosed after 90 have distinct clinicopathological features, but comparable relapse free survival, unless clinical practice guidelines recommendations are not applied. Standard management should be proposed to these patients if oncogeriatric status allows.

11565 Poster Session (Board #310), Sat, 8:00 AM-11:30 AM

Identification of leiomyosarcoma circulating tumor DNA through ultra-low passage whole genome sequencing and correlation with tumor burden: A pilot experience. *First Author: Matthew Louis Hemming, Dana-Farber Cancer Institute, Boston, MA*

Background: Detection of circulating tumor DNA (ctDNA) has emerged as a new approach for identifying oncogenic mutations, measuring disease burden, clinical prognostication, and assessing response to therapy. Most ctDNA assays detect single-nucleotide variants (SNVs) that are highly recurrent in carcinomas. Though there are few recurrent SNVs in leiomyosarcoma (LMS), LMS is characterized by numerous chromosomal copy-number alterations (CNAs). We therefore evaluated plasma from patients with LMS for the presence of ctDNA using an ultra-low passage whole genome sequencing (ULP-WGS) approach designed to detect somatic chromosomal CNAs. **Methods:** We identified 30 tumor/plasma pairs from patients with advanced LMS. Ten pairs have undergone ULP-WGS, with an additional 20 pairs currently in process. Of the 10 pairs evaluated, 7 were of uterine and 3 of extrauterine origin. DNA from plasma samples was subjected to ULP-WGS and compared to tumor DNA. Differences in genome-wide sequencing coverage were used to identify chromosomal amplification or deletion and ichorCNA software was used to estimate tumor fraction of each sample. Identified CNAs from tumor specimens were used to confirm the specificity of ULP-WGS to detect CNAs in plasma. Clinical data were reviewed to assess disease burden and progression status. **Results:** ctDNA was identified in 5 of 10 cases including 5 out of 6 patients with progressive disease. None of the patients with no evidence of disease (NED) or with stable disease had detectable ctDNA. We identified ctDNA in patients with both metastatic uterine LMS and extrauterine LMS. CNAs in plasma correlated with CNAs detected in matched tumor samples. **Conclusions:** Identification of plasma ctDNA by ULP-WGS is feasible in patients with advanced LMS and correlates with tumor burden/progression. An additional 20 cases will be presented. These preliminary results support further investigation of ULP-WGS as a novel blood-based assessment of tumor burden in LMS. Future experiments will assess the utility of ULP-WGS in detecting residual disease following surgery, surveillance for disease recurrence, and monitoring response to therapy.

11566 Poster Session (Board #311), Sat, 8:00 AM-11:30 AM

Impact of pathological stratification of advanced well differentiated/dedifferentiated (WD/DD) liposarcoma (LPS) on the response to trabectedin (T). *First Author: Roberta Sanfilippo, Medical Oncology Unit 2, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Recently, we showed that the FNCLCC grading system can prognosticate the outcome of retroperitoneal LPS. We aimed to explore the impact of pathological stratification using the FNCLCC grading system on the response to Trabectedin (T) of advanced/metastatic WD/DD LPS. **Methods:** We analyzed patients (pts) with advanced WD/DD LPS and treated with T at our Institution for whom formalin-fixed paraffin-embedded (FFPE) tumor samples were available. Histologically, samples were categorized according to the 2013 WHO classification, complemented by Evans' refinements. The "cellular subvariant" (CS) was diagnosed in the presence of a non-lipogenic area with a mitotic count $<$ 5/10HPF. In cases in which the mitotic count was $\geq$5/10 HPF, the diagnosis was DDLPS and graded as 2 or 3 according to the FNCLCC grading system. Patients were divided into two subgroups: WDLPS/CS and G2/G3 DDLPS. Response rate (RR) and progression-free survival (PFS) were compared using the Fisher's exact test and the log-rank test, respectively. **Results:** We included a total of 39 pts with advanced WD/DD LPS treated with T from April 2003 up to present. In 21 pts the sample analyzed was the primitive tumor prior to starting any systemic treatment. In 18 pts we analyzed the sample obtained at the closest date to T initiation. Four patients had a WDLPS, 7 a CS, 21 a G2 DDLPS and 7 a G3 DDLPS. In the subgroup of 11 WDLPS/CS, 5 partial responses, two minor responses and two stable diseases were observed, while in the subgroup of 28 G2/G3 DDLPS we observed one PR and 13 SD. RR was 45% for WDLPS/CS versus 4% for G2/G3 DDLPS (p = 0.0165). Median PFS was 14 months for WDLPS/CS and 3 months for G2/G3 DDLPS (HR 0.28; 95% CI 0.14-0.59; p = 0.0006). **Conclusions:** In this series, sensitivity to T was higher in WDLPS/CS. If what suggested by this limited retrospective case series analysis were confirmed on larger series, WD/CS vs G2/G3 DD histologies could serve as predictive factors for T in advanced WD/DD LPS.

11567 Poster Session (Board #312), Sat, 8:00 AM-11:30 AM

Nodal involvement and survival in synovial, clear cell, angio, rhabdo, and epithelioid sarcoma. *First Author: Haotong Wang, Massachusetts General Hospital, Boston, MA*

Background: Synovial, Clear cell, Angiosarcoma, adult Rhabdomyosarcoma and Epithelioid sarcoma is often referred to by the mnemonic SCARE as soft tissue sarcoma subtypes with higher risk of lymph node involvement(LNI). This study is to identify the incidence of LNI, prognosis and predictors of LNI, treatment and patterns of failure. **Methods:** We identified 829 patients with the diagnosis of the above 5 histologies who were treated in our institution and retrospectively reviewed 343 patients who were diagnosed from 2000 to 2017. Statistical significance was assessed with Chi-square and Wald tests. Kaplan-Meier analysis was used to analyze survival outcomes. **Results:** Primary SCARE sarcoma sites include head and neck(71, 21%), upper extremity(57, 17%), lower extremity(90, 26%), thorax, abdomen and pelvis(47, 14%), trunk and retroperitoneum(44, 13%), GU, GYN and other(34, 10%). 152 present with Stage 2 and 109 with Stage 3 disease (AJCC7). Primary tumor size was = $<$ 5 cm in 123, 5-10 cm in 77 and $>$ 10 cm in 57. LNI was found in 54(16%) patients, of whom 48 were positive at diagnosis and 6 were found during follow up. LNI rates differed significantly (table 1). Tumor size(p = 0.05), histology(p $<$ 0.001), metastasis(p $<$ 0.001) were found as predictors of LNI. 282(82%) patients underwent resection with R0 in 177 patients. Sentinel lymph node biopsy was performed in a limited number of patients. 171(50%) patients received chemotherapy. 247(72%) patients received radiation therapy. Median follow up is 26.5 months. 5-year overall survival (OS) in SCARE histology is 72.7, 41.3, 34.5, 30.8, 45.4% respectively. Synovial sarcoma(SS) has better survival compared to others(p $<$ 0.001). LNI was associated with worse OS (p = 0.001) and DFS(p = 0.001). Multivariate analysis identified LNI(HR = 1.89, p = 0.005), large tumor size (HR = 1.05 per cm, p = 0.003), metastasis(HR = 3.31, p $<$ 0.001) as significant factors affecting OS. **Conclusions:** LNI is significantly higher in clear cell, angiosarcoma, rhabdomyosarcoma and epithelioid sarcoma than SS, is predicted by larger tumor size, and has poorer prognosis.

	Synovial	Clear cell	Angiosarcoma	Rhabdomyosarcoma	Epitheloid Sarcoma
Overall: 343	125	18	78	73	49
LNI (p = 0.0015)	6%	28%	15%	21%	29%
M+ at presentation (N.S.)	10%	3%	23%	27%	24%

11568 Poster Session (Board #313), Sat, 8:00 AM-11:30 AM

Survival impact of surgical management in reference centers for retroperitoneal sarcoma: A nationwide study of FSG-GETO and NETSARC. *First Author: Sylvie Bonvalot, Institut Curie, Paris, France*

Background: Retroperitoneal sarcoma (RPS) are complex to treat. We previously reported that management and surgery in a reference center are independent prognostic factors for relapse free survival (RFS) in sarcoma. Here, we investigated the impact of the surgery in a reference center on RFS and overall survival (OS) in the nationwide NETSARC study. **Methods:** NETSARC (netsarc.org) is a network of 26 reference sarcoma centers, funded by the French NCI. Since 2010, second pathological review are mandatory for sarcoma patients (pts) facilitating exhaustive collection. Pts characteristics and follow-up are collected in a database regularly monitored. From 2010 to 2016, RPS represented 10.0% (range 8.3-10.5%) of all sarcomas included in Netsarc. **Results:** 1286 RPS (M/F ratio: 1.09, median age 63, range 20-94) are reported in NETSARC from 01/2010 to 12/2016. WD/DDDLPS (63.7%), LMS (21,3%), UPS (6,3%) were the most frequent histotypes. 155 (12%) pts had metastasis (met) at diagnosis. 699 (54%) and 587 (46%) were presented to one of the 26 NETSARC multidisciplinary board before and after initiation of treatment. 477 (37%) and 809 (63%) were operated within vs outside a NETSARC reference center. The former group had larger tumor size, p $<$ 0.0001, but no difference of age, grade, histotypes. More pts treated in NETSARC centers had documented imaging (92% vs 80%) and preoperative biopsy (81% vs 63%, p $<$ 0.0001 both). Quality of final surgery was R2 or unknown, in 24% vs 69% in NETSARC vs non NETSARC centers (p $<$ 0.0001). In univariate analysis on non met patients, surgery within a reference center was associated with a better OS (median not reached: 30-months OS 84% vs 63% respectively, logrank p $<$ 0.001). Local RFS and RFS were significantly better for pts operated in reference centers (p $<$ 0.0001). Surgery in reference center was an independent good prognostic factor for OS (HR: 0.23), LRFS (HR:0,56), RFS (HR:0,79) using Cox model (p $<$ 0.001 all). **Conclusions:** In this nationwide unselected population of RPS over 7 years period, surgery in reference center is associated with a major reduction of the risk of relapse and death.

11569 Poster Session (Board #314), Sat, 8:00 AM-11:30 AM

Upfront isolated limb perfusion (ILP) in untreated patients with unresectable non-metastatic primary soft-tissue sarcomas (STS) of the limb: The Gustave Roussy experience. *First Author: Tarek Assi, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Options for limb-preserving surgery in locally advanced (LA) STS include chemotherapy and/or radiotherapy (RT), or ILP with tumour necrosis factor-alpha (TNFa) + melphalan, if the tumour is confined to an extremity. The aim of this study is to evaluate the benefit of upfront ILP in untreated unresectable patients (pts). **Methods:** All pts with unresectable non-metastatic primary LA STS of the limb treated at Gustave Roussy with exclusive ILP as induction treatment between 2003 and 2016 were included in this study. Demographic, clinical and long-term characteristics were obtained from the electronic medical records and retrospectively analyzed. **Results:** 41 pts were identified, with a median age of 51 yrs [range: 21-76]. Liposarcoma and undifferentiated pleomorphic sarcoma were the most common subtypes (27% and 22 % respectively) with tumors classified as FNLCC grade 3 in 11 pts, grade 2 in 16 and grade 1 in 13. Acute regional toxicities after ILP (Wieberdink classification) were grade 2 in 35 pts (85%), and grade 3 in 2 (5%). No grade IV-V were observed. Objective response rate and disease stabilization were observed in 22% (including 2 CR) and 65% respectively. 8 pts were not operated (4 had exclusive RT, 1 pt progressed, 2 pts were in CR and 1 pt died after 3 months after ILP of a massive pulmonary embolism). 1 patient had early amputation due to PD after ILP. Out of 41 pts, 32 patients had conservative resection (78%). 2 pts (6%) experienced pathological CR, 17 (53%) had pathological PR ($\geq$ 50% necrosis) while 13 (41%) were considered refractory ($<$ 50% necrosis). All but 5 pts (84 %) received post-operative RT. After a median follow-up (FU) of 43 months 18 pts (47%) relapsed; one locally, 13 at distance (62% in the lung) and 4 in both sites. Median disease-free survival after surgery was 6.7 yrs. The 1-yr, 5-yrs and 10-yrs DFS rates were 75%, 50% and 45% respectively. Median overall survival (OS) was not reached after median FU of 6.3 yrs.1-yr, 5-yrs and 10-yrs OS rates were 90%, 63% and 55%. **Conclusions:** This study suggests that upfront ILP in unresectable STS pts is a potentially curative limb saving procedure and is well tolerated without affecting OS.

11570 Poster Session (Board #315), Sat, 8:00 AM-11:30 AM

Treatment of angiosarcoma with pazopanib and paclitaxel: Results of the phase II trial of the German Interdisciplinary Sarcoma Group (GISG-06 EVA) study. *First Author: Daniel Pink, Helios Klinikum Bad Saarow, Bad Saarow, Germany*

Background: Angiosarcomas (AS) account for 2-3% of all soft tissue sarcomas. About 60% develop at the skin, and radiation-induced AS following breast cancer therapy represent a characteristic feature. In metastatic or locoregionally advanced AS paclitaxel may induce tumor response. Data also show positive effects of VEGF-inhibiting drugs in AS patients. Thus, the combined application of chemotherapy and TKI seems warranted. **Methods:** This multicentre, open, prospective, single-armed phase II trial (NCT02212015) evaluates efficacy and safety of combined pazopanib (800mg/d) and paclitaxel (70mg/msq d1, 8, 15 of a 28d cycle) in advanced or metastatic AS. Primary endpoint is PFS at 6 mos. after start of therapy. Statistical analysis looks for 6 m-PFS $>$ 35% using RECIST 1.1. The trial is conducted in two steps with an interim futility analysis. Twenty-six patients were recruited (23 f, 3 m, median age 60.5 yrs), ECOG 0/1: n = 20/6 (80%/20%), 5 pts had local tumor progression, 21 pts (80.8%) showed metastatic disease, tumor description see table 1. **Results:** At interim analysis, the full analysis set consisted of 26 pts who received study medication at least once. The number of successes (6-m PFS yes) was n = 12 (46%). We had to adapt type-I-error for overrunning the pre-specified interim sample size, prompting a boundary of 17/26 pts with 6-m PFS, which the study did not meet (2-sided Clopper-Pearson CI). The formal decision was to stop the trial for futility. Analysing the non-responders showed that none of pts with hepatic involvement and 2nd AS after total body irradiation (TBI) did profit from study therapy. **Conclusions:** Combined paclitaxel and pazopanib is an active treatment in AS particularly in tumors located superficially. Patients with visceral metastases and those with hepatic angiosarcoma after TBI did not respond. The study protocol is about to be amended with refined inclusion citeria. Clinical trial information: NCT02212015.

Location of AS: skin.	17 (65.4%)
Loc. of AS: visceral/deep	12 (46.2%)
of loc. skin: chest/chest wall	13 (76.5%)
of loc. visc/deep: liver	5 (41.7%)
of loc. visc/deep: other	6 (50.0%)
Haemangiosarcoma	22 (84.6%)
Lymphangiosarcoma	4 (15.4%)
1ry AS	13 (50.0%)
2ndary AS	13 (50.0%)

11571 Poster Session (Board #316), Sat, 8:00 AM-11:30 AM

Inherited BRCA2 mutations and tumor hemi/homozygosity of metastatic soft tissue sarcoma in up to one-third of the 55 patients with shorter survival time. *First Author: Katsuhito Takahashi, International University of Health and Welfare, Mita Hospital, Sarcoma Center, Tokyo, Japan*

Background: Soft tissue sarcoma (STS) is well-known rare cancer with few therapeutic options. Although recent comprehensive genomic analyses of adult STS revealed few somatic mutations and many copy number variations (CNVs), the pathogenesis, prognostic markers and drug sensitivity mechanisms remain to be understood. **Methods:** We recruited 55 patients (50 female and 5 male, mean age 49) with a confirmed metastasis, information on familial cancer burden and detailed sarcoma pathology under written informed consent approved by IRB. Whole-exome sequencing was performed on the illumina HiSeq 2500 with the mean coverage depth of 178x in tumor and 68x in germline samples. In order to find CNVs and germline contributions in tumor, we used Strelka and Virmid analysis software filtering all mutations with allele frequencies more than 80%. CNVs and specific mutations in the BRCA2 locus identified were validated by multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing. **Results:** Among the somatic mutations, TP53, MED12, ATRX and RB1 are most frequently affected under mean total mutation numbers 1.26/Mb. All patients show MSS phenotype. Of the 72 genes with heritable cancer risk evaluated by Ballinger et al.(2016) in sarcoma germline, 25 have mutations with tumor bialletic loss of wild type sequence in 44/55 (80%) patients. Of these, six BRCA2 missense mutations recognized as variants of unknown significance (VUS) are most frequently found in 15/55 patients (27%, 12/37 LMS, 1/9 LPS, 1/1 MPNST, 1/1 AS) in both female and male. CNVs analysis by MLPA showed complete deletion of wild type BRCA2 locus, leading to hemizygosity of the VUS. Kaplan-Meier analysis revealed that patients with the BRCA2 mutations (N = 15) significantly reduced the 5-year survival rate as compared with patients with normal sequence or mutations in heterozygosity (N = 40) (48% vs 93%, P = 0.00272). **Conclusions:** Our results unveiled a different landscape of STS genomics from previous studies, indicating more germline and CNVs contributions in prognosis. Tumor loss of wild type allele and hemizygosity in BRCA2 implicates defective HRR as a potential therapeutic target in STS.

11572 Poster Session (Board #317), Sat, 8:00 AM-11:30 AM

Effect of JS001, a monoclonal antibody targeting programed death-1 (PD-1), on responses and disease control in patients with advanced or refractory alveolar soft part sarcoma: Results from a phase 1 trial. *First Author: Sheng Yang, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Alveolar soft part sarcoma (ASPS) is a rare and lethal malignancy mainly affecting youth, with no effective standard systemic treatment. Checkpoint inhibitors has showed efficacy in a variety of tumors, but its role in ASPS remains elusive. Here we report data of JS001, a humanized IgG4 anti-PD-1 antibody developed by Shanghai Junshi Biosciences Co., Ltd., China, in advanced or refractory alveolar ASPS from a phase 1 trial. **Methods:** After a dramatic tumor shrinkage with a single injection of JS001 in a patient with ASPS, we decided to expand a cohort in this tumor. Following patients(pts) were planned to receive JS001 at 3mg/kg or 10mg/kg, repeated every 2 weeks (up to 6 doses). The diagnosis was confirmed with central histological review. PD-L1 and CD8 IHC were performed when tissue sample available. **Results:** From October 2016 to June 2017, 12 pts were enrolled and all are efficacy-evaluable. One achieved CR and 2 had PR, with a response rate of 25%. Two additional pts had some degree of tumor shrinkage. Response heterogeneity was common: some lesions enlarged while others reduced in a same patient. In three pts with responses, the time to responses were 5.7, 7.7 and 23.9 weeks, respectively and the durations of response were 48.3, 31.1+ and 36.0+ weeks, respectively. Six pts remained under disease control at 6 months, and 4 at 12 months. The estimated median progression-free survival was 12.4 months. Toxicities were mostly grade 1-2. Grade 1 pneumonia and hepatitis, each in 1, were considered immune-related. No DLT or treatment-related death occurred. Tissue samples were available in 10 pts. In 4 PD-L1 positive cases, there were 2 PR, 1 SD and 1 PD; while in 2 pts with minimal CD8+ T-cell infiltration, there were 1 SD and 1 PD. In-depth biomarker analysis is in progress. **Conclusions:** In this first prospective cohort of PD-1 antibody in ASPS, JS001 showed satisfactory response rate and prolonged disease control. Responses heterogeneity highlights the importance of biomarker and microenvironment study in ASPS. Our findings may prelude a new option for advanced ASPS. Clinical trial information: NCT02836834.

11573 Poster Session (Board #318), Sat, 8:00 AM-11:30 AM

Prognostic role of HMG proteins in a series of 301 advanced soft tissue sarcoma patients: A Spanish Group for Sarcoma Research Study (GEIS). *First Author: Nadia Hindi, Institute of Biomedicine Research (IBIS)- Universitary Hospital Virgen del Rocio/CSIC/Universidad de Sevilla, Sevilla, Spain*

Background: High Mobility Group (HMG) proteins act as architectural transcription factors and can influence the expression of many genes. The role of promoting an undifferentiated pluripotent stem-like cell state makes HMGA proteins attractive for sarcoma research. Overexpression of HMGA1 and HMGA2 have been correlated with poor prognosis in some epithelial tumors but there is hardly any data on the prognostic role of HMGA in soft tissue sarcoma (STS). We present the analyses of protein expression of HMGA1/2 and B1 as prognostic factor in STS. **Methods:** Selection criteria were: advanced STS (at diagnosis or at any time from then on), paraffin block available, treated with at least 2 lines in advanced disease (one of them with trabectedin) and ethic committee's approval. A TMA was set up for nuclear expression of HMGA1 (Abcam), HMGA2 (Sigma-Aldrich) and HMGB1 (Abcam) with block from diagnostic time. An expert blinded pathologist reviewed and classified the intensity staining into negative, weak or strong and the extension as high (at least 50% of stained cells) or low ($<$ 50%) for each protein. Kaplan–Meier was used for time-to-event variables and the log-rank test was used to compare groups. **Results:** A series of 301 patients was studied, median age 52, 53% females and median follow-up from metastasis (M1) of 42 m. Strong and high expression were distributed as follows: HMGA1 24% and 18%, HMGA2 58% and 63%, HMGB1 69% and 75%, respectively. Strong expression of HMGA1 showed significant worse prognosis for OS from M1 time (31 vs 22 m; p = 0.007) and for PFS of trabectedin line (3.8 vs 2.6 m; p = 0.002). Similar results were obtained with high HMGA1 expression. In multivariate analyses, age ($>$ 60y) HR 1.52 (1.10-2.09) p = 0.009, short lapse to metastases ($<$ 10 months) HR 1.44 (1.08-1.92) p = 0.013, and strong expression of HMGA1 HR 1.45 (1.06-1.48) p = 0.018 showed to be independent prognostic factors for worse survival from M1. **Conclusions:** Protein expression of HMGA1 exhibited a significant prognostic role in a series of advanced STS. Validation studies are ongoing to confirm its prognostic and potential predictive role. These results could open new target in STS.

11574 Poster Session (Board #319), Sat, 8:00 AM-11:30 AM

Doxorubicin plus dacarbazine (DoDa), doxorubicin plus ifosfamide (DI) or doxorubicin alone (Do) as first line treatment for advanced leiomyosarcoma (LMS): A retrospective study from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG). *First Author: Lorenzo D'Ambrosio, University of Torino, Department of Oncology, Torino, Italy, Torino, Italy*

Background: LMS is one of the most common soft tissue sarcoma histotypes that may arise in any site of the body. In advanced disease, first line treatment is still based on Do alone or in combination. Previous retrospective data suggested limited activity of ifosfamide (Sleijfer 2010), whereas Da showed interesting results in limited series. DoDa, DI and Do regimens were retrospectively evaluated as first line treatment in advanced LMS. **Methods:** Inclusion criteria: confirmed histological diagnosis, treatment between 1/2010 and 12/2015, measurable disease (RECIST 1.1), ECOG performance status (PS) $\leq$2, age $\geq$18 years, no major comorbidities. Endpoints: progression-free survival (PFS), overall survival (OS), overall response rate (ORR), toxic death (TD) rate. **Results:** 303 patients, 87 males (29%), median age 58 (range 20-87), were enrolled from 18 EORTC STBSG sites and were distributed as follows: 117 DoDa (39%), 71 DI (23%), 115 Do (38%). No significant differences were detected between treatment arms in terms of dose reductions $>$ 10%, delays $>$ 72h, G-CSF use, or TD. Median PFS was 9.4 (95% CI 6.1-9.7), 6.8 (4.5-9.5), 5.4 months (3.8-6.8), and ORR was 36.8%, 21.5%, and 25.9%, for DoDa, DI and Do, respectively. When attempting to adjust for lack of randomization by balancing baseline characteristics among arms, a non-significant trend for PFS and ORR in favor of DoDa was observed. Shorter median follow-up was observed in DoDa (32 months; IQR 23-47) compared to DI (50; 37-73) and Do arms (46; 31-58), weakening a direct comparison of OS. Subsequent treatments were well balanced across arms. **Conclusions:** To our knowledge, this is the largest retrospective study on the first line treatment of advanced LMS. Acknowledging the limitations of such retrospective analysis and the unbalanced follow up, DoDa may favorably compare with both DI and Do showing interesting activity in advanced LMS in terms of both ORR and PFS similar to previous single center-based experiences. Consistency of both DI and Do arms outcomes with EORTC 62012 trial results increases the reliability of these results.

11575 Poster Session (Board #320), Sat, 8:00 AM-11:30 AM

Subgroup analysis of elderly patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide (SARC021) trial. *First Author: Eugenie Younger, Royal Marsden Hospital, London, United Kingdom*

Background: Approximately 50% of patients diagnosed with soft tissue sarcoma (STS) are aged $\geq$65 years (yrs). The management of elderly STS patients ($\geq$65yrs) is challenging and there are few prospective data on the outcome of those with advanced disease. This study aims to document the safety and efficacy of first-line chemotherapy in elderly patients within the SARC021 trial and provide a benchmark for future research. **Methods:** SARC021 randomized patients to receive first-line doxorubicin (Dox) or doxorubicin + evofosfamide (DE) with overall survival as the primary end point. The eligibility criteria have been described previously. Patients aged $\geq$65yrs were identified from the trial database. **Results:** Of 640 participants, 209 (33%) elderly were treated (Dox: n = 103, median age 70 [65-84] yrs. DE: n = 106, median age 69 [65-89] yrs). There was no significant difference in OS, PFS or response rate (RR) for elderly patients between the 2 arms (OS: median OS Dox 517 days {95%CI 393-628} vs DE 494 days {95%CI 351-701}, p = 0.99. PFS: median PFS Dox 185 days {95%CI 142-218} vs DE 197 days {95%CI 150-250}, p = 0.28. RR: Dox 19{18%} vs DE 27{25%}, p = 0.22). Non-hematological toxicity was significantly more common in the DE arm (Dox 53{51%} vs DE 78{74%}, p = 0.001). Differences in hematological, cardiac and $\geq$grade 3 toxicities were not significant. In 431 patients aged $<$ 65yrs the median OS (whole cohort) was 614 days (95%CI 515-708) compared to 509 days for those $\geq$65yrs (p = 0.057). No significant differences were observed for PFS ($<$ 65yrs 183 days {95%CI 154-194} vs $\geq$65yrs 191 days {95%CI 176-218}, p = 0.14) or RR ($<$ 65yrs 103{24%} vs $\geq$65yrs 46{22%}, p = 0.596). Patients $\geq$65yrs had significantly more hematological (208{48%} vs 141{67%}, p $<$ 0.0001), non-hematological (215{50%} vs 131{63%}, p = 0.0097) and $\geq$Grade 3 toxicity (299{69%} vs 178{85%}, p = 0.0002). Significantly more patients $\geq$65yrs (22{5%} vs 30{14%} p = 0.0001) stopped therapy due to toxicity. **Conclusions:** For elderly patients no significant difference in outcome was observed between those treated with Dox or combination DE. Elderly outcomes were similar to those $<$ 65yrs, however considerably more toxicity was observed in patients $\geq$65yrs.

11576 Poster Session (Board #321), Sat, 8:00 AM-11:30 AM

Genomic subtypes of angiosarcoma: A comprehensive genomic profiling (CGP) study. *First Author: Vinod Ravi, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Angiosarcomas (AS) arise from the vascular endothelium of skin and other visceral organs and from such diverse etiologies as exposure to carcinogenic agents or therapeutic radiation. We used CGP to sub-classify AS and to identify genomic alterations (GA) linked to responsiveness to targeted therapy and immune checkpoint inhibitor (ICPI) therapies. Median overall survival of metastatic AS is only 13.1 months. **Methods:** Hybrid capture based CGP including RNA-seq in a subset of cases was performed on 278 cases of AS including 53 breast angiosarcomas (BA) and 207 soft tissue (STA). Tumor mutational burden (TMB), was calculated from 1.1Mb of sequenced DNA and UV exposure signature was determined. **Results:** For all AS, the most commonly altered genes were *TP53* (38%), *MYC* amplification (22%), *CDKN2A* (17%), *KDR* (12%) and *PIK3CA* (8.6%). 4q12 (*KIT/KDR/PDGFRA*) amplifications were increased in STA relative to BA (p = 0.18). *MYC* amplifications were more frequent in BA than STA (p $<$ 0.001) likely due to radiation associated BA. Three genomic subsets were identified within BA: *MYC* amplified (mean 60 copies, range 16-277) with increased age (p $<$ 0.0001), *KDR* altered mutually exclusive to *MYC* amplified (p $<$ 0.05) and *MYC/KDR* wildtype, 42% of which have *PI3K* pathway alterations. A subset (19%) of STA had a UV signature (UV-STA) with a median TMB of 21. We identified 14 AS cases (5%) with *KDR* T771R none of which harbor other *KDR*, *MYC* or tyrosine kinase mutations. **Conclusions:** Broadly assessing GA in AS has potential benefit from matched therapy and correlates with anatomic and etiologic origin. AS patients may benefit from matched TKIs to kinase fusions, 4q12amp and *KDR* GAs. *KDR* T771R defines a new class of AS which should be investigated for a unique non-radiation etiology. The high TMB UV-STA cases suggest potential benefit from ICPI and indicates cutaneous non-melanocytic, non-squamous neoplasms can arise from UV damage.

Type (n)	Median age	Median TMB	4q12 amplified (%)	MYC amplified (%)
AS (278)	64 (5-88)	2.5 (0-151)	4	22
STA (207)	64 (10-88)	3.2 (0-151)	4.8	18
UV-STA (39)	72 (33-86)	21 (2.4-151)	5.1	2.6
BA (54)	61 (19-88)	2.4 (0-8.9)	0	46
BA-*MYC* (25)	72 (19-88)	3.2 (0.8-8.9)	0	100
BA-*KDR* (10)	36 (22-66)	2.4 (0.8-6.45)	0	0
BA-*KDR/MYC*wt (19)	49 (23-71)	1.6 (0-8.1)	0	0

11577 Poster Session (Board #322), Sat, 8:00 AM-11:30 AM

Identification of novel intra-genic deletions of *CTNNB1* gene in WT desmoid-type fibromatosis. *First Author: Milena Urbini, Interdepartmental Centre of Cancer Research "Giorgio Prodi", University of Bologna, Bologna, Italy*

Background: Desmoid-type fibromatosis (DT) are characterized by molecular alterations of *CTNNB1* or *APC* genes. These abnormalities have been described in ~85% of DT using Sanger sequencing. Recently, whole-exome sequencing allowed to detect molecular aberrations in *CTNNB1* or *APC* in approximately 95% of DT. In order to characterized the true WT DT, we performed this study on DT WT Sanger-sequenced samples. **Methods:** Deep sequencing of *CTNNB1* and of *APC* was performed using TruSeq Custom Amplicon Low Input kit (Illumina) on 11 WT FFPE DT samples from patients treated with surgery. Whole Exome sequencing (WES) was performed using Nextseq500 (Illumina, CA) sequencer. Mutations were validated through Sanger sequencing, and expression of *CTNNB1* mutated alleles was evaluated through RT-PCR. **Results:** *APC* mutation was found in 2 cases, while low-frequency *CTNNB1* mutations were discovered in 5 samples (45%) (mean of 16% reads) and 4 cases remained WT. WES was performed in 6 cases (3 *CTNNB1* WT and 3 with low frequency mutations). Through in-depth analysis of reads spanning exon 3 of *CTNNB1*, 2 large intra-genic deletions were detected in 2 cases, one carrying also a T41A low frequency mutation. Both deletions were approximatively of 190bp and led to the loss of the T41 codon hotspot of mutation. In one case, the deletion led to the loss of the second half of exon 3 and part of intron 3, in the other it involved part of intron 2 and the 5' part of exon 3 losing the splicing acceptor site. We demonstrated that even if the acceptor splicing site was lost, the deleted allele of *CTNNB1* was expressed, with the retention of 32 bp of intron 2 in the mature mRNA. Moreover, we demonstrated that, at mRNA level, low frequency T41A mutated allele was the prevalent isoform expressed with respect to the WT allele. The importance of these molecular alterations in the natural history of DT needs further investigations. **Conclusions:** A minority of DT is WT for either *CTNNB1*, *APC* or any other gene involved in the WNT pathway. In this subgroup novel and hard to be detected molecular deletions of *CTNNB1* were discovered, contributing to explain a portion of the allegedly WT DT cases.

11578 Poster Session (Board #323), Sat, 8:00 AM-11:30 AM

Doxorubicin (D), gemcitabine (G), ifosfamide (I) and the EZH2 inhibitor EPZ-011989 in epithelioid sarcoma (ES): A comparison of different regimens in a patient-derived xenograft (PDX) model. *First Author: Nadia Zaffaroni, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: ES is a rare soft tissue sarcoma with two variants, i.e., the proximal and the distal. Retrospective data on the activity of anthracycline- and G-based regimens are available. EZH2 inhibitors, which target the INI1 pathway that is inactivated in ES, are currently being tested in clinical trial. Comparisons of these agents are not available and unlikely to be prospectively evaluated. We comparatively assess these agents in a proximal-type INI1-deleted ES PDX. **Methods:** A PDX model (ES-1) was established by subcutaneously xenotransplanting into immunodeficient (SCID) mice tumor fragments obtained from a patient with primary, proximal-type, INI1 deleted ES of the forearm. After tumor propagation in SCID mice for three consecutive passages, the PDX was considered established. Mice were randomized to receive D and I, as single agents or in combination (D+I), G and the EZH2 inhibitor EPZ-011989 (E) (8 mice/experimental group). Drug activity was assessed in terms of tumor volume inhibition (TVI%). RNA-seq was performed on samples obtained from patient primary tumor and from ES-1 before and after treatment with E. **Results:** As single agents, both D and I showed a modest antitumor effect. Conversely, D+I induced an almost complete tumor growth inhibition (max TVI: 94%). A comparable antitumor activity was caused by G (max TVI: 98%). E initially induced a tumor growth stabilization, followed by a progressive reduction of tumor volume starting from end of treatment (max TVI: 89%). Consistently with its mechanism of action, E inhibited trimethylation and increased acetylation of H3K27, as detected by Western Blot in tumor samples at different intervals from the end of mouse treatment. Analysis of RNAseq data is ongoing. **Conclusions:** Our preclinical results in a proximal-type ES INI1-deleted PDX model showed a strong and comparable antitumor activity for D+I, G and E. These data support clinical use of G and D+I and confirm that EZH2 is a therapeutic target in proximal-type ES. Experiments with D and G combined to E are planned. To which extent these preclinical findings can be extended to distal ES subtype is left to be defined.

11579 Poster Session (Board #324), Sat, 8:00 AM-11:30 AM

Frequency of genomic biomarkers of response to immunotherapy in sarcoma. *First Author: Sally E. Trabucco, Foundation Medicine, Inc, Cambridge, MA*

Background: Recent data (D'Angelo et al, 2018) has suggested possible benefit for a subset of sarcoma patients from immune checkpoint inhibitors (ICPI). We assessed a large sarcoma population for genomic alterations (GA) suggesting benefit from ICPI including high tumor mutational burden (TMB-H) [> = 20 mutations/mb (m/mb)], presence of microsatellite instability (MSI-high) and genomic amplification of *PDL1*. **Methods:** Hybrid capture based comprehensive genomic profiling including RNA-seq in a subset of cases was performed on > 6100 cases of sarcoma and included TMB and MSI status. UV exposure signature was determined as previously described (Zehir et al, 2017). **Results:** TMB was distributed throughout sarcoma cases with a median of 1.7 (range 0-160) and 2% TMB-H. The sarcomas frequently TMB-H were skin atypical fibroxanthoma (86%, 6/7), skin sarcoma NOS (50%, 3/6), and lung sarcoma (14%, 2/14). Presence of a fusion gene, such as the frequent fusions EWSR1:FLI1, SS18:SSX1, and STAT6:NAB1, were mutually exclusive with TMB-H, *PDL1* amplification and MSI-high ($p < 0.0001$). MSI-high cases (0.23%), with median TMB of 26 (11-67), were predominantly a subset of TMB-H. 0.83% of sarcoma cases had *PDL1* amplification (6/51 TMB-H), most frequently soft tissue sarcoma NOS (35% of *PDL1* amplified cases). 2% of sarcoma cases have a UV signature, with median TMB of 36 (2.4-160), and make up 72% of TMB-H sarcomas. Notably, 14% of angiosarcomas have a UV signature; these cases have median TMB of 19 m/mb (2.4-148). Of sarcomas with a UV signature, 26% harbored GA associated with melanoma (*BRAF* V600x, *NRAS* or *KIT* mutation) and 27% were assayed from a cutaneous specimen. An index case of high grade sarcoma with an initial intrabdominal presentation was identified as harboring high TMB and a UV signature on CGP. **Conclusions:** Identification of one or more of TMB-H, *PDL1* amplification and/or MSI-high is detected in 2.8% of unselected sarcoma cases, which may be more likely to benefit from ICPI and such cases lack oncogenic fusions. Notably, 72% of the TMB-H cases harbored a UV signature which may raise the possibility of an alternative diagnosis of melanoma, particularly desmoplastic melanoma.

11580 Poster Session (Board #325), Sat, 8:00 AM-11:30 AM

Management and outcome of patients with neo-adjuvant chemotherapy (CT) in locally advanced soft-tissue sarcoma (LASTS): The Gustave Roussy experience. *First Author: Sarah Naomie Dumont, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Neo-adjuvant CT with anthracyclines plus ifosfamide (AI) is a therapeutic option in patients (pts) with marginally LASTS, aiming at a local benefit, facilitating surgery, in addition to the systemic one (ESMO guidelines 2017). **Methods:** We retrospectively reviewed all consecutive pts with LASTS who received AI (doxorubicin 60 mg/m2 plus ifosfamide 9g/m2) regimen treated from 1996 to 2015 in neo-adjuvant setting in our institution. Clinical, biological, imaging and pathology data were collected from patient files. Survival curves were calculated according to Kaplan-Meier and compared with the log-rank test or a Cox proportional hazard model, using R 3.4.3. **Results:** The data of 161 pts (89 males, 72 females) was collected. The median age was 45 years and the median tumor size was 10 cm (range 3-27 cm). LASTS were located in the extremities (67%), trunk (17%) and retroperitoneal (8%). The main histotypes were UPS 73 (45%), L-sarcomas 36 (23%), and synovial sarcoma 26 (16%). Fifty-eight % of pts had a grade 3, 38% a grade 2 and 4% a grade 1 disease. The median number of cycles of CT administered was 3 (range 1-6). The clinical benefit rate was 87 % pts (49.5%) (partial response and stable disease according to RECIST). All patients were subsequently operated, including 5 amputations, 85% R0 and 15% R1 resections. Eighty percent of pts received adjuvant radiation therapy and 10% received adjuvant CT. Twenty-one pts experienced a local relapse and 48 developed distant metastases. After a median follow-up of 57 months, the 5-yr-DFS was 56% (CI 95% [47-65]) and the 5-yr OS was 70% (CI 95% [61-79]) . There was a quasi-linear significant relationship between the rate of residual identifiable cells (RIC) and both DFS and OS, with the most discriminating cut-off being 35% (respectively for OS and DFS, $p = 0.012$ and $p = 0.0054$); each additional percent worsening the prognosis. Grade was correlated to a good histologic response ($p = 0.00019$). A R0 resection was significantly related to a better DFS ($p = 0.025$) with a trend on OS ($p = 0.058$). **Conclusions:** Neo-adjuvant CT with AI regimen in LASTS facilitates surgery, with a R0 resection achieved in 85% of pts. The rate of RIC correlates to outcome.

11581 Poster Session (Board #326), Sat, 8:00 AM-11:30 AM

Genomic amplification of CDK4 in dedifferentiated liposarcomas as a predictive biomarker for microtubule disrupting agents. *First Author: Bryce Demoret, Ohio State University, Columbus, OH*

Background: Dedifferentiated liposarcoma (DDLPS) represents a common but morbid subtype of sarcoma. Microtubule disrupting agents (MDA), including eribulin and taxanes, disrupt the cell cycle and have modest clinical activity in patients with DDLPS. Unfortunately, no clinically validated biomarkers exist to predict MDA response in this population. DDLPS is characterized by amplification of *cyclin-dependent kinase 4* (*CDK4*), which regulates the cell cycle. We hypothesized that *CDK4* amplification may predict response to MDAs. **Methods:** 25 DDLPS trial patients (NCT01574716) who received docetaxel as part of their therapy and for whom tissue was available were profiled using DNA next generation sequencing (NGS) to quantify *CDK4* copy number alteration. Patients were divided into *CDK4*-high and -low cohorts based on median amplification level. Progression-free survival (PFS) was calculated using Kaplan-Meier analysis. Patient derived DDLPS cell lines (LPS246, LPS815, LPS863) were analyzed for *CDK4* amplification level via NGS. Sensitivity to MDA (eribulin and docetaxel) was quantified using cell viability assays. CDK4 activity was attenuated using palbociclib and drug synergy was ascertained via Chou-Talalay algorithm. **Results:** DDLPS patients treated with MDA revealed patients' *CDK4* levels greater than median had improved median PFS compared to patients with *CDK4* levels lower than median (19.7 vs 11.1 m, $p = 0.03$). This suggested improved biologic activity of MDAs in *CDK4*-high tumors, and was further investigated using in vitro models. DDLPS cell lines were characterized for sensitivity to eribulin and docetaxel. LPS246 had the highest *CDK4* gene copy number vs. LPS815 and LPS863 (1373, 533, 563 transcripts per cell, respectively) and showed a greater sensitivity to both docetaxel and eribulin compared to LPS815 and LPS863 in cell viability assays. Pharmacologic inhibition of CDK4 demonstrated drug antagonism (avg. CI > 1.3). **Conclusions:** These data suggest that MDA sensitivity in DDLPS may be associated with levels of *CDK4*. Prospective clinical trials are needed to confirm whether CDK4 expression levels may predict response to eribulin and other microtubule disrupting agents.

11582 Poster Session (Board #327), Sat, 8:00 AM-11:30 AM

Combination of CDK and Bcl-2 inhibitors in the treatment of soft-tissue sarcomas. *First Author: Xavier Garcia del Muro, Instituto Catalan de Oncologia de Hospitalet, Barcelona, Spain*

Background: Soft tissue sarcomas (STSs) present high mortality rates when metastatic and therefore identification of new active therapies is needed. Dinaciclib is a promising CDK inhibitor under evaluation in clinics, targeting principally CDK1 and CDK9 (involved in cell cycle and transcription regulation). BH3-mimetics are a promising new class of pro-apoptotic drugs for cancer treatment. **Methods:** We analyzed the response to Dinaciclib in a series of different STSs established cell lines, as apoptotic induction visualized in Flow Cytometry. Cell lines were categorized as Dinaciclib-sensitive and Dinaciclib-tolerant. Differences were studied by relevant protein expression changes during treatment leading to hypothesis proposal for key regulators. Validation of targets was performed by siRNA technology prior to engage in drug combination testing. *In vivo* experiments encompassed drugs safety and effectivity. **Results:** Dinaciclib induced apoptotic cell death, with important differences in the extent and timing among cell lines. Liposarcoma 402-91 was the most sensitive (cell death $> 75\%$ after 72 h), whereas leiomyosarcoma SK-LMS-1 was highly tolerant to Dinaciclib (cell death $< 25\%$). Major partners in cell cycle and apoptosis induction signaling networks were affected by Dinaciclib treatment. The inhibition status of anti-apoptotic protein Bcl-x_L was identified as the main determinant of the rhythm and extent of apoptosis triggering. *In vitro* combination of Dinaciclib with chemical Bcl-x_L inhibitors (ABT-747 and A-1331852) overcame tolerance and triggered massive cell death in cultures (95% of cell death after 24 h). Once safely scalated to mice experimentation, drug combination effectiveness on mice engrafted tumors is currently ongoing. **Conclusions:** CDK inhibitors are active in STSs cell lines. The inhibition status of Bcl-x_L can be considered as a predictor of Dinaciclib sensitivity in STS. Combinatorial strategies with CDK inhibitors and BH3-mimetics are worth examination as a new proposal for STS treatment.

11583 Poster Session (Board #328), Sat, 8:00 AM-11:30 AM

Identification of histone deacetylase 2 (HDAC2) as a novel target for MDM2 directed therapies in dedifferentiated liposarcoma. *First Author: Colin W Stets, The Ohio State Comprehensive Cancer Center, Columbus, OH*

Background: Dedifferentiated liposarcoma (DDLPS) is a common, but morbid mesenchymal tumor driven by amplifications in the mouse double minute 2 homolog (MDM2) gene. Prior studies have indicated that pan-HDAC inhibition may be able to lower MDM2 levels in vitro. However, there are multiple HDAC isoforms and pan-HDAC inhibitors used in the clinic have significant toxicities. We hypothesize that isoform specific HDAC inhibition may achieve modulation of MDM2 and limit the toxicities associated with pan-HDAC inhibition. We report here that HDAC2 is sufficient to lower the expression of MDM2 and improve tumor response to doxorubicin in DDLPS *in vitro* and *in vivo*. **Methods:** Bioinformatics analysis of RNA-Seq data from DDLPS cell lines was used to identify HDAC proteins associated with MDM2 expression. Potential targets were validated using shRNA mediated knockdown and pharmacologic agents. We examined and quantified MDM2 protein expression via immunoblotting. Cytotoxicity was determined using XTT reagents *in vitro*. Synergy calculations were performed using the Chou-Talalay algorithm on *in vitro* cytotoxicity assays. *In vivo* response was measured using mouse xenograft models. **Results:** Small molecule pan-HDAC inhibitor AR42 and HDAC2 specific inhibitor Mi-192 decreased MDM2 expression (2.5-fold and 7.1 fold decrease, respectively) and induced a 6500-fold increase in the expression of the tumor suppressor P21. HDAC2 shRNA knockdown further corroborated the HDAC2 specific effect on MDM2 expression (5-fold reduction). *In vitro* synergism with doxorubicin in DDLPS (cooperativity index < 0.7) was observed across a range of HDAC2i concentrations. In mouse xenograft model, MI-192 significantly reduced tumor volume ($p = 0.02$) without the induction of MDM2 mRNA expression. **Conclusions:** HDAC2 specific inhibition lowers MDM2 expression and synergizes with doxorubicin in DDLPS cell lines and slows tumor growth *in vivo*. Prospective clinical studies are necessary to confirm these findings.

11584 Poster Session (Board #329), Sat, 8:00 AM-11:30 AM

Immune signature in sarcoma with prognostic and predictive implications. *First Author: Shailaja KS Raj, Wake Forest School of Medicine and VAMC, Winston-Salem, NC*

Background: While immunotherapy has established its benefit in the management of many solid tumors, its efficacy in sarcoma is still not well understood. In this study, we sought to evaluate the protective effects of intrinsic anti-tumor immunity in sarcoma by analyzing genomic measures of immune response and tumor immunogenicity in a multi-institutional convenience cohort of sarcoma patients. **Methods:** Publicly available RNAseq and exome mutation data were assembled from The Cancer Genome Atlas (TCGA) sarcoma cohort ($n = 259$). For each tumor, a relative measure of abundance of tumor-infiltrating effector immune cells was estimated using three previously published immune gene signatures, reflective of T-cells, cytotoxic T lymphocytes and/or natural killer cells derived from co-expressed, leukocyte-specific genes (named CYT, CD8T and T/NK). Tumor mutational burden (TMB), expressed as the rate of non- synonymous mutations per megabase of sequenced DNA, was used as a measure of tumor immunogenicity. Interactions between immune infiltration, tumor immunogenicity and patient overall survival (OS) were assessed by Cox regression and Kaplan-Meier analysis. **Results:** In the full cohort, the 3 immune signatures were highly correlated with one another and univariately associated with patient OS (T/NK; $p < 0.001$; CYT; $p < 0.001$ and CD8; $p = 0.004$ Cox regression). A single immune signature T/NK, selected for further analyses was associated with OS in TMB-high tumors ($p < 0.001$) but not TMB-low tumors ($p = 0.129$). Univariable and multivariable survival analysis of T/NK with significant variables included age, and tumor size, that were significant. **Conclusions:** Our findings fit a model where patients whose tumors were characterized by a TMB-high genotype and elevated effector immune infiltration exhibited the highest survival rates ($p < 0.035$). In the full cohort multivariable analysis we showed that T/NK remained a significant prognostic factor independent of age, tumor size, radiation therapy, margin status, tumor necrosis and subtype analysis indicating that the T/NK signature provided additive prognostic information and can utilized in the future for therapeutic stratification.

11585 Poster Session (Board #330), Sat, 8:00 AM-11:30 AM

Lack of cardiac toxicity in patients treated with aldoxrubicin with doxorubicin equivalent doses beyond 1000mg/m2. *First Author: Kamalesh Kumar Sankhala, Sarcoma Oncology Center, Santa Monica, CA*

Background: Aldoxrubicin is classical Doxorubicin with a linker which rapidly binds to albumin on IV administration. Doxorubicin, either alone or in combination with ifosfamide, is still considered standard therapy for sarcomas. Aldoxorubicin alone or in combination with ifosfamide have been shown to improve antitumor activity and lack of cardiac toxicity. The allowable maximum cumulative lifetime dose of doxorubicin is 550 mg/m2. We report on the evaluation of cardiac function in patients who received aldoxorubicin with Doxorubicin equivalent at doses beyond 1000 mg/m2. **Methods:** Fifty-two patients enrolled in a Phase 1/2 study of aldoxorubicin and ifosfamide/mesna and a Phase 3 study using aldoxorubicin alone were treated for at least 6 cycles of aldoxorubicin at either 250 mg/m2 or 350 mg/m2 per dose i.v. every 3 weeks. Cardiac function using 2D echocardiogram was evaluated at regular intervals every two cycles of aldoxorubicin until end of treatment and every six months after completion of the treatment. **Results:** In eleven patients, the median cumulative doxorubicin dose prior to aldoxorubicin treatment was 158 (range: 64-360) mg/m2. The cumulative aldoxorubicin dose ranged from 1000 to 7500 mg/m2. No patient developed any sign or symptom of clinical congestive heart failure. Ventricular ejection fractions ranged from 45-74% baseline, and 50-77% at end of treatment, median being 60% both at the beginning and end of treatment. **Conclusions:** Aldoxorubicin lacks cardiotoxicity in these patients treated with aldoxorubicin alone or in combination with ifosfamide/mesna. We did not find any evidence of cardiac toxicity of aldoxorubicin up to doxorubicin equivalent dose of 7500mg/m2. Clinical trial information: NCT# 02235701.

TPS11586 Poster Session (Board #331a), Sat, 8:00 AM-11:30 AM

A phase I trial of pomalidomide in combination with liposomal doxorubicin in the treatment of advanced or refractory Kaposi sarcoma in individuals with or without HIV. *First Author: Ramya Ramaswami, HIV/AIDS Malignancy Branch, CCR, NCI, Bethesda, MD*

Background: Kaposi sarcoma (KS) is a multicentric angioproliferative tumor caused by the gammaherpesvirus Kaposi-sarcoma herpesvirus (KSHV, or human herpesvirus 8 [HHV-8]) that is commonly seen among people living with HIV. KSHV also contributes to the pathogenesis of multicentric Castleman disease (KSHV-MCD) and KSHV inflammatory cytokine syndrome (KICS). Advanced KS can occur alone or in combination with KSHV-MCD or KICS. KS can be difficult to treat when it occurs with KSHV-MCD or KICS and can result in high mortality rate. Pomalidomide is an orally available third generation thalidomide analog with immunomodulatory and antiangiogenic properties that has been shown to be safe and to have activity in patients with KS with or without HIV. Liposomal doxorubicin (LD) is a preferred treatment for KS. The tolerability and activity of pomalidomide in combination with LD with advanced KS or KS and concurrent KSHV-MCD or KICS are unknown. **Methods:** The primary objective is to evaluate the safety, tolerability and pharmacokinetics of pomalidomide (in escalating dose levels I - 2mg, II - 3mg, or III- 4mg) in combination with liposomal doxorubicin in two groups of patients: Group I) KS requiring systemic therapy; Group II) KS with concurrent KSHV-associated MCD or KICS. Patients will receive LD intravenously on day 1 of a 28-day cycle combined with pomalidomide once a day, days 1 to 21 at a specific dose level. Dose escalation of pomalidomide for each cohort will stop when 2 or more dose-limiting toxicities (DLTs) occur (in a cohort of 3 or 6 patients). Assessment of the KS antitumor effect, using a modified AIDS Clinical Trials Group KS response criteria; effects on manifestations of KSHV-MCD or KICS in those patients with these diseases; and changes in quality of life in patients receiving pomalidamide and LD will be evaluated. Patients with confirmed cutaneous, pulmonary or visceral KS are eligible. Adherence to combination antiretroviral therapy for 1 month is required for participants in Group I except for those with progressive disease or end-organ disease. The study began enrollment in January 2016. Clinical trial information: NCT02659930.

TPS11587 Poster Session (Board #331b), Sat, 8:00 AM-11:30 AM

PEMBROSARC combination of MK3475 and metronomic cyclophosphamide (mCP) in patients (pts) with advanced sarcomas a multicentre phase II trial with 3 new combination strategies. *First Author: Maud Toulmonde, Institut Bergonié, Department of Medical Oncology, Bordeaux, France*

Background: PD-L1 is expressed in soft tissue sarcomas (STS) but PD-1 inhibition alone has limited activity. This primary resistance may partly be explained by IDO pathway activation. Epigenetics modifications have also been recognized as mechanisms of resistance to PD-1 inhibition. We hypothesized that the association of MK3475 (PZ) + mCP, either alone or with IDO inhibitor Epacadostat (EP), TLR4 agonist G100 or EZH2 inhibitor Tazemetostat (TZ) could have a synergistic activity with good safety in pts with advanced STS, with a focus on Undifferentiated Pleomorphic Sarcoma (UPS). **Methods:** This is a multicenter, prospective open-labeled single-arm phase II trial with ten independent strata assessing: PZ 200 mg IV on day 8 of a 3 weeks cycle, mCP 50 mg b.i.d. orally one week on /one week off: - in leiomyosarcoma (stratum 1), UPS (stratum 2), other STS (stratum 3), osteosarcoma (stratum 4) and GIST (stratum 5) - + EP orally 100 mg b.i.d. in UPS (stratum 6) and other STS (stratum 7) - + G100 intratumor at 20 μg once weekly for 6 weeks in STS (stratum 8) - + TZ orally 800 mg b.i.d. in UPS (stratum 9) and other STS (stratum 10) Main eligibility criteria are - adult pts with metastatic or unresectable locally advanced, histologically confirmed sarcoma by central review, - measurable progressive disease (RECIST v1.1) – no more than 2 previous lines of systemic treatment – PDL1 and/or IDO expression on immune cells $>$ 1% on $<$ 3 months old tumor sample (strata 6 and 7) Primary endpoint is 6-month non progression as per RECIST v1.1. Secondary endpoints encompass toxicity according to NC-CTCAE v4.03, best overall response RECIST v1.1, 1-year progression-free survival and overall survival, growth modulationi, pharmacodynamics on mandatory collection of blood and tumor samples at baseline and on treatment. Each strategy will follow a 2-stage Simon's design. PZ+mCP + either EP, G100 or TZ will be considered promising if at least 8 non-progressions at 6 months are observed among 29 evaluable pts. In this regards, 32 pts will be recruited in each stratum. Strata 1-3, 5 have been reported. Stratum 4 is on hold for intermediate analysis. Opening of strata 6-10 is awaited by June 2018. Clinical trial information: NCT02406781.

TPS11588 Poster Session (Board #332a), Sat, 8:00 AM-11:30 AM

SU2C-SARC032: A phase II randomized controlled trial of neoadjuvant pembrolizumab with radiotherapy and adjuvant pembrolizumab for high-risk soft tissue sarcoma. *First Author: Yvonne Marie Mowery, Duke University Medical Center, Durham, NC*

Background: Radiotherapy (RT) and surgical resection achieve local tumor control for most large, high-grade soft tissue sarcomas (STS) of the extremity. However, many patients (pts) subsequently develop metastatic disease that is associated with median survival $<$ 2 yr. SARC028 (NCT02301039), a phase II clinical trial of pembrolizumab (pembro) for metastatic sarcoma, showed promising results with PD-1 blockade with RECIST 1.1 responses in 40% of undifferentiated pleomorphic sarcoma (UPS) pts and 20% of liposarcoma (LPS) pts. RT can augment the anti-tumor immune response and synergize with immune checkpoint blockade. We hypothesized that anti-PD-1 therapy with concurrent RT will stimulate a host immune response to eliminate micrometastatic deposits of STS, preventing progression to metastatic disease. To test this hypothesis, we opened SU2C-SARC032 (NCT03092323) in July 2017. This multi-institutional (11 of 12 US sites open; 5 international sites planned) randomized phase II trial is examining the safety and efficacy of neoadjuvant pembro with RT and adjuvant pembro for high-risk STS. **Methods:** Eligible patients for SU2C-SARC032 are adults with non-metastatic UPS or dedifferentiated/pleomorphic LPS of the extremity or limb girdle (FNCLCC grade 2 or 3, tumor $>$ 5 cm; stage III). Patients are randomized to neoadjuvant RT (50 Gy/25 fractions) then surgical resection vs neoadjuvant pembro and RT followed by surgical resection and adjuvant pembro. Pts receive 200 mg pembro Q3 wk for 3 neoadjuvant cycles (before, during and after RT) and up to 14 adjuvant cycles (1 yr of pembro). The primary endpoint is 2-yr disease-free survival (DFS). Target enrollment is 110 pts to achieve 51 evaluable pts/arm. This provides 80% power with a = 0.05 to distinguish between a null hypothesis of 50% 2-yr DFS and alternative hypothesis of 75% 2-yr DFS using a logrank test. Tumor specimens (pre- and post-neoadjuvant therapy) and blood will be collected for correlative studies including immunophenotyping, whole exome sequencing, RNAseq, and circulating tumor DNA analysis. Four pts have accrued. A planned toxicity evaluation is ongoing for the first 3 pts on pembro. Clinical trial information: NCT03092323.

TPS11589 Poster Session (Board #332b), Sat, 8:00 AM-11:30 AM

Mutational analysis and safety/efficacy in a phase 2 multi-center investigation of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa). *First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA*

Background: PEComas are rare mesenchymal tumors with a female predominance, composed of epithelioid cells that show a focal association with blood vessel walls and usually express both melanocytic and smooth muscle markers. The prognosis of advanced malignant PEComa is poor, with a median survival of 12-17 months. There have been no prospective trials for PEComa. Case reports have shown that PEComas are often associated with the loss of tumor suppressor genes *TSC1* or *TSC2* which results in downstream activation of the mTOR complex, making mTOR inhibition a promising therapeutic strategy. ABI-009, albumin-bound rapamycin nanoparticle, is a novel mTOR inhibitor that can utilize albumin-mediated transport pathways to achieve enhanced tumoral drug delivery. This is the first prospective open-label multicenter study to assess mutational status and safety/efficacy of an mTOR inhibitor for advanced PEComa. **Methods:** At least 30 patients naive to mTOR inhibitors, with pathologically confirmed malignant PEComa that is either metastatic or locally advanced and for which surgery is not a recommended option, will be enrolled. ABI-009 at 100 mg/m^2 IV, is given weekly for 2 out of 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The primary endpoint is overall response rate (ORR) assessed with CT/MRI scans via RECIST v1.1. This sample size will be sufficient to exclude an inactive regimen ($<$ 15% ORR) with 95% confidence. Secondary endpoints are duration of response, 6-month progression-free survival (PFS), median PFS, median overall survival, and safety. Patient tumor mutational analysis, including exome sequencing of 300 genes including TSC1/2 and mTOR pathway genes, and circulating DNA analysis, will be performed. Exploratory endpoints include PK/PD relationships for safety and/or efficacy endpoints, and correlative studies with baseline TSC mutational analysis and tumor biomarkers. The study is ongoing as of February 2018. Clinical trial information: NCT02494570.

TPS11590 Poster Session (Board #333a), Sat, 8:00 AM-11:30 AM

TAPPAS: An adaptive enrichment phase 3 trial of TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcoma. *First Author: Vinod Ravi, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Angiosarcoma (AS) is an aggressive soft tissue sarcoma (STS) of endothelial origin with reported median OS of 8-12 months. Pazopanib (P) is approved for treatment of advanced STS refractory to an anthracycline. In a retrospective study of 40 AS patients treated with single agent P, median PFS was 3.1 months and median OS 9.9 months with a low response rate and no complete responses. Endoglin is an essential angiogenic receptor expressed on AS that is upregulated following VEGF inhibition. TRC105, an endoglin antibody, combined with P achieved durable complete responses in two of 18 AS patients, with median PFS of 7.8 months in chemotherapy-refractory and P-naïve patients enrolled in a Phase 1/2 trial. The TAPPAS Phase 3 trial was initiated following protocol assistance from the EMA and Special Protocol Assessment from the FDA. **Methods:** TAPPAS (NCT02979899) is a randomized multicenter study of TRC105/P vs P alone actively enrolling cutaneous and non-cutaneous AS patients at $>$ 25 sites in the United States and Europe, and incorporates an adaptive enrichment design. Key inclusion criteria: 0, 1 or 2 prior lines of therapy, ECOG $\leq$ 1. Primary endpoint is PFS. Secondary endpoints include ORR and OS. The initial sample size of 124 patients, followed until 95 PFS events, provides more than 80% power to detect a hazard ratio of 0.55. At the time of interim analysis, projected to occur upon the occurrence of 40 events in approximately 70 patients, the trial will be classified as belonging to either the favorable, promising, enrichment or unfavorable zones, based on conditional power. Sample size and PFS events will be unchanged in the favorable and unfavorable zones, and will be increased to a total of 200 patients followed for 170 events in the promising zone. The trial will enroll a total of 135 patients with cutaneous disease followed for 110 events in the enrichment zone. An independent Data Monitoring Committee will follow the trial for safety and futility and recommend sample size or population adaptation. The adaptive design permits enrollment of fewer and more responsive patients over a shorter time compared to a fixed sample size design, while preserving type-1 error. Clinical trial information: NCT02979899.

TPS11591 Poster Session (Board #333b), Sat, 8:00 AM-11:30 AM

Phase 1/2 study of safety/efficacy using trabectedin, ipilimumab and nivolumab triple therapy as first line treatment of advanced soft tissue sarcoma. *First Author: Erlinda Maria Gordon, Sarcoma Oncology Center, Santa Monica, CA*

Background: Sarcoma cells are most immunogenic at the onset of cancer when the immune system can recognize and destroy them (Schreiber 2011). Hence, immune checkpoint inhibitors would be most effective when given as first line therapy. Objectives: Primary: To investigate the maximum tolerated dose of trabectedin, an alkylating agent, when given sequentially with ipilimumab, a CTLA4 inhibitor, and nivolumab, a PD-1 inhibitor, in advanced STS. Secondary: To investigate the objective response rate (ORR), progression free survival (PFS) and overall survival (OS). Exploratory: To correlate PFS with PD-L1 and other biomarker expression in patients' tumors. **Methods:** Forty patients $\geq$18 years of age with advanced STS will be enrolled. This is an open label, dose-seeking phase $^1/_2$ study using a defined dose of ipilimumab (1 mg/kg i.v. q 12 weeks), nivolumab (3 mg/kg i.v. q 2 weeks), and escalating doses of trabectedin (1.0, 1.3, 1.5 mg/m^2 i.v. q 3 weeks). I. Dose Escalation Phase 1 (previously treated patients): The study will employ the standard "cohort of three" design. The maximum tolerated dose is defined as the highest safely tolerated dose, where not more than one patient experienced DLT, with the next higher dose level having at least two patients who experienced DLT. II. Expansion Phase 2 (previously untreated patients): An additional 22-28 patients will receive trabectedin at the MTD and defined doses of ipilimumab and nivolumab to assess overall safety and potential efficacy in a greater number of patients. Patients may continue treatment until significant disease progression or unacceptable toxicity occurs. Statistical Considerations: NIH CTCAE v4.03 and RECIST v1.1 will be used. Categorical variables will be summarized by the n and percent in each category. Point estimates for efficacy endpoint incidences will be accompanied by a 2-sided 95% exact binomial CI. Time to event endpoints will be summarized descriptively using the KM method. The analyses of all study objectives will be descriptive and hypothesis generating, for planning Phase 2/3 studies. Clinical trial information: NCT 03138161.

12000 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Association of high tissue TMB and atezolizumab efficacy across multiple tumor types. *First Author: Fatema A. Legrand, Roche/Genentech, South San Francisco, CA*

Background: PD-L1 expression has limitations as a biomarker for checkpoint immunotherapy (CI). Prior atezolizumab (atezo) monotherapy studies suggest improved efficacy in high tissue tumor mutational burden (tTMB-H) cohorts. We report a large retrospective analysis associating tTMB with neoantigen load (NAL) and CI efficacy across multiple studies, tumor types and lines of therapy. **Methods:** Tissue TMB was evaluated by the FoundationOne (F1) assay across 7 atezo monotherapy studies: NSCLC n= 342 (FIR, BIRCH, POPLAR, OAK), metastatic urothelial carcinoma (mUC) n=400 (IMvigor210, 211), and other advanced solid tumors n=245 (PCD4989g). Pooled data yielded a biomarker evaluable population (BEP) of 987 patients (pts); 175 (17.7%) had TMB-H defined as ≥16 mutations/megabase (mut/Mb). Efficacy endpoints were overall response rate (ORR) and duration of response (DoR). Survival analysis is ongoing. Neoantigen load (NAL) was calculated by whole-exome sequencing (WES) and RNA-Seq. **Results:** tTMB was associated with efficacy across tumor types and lines of therapy. In the BEP, ORR was 16.4% (95% CI 14.2, 18.9), vs. 29.7% (95% CI 23.1, 37.1) in tTMB-H (≥16 mut/Mb, N=175), and 13.5% (95% CI 11.3, 16.1) in tTMB-Low (<16 mut/Mb, N=812). DoR benefit was also observed: median DoR=29.0 mths (95% CI 18.6, NA) in tTMB-H vs. 16.6 mths (95% CI 13.8, 23.1) in BEP and 13.8 mths (95% CI 12.5, 17.4) in tTMB-Low cohorts. This association was not seen in control cohorts of randomized studies OAK, POPLAR, and IMvigor211. Pooled ORR in controls was 14.9% in BEP, 14.4% in tTMB-H and 15.1% in tTMB-Low. Survival analysis by tTMB is ongoing. tTMB-H also identified a population independent of PD-L1 status. tTMB by F1 was positively correlated with WES-based NAL in mUC (Pearson=0.85, N=218) and NSCLC (Pearson=0.78, N=70). NAL was associated with atezo ORR in mUC (p=2.7 x 10-9). **Conclusions:** High tTMB (≥16 mut/Mb) is associated with improved atezo response and DoR across NSCLC, mUC and melanoma and lines of therapy. tTMB-H by F1 may serve as a surrogate biomarker for NAL and may complement PD-L1 expression in providing predictive value. Ongoing studies are prospectively evaluating both tissue TMB and blood-based TMB for efficacy with CI. Clinical trial information: NCT02008227 NCT01903993 NCT02031458 NCT01846416 NCT02951767 NCT02302807 NCT01375842.

12001 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Prospective clinical evaluation of blood-based tumor mutational burden (bTMB) as a predictive biomarker for atezolizumab (atezo) in 1L non-small cell lung cancer (NSCLC): Interim B-F1RST results. *First Author: Vamsidhar Velcheti, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Background: TMB in both tissue and blood has shown promise in selecting for patients (pts) who clinically benefit from PD-L1/PD-1 inhibitors. In the randomized, 2L NSCLC Phase III OAK and Phase II POPLAR studies, high bTMB enriched for a PFS benefit in patients treated with atezo monotherapy. Here we report interim results from the single-arm, 1L NSCLC Phase II B-F1RST atezo monotherapy trial, which prospectively evaluated bTMB as a predictive biomarker for atezo using an NGS-based panel. **Methods:** Of 78 treated pts in the interim analysis population (IAP), 58 had adequate blood samples with sufficient detection of circulating tumor DNA (MSAF≥1%) and comprised the biomarker-evaluable population (BEP). A bTMB score of 16 (prevalence, 19% [11/58]) was prespecified to evaluate clinical efficacy in the BEP (bTMB high, ≥16; bTMB low, < 16). Statistical tests were 2-sided at a 0.1 level and 90% confidence interval. **Results:** Baseline characteristics were similar in the IAP and BEP. With a minimum follow-up of 6 mo, median PFS was 9.5 vs 2.8 mo for bTMB high vs low; HR, 0.49 (90% CI, 0.23, 1.04; *P*= 0.11). PFS HRs improved as bTMB scores increased (Table). In the BEP, the ORR was 12.1% (7/58) and disease control rate was 25.9% (15/58). In the bTMB high vs low groups, the ORR was 36.4% (4/11) vs 6.4% (3/47); odds ratio, 8.38 (90% CI, 2.02, 34.79; *P*= 0.02). Treatment-related serious AEs and treatment-related grade 3/4 AEs occurred in 14.1% and 16.7% of pts, respectively; 15.4% experienced AEs leading to discontinuation. **Conclusions:** PFS by various bTMB scores show preliminary utility of bTMB as a predictive biomarker for PFS and ORR, and further support bTMB selection of patients in the ongoing 1L BFAST study (NCT03178552). The safety profile in B-F1RST is consistent with the known AE profile for atezo. Additional biomarker and clinical data will be reported. B-F1RST is ongoing and has completed enrollment at 153 patients. Clinical trial information: NCT02848651.

PFS (mo) by bTMB cutoff scores (BEP, n = 58).

bTMB Score	bTMB High Median (n)	bTMB Low Median (n)	HR	90% CI
12	3.0 (22)	3.2 (36)	0.95	0.55, 1.63
14	3.4 (14)	3.2 (44)	0.73	0.39, 1.39
16	9.5 (11)	2.8 (47)	0.49	0.23, 1.04
20	9.5 (8)	2.7 (50)	0.23	0.08, 0.62

12002 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Multiplexed analysis of myeloid cell (MC) markers to characterize the innate immune composition and clinical features of human non-small cell lung carcinomas (NSCLC). *First Author: Brian S. Henick, Yale School of Medicine, New Haven, CT*

Background: Despite innate immunity's prominent role in the anti-tumor response, little is known about the MC composition of human NSCLC. We used multiplexed quantitative immunofluorescence (QIF) to determine MC subtypes' distribution, functional state and clinical significance in large cohorts. **Methods:** We established a novel QIF panel to map distinct MC subsets in fixed human NSCLC including DAPI for all cells, pancytokeratin for tumor-epithelial cells, CD11b for all MCs, CD68 for M1-type macrophages and HLA-DR to interrogate maturation state/antigen-presenting potential. We interrogated 834 NSCLC represented in 5 tissue microarray-based cohorts: #1 (Yale, n = 55) with patient-matched NSCLC and morphologically-normal lung tissue; #2 (Yale, n = 379) and #3 (Greece, n = 230) with different/mixed NSCLC subtypes; #4 (Yale, n = 138) with molecularly annotated lung adenocarcinomas (ADC); and #5 (Yale, n = 32) including baseline samples from anti-PD-1-treated patients. We examined associations between marker levels, MC-profiles, clinicopathologic/molecular variables and survival. **Results:** Stromal CD11b-levels were significantly higher in tumor than in non-tumor lung tissues. HLA-DR was consistently higher in MCs from tumors with elevated CD68 expression, supporting a more mature phenotype. Stromal CD11b was significantly higher in squamous-cell carcinomas (SCC) than ADC across the cohorts. In SCC, increased stromal CD11b or HLA-DR expression was associated with shorter 5-year survival. EGFR-mutated lung ADC had significantly lower CD11b levels than KRAS-mutant ADC. In a limited sample set/preliminary analysis, MC markers did not significantly stratify clinical benefit to PD-1 axis inhibitors (cohort #5). **Conclusions:** NSCLCs contain more tumor-associated MCs than non-tumor lung and exhibit distinct myeloid compositions across histologies and presence of major oncogenic driver-mutations. ADC lacking EGFR variants and SCC display higher stromal MC content associated with worse outcome. Studies with larger datasets are ongoing to confirm the role of MC markers for prediction of sensitivity/resistance to PD-1 axis blockers.

12003 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Prevalence of clonal hematopoiesis of indeterminate potential (CHIP) measured by an ultra-sensitive sequencing assay: Exploratory analysis of the Circulating Cancer Genome Atlas (CCGA) study. *First Author: Charles Swanton, Translation Cancer Therapeutics Laboratory, The Francis Crick Institute, London, United Kingdom*

Background: CHIP is defined by the presence of age-dependent acquired mutations in hematopoietic progenitor cells and has been reported to occur in up to 30% of individuals 60-70 years of age. CHIP is a risk factor for hematologic malignancies and cardiovascular disease; its biological mechanisms and clinical significance are just now being studied. Using an assay ~100X more sensitive than exome sequencing, we determined the prevalence and features of CHIP in the CCGA cohort, and the impact on interpretation of cell-free DNA (cfDNA) somatic variants. **Methods:** Blood was prospectively collected (N = 1627) from 749 controls (no cancer, C) and 878 participants (pts) with newly-diagnosed untreated cancer (20 tumor types, all stages) for WBC and cfDNA isolation. Paired white blood cell (WBC) and cfDNA targeted sequencing (507 genes, 60,000X median coverage) identified somatic single nucleotide variants/indels. Unique molecular barcodes and a machine learning-based noise model achieved a specificity of 1 false positive variant call per Mb of genome targeted at a limit of detection of ~0.1% variant allele frequency (VAF). **Results:** 1412 samples were eligible and evaluable (576 C, 836 pts; 18 solid tumor types, all stages). Of somatic cfDNA variants matched in WBC (CHIP), 7% of individuals had CHIP with VAF > 10%, 39% had CHIP with VAF > 1%, and nearly all pts (92%) had a somatic mutation with VAF > 0.1%. The rate was similar between C and pts (median age 62, 60), increasing in prevalence by 160% per decade, such that we observed 2.5 variants/Mb at age 60. Of CHIP variants identified, 92% were unique to individual patients, most of which were present at low VAF. Genes impacted by CHIP included *DNMT3A* (40%), *TET2* (27%), and *TP53* (10%), consistent with previous reports in patients with solid tumors. **Conclusions:** An ultra-sensitive sequencing assay demonstrated that CHIP signal in WBC and cfDNA is much more common than previously appreciated. The clinical significance of CHIP warrants further study and must be accounted for when interpreting cfDNA variants for both early cancer detection and tumor genotyping (liquid biopsy). Clinical trial information: NCT02889978.

12004 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Confounding effects of clonal hematopoiesis in clinical genomic profiling of solid tumors. *First Author: Ahmet Zehir, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clonal hematopoiesis (CH) is the somatic acquisition of genomic alterations in hematopoietic stem/progenitor cells, leading to clonal expansion. While a few reports showed CH-derived mutations can contaminate solid tumor sequencing results, a comprehensive analysis has not been reported before. Here, we set out to identify and quantify CH-related mutations in patients with solid tumors using matched tumor-blood sequencing, and to establish the proportion that would be misattributed to the tumor from unmatched analysis. **Methods:** We retrospectively selected 17,469 solid tumor patients that underwent prospective clinical sequencing of DNA isolated from tumor tissue and matched peripheral blood using the MSK-IMPACT assay between January 2014 and August 2017. We identified the presence of CH-related mutations in each patient's blood leukocytes by performing mutation calling in the blood and genotyping the tumor DNA at the mutated positions. We then considered variants passing our detection thresholds for somatic mutation calling in tumor NGS data to quantify the prevalence of CH alterations detected in solid tumor specimens. **Results:** We identified 7,608 CH-associated mutations in the blood of 4,628 (26.5%) patients. 14% of CH-associated mutations (n = 1,075) were also detectable in the matched tumor above established thresholds for calling somatic mutations. In total, 5% of the patients (n = 912) would have had at least one CH-associated mutation erroneously called as tumor-derived in the absence of matched blood sequencing. 99% of these mutations were absent from population scale databases of germline polymorphisms (ExAC and gnomAD) and therefore would have been challenging to filter informatically. Of these, 534 were identified as oncogenic or likely oncogenic based on OncoKB database and 3% of the oncogenic mutations were associated with clinical actionability. **Conclusions:** Our results demonstrate how CH-derived mutations could lead to erroneous reporting and treatment recommendations when tumor-only sequencing is employed.

12005 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Whole exome sequencing (WES) to define the genomic landscape of young lung cancer patients (pts). *First Author: Xiaoliang Wu, West Virginia University Cancer Institute, Morgantown, WV*

Background: Previous studies have identified specific genomic driver alterations in non-small cell lung cancer (NSCLC). However, the causative molecular mechanisms that underlie the pathogenesis of most lung cancers in young patients (pts) remain largely undefined. We hypothesized that the key driving molecular events underlying lung cancer in young pts differ from that in older pts. **Methods:** We identified 45 pts diagnosed with NSCLC at an age $\leq$45 (median: 41; range: 21-45), at Cleveland Clinic, USA (2000-12) (n = 17) and Sun Yet-sen University Cancer Center, China (2007-13)(n = 28), with primary tumors or metastatic lesions sufficient for WES. Tumor histology was adenocarcinoma (n = 29), squamous cell (n = 13), mucous epidermoid (n = 2) and large cell (n = 1). Thirty two pts were female (71%). There were 34 non/never smokers, while others had a median smoking history of 30 pack-year. Genomic DNAs from both FFPE tumors and paired-normal lung tissues/peripheral blood were analyzed by WES (Illumina HiSeq2000). Sequencing reads were cleaned and then aligned to the human genome using the BWA algorithm. The aligned data were sorted, validated and indexed. Somatic variants were identified using GATK (genome analysis toolkit)(https://gatkforums.broadinstitute.org/gatk) and the Mutect 2 algorithms. The location and predicted functional impact of the somatic variants was identified using SnpEff. Pathway enrichment analysis was performed with Enrichr (http://amp.pharm.mssm.edu/ Enrichr). **Results:** Unique mutations associated with young NSCLC but not with other types of lung cancer were identified by comparison with The Cancer Genome Atlas (TCGA) lung cancer mutations in pts $>$ 65 years. Among the 426 unique mutated genes identified in young pts, 125 mutations were predicted to be highly disruptive to protein structure and/or function. Bioinformatic pathway enrichment analysis revealed a number of trending pathways including oxidative ethanol and nicotine degradation pathways (both $p < 0.05$), and TGF-beta receptor signaling enrichment ($p < 0.05$). **Conclusions:** Our study nominates novel biologically relevant candidate genes/pathways involved in young lung cancer pathogenesis that merit further analysis.

12006 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Application of a real world endpoint to identify and characterize genetic profiles of patients (pts) with poor prognosis in advanced non-small-cell lung cancer (aNSCLC). *First Author: Gracy Crane, Roche Products Ltd., Welwyn, United Kingdom*

Background: There is an unmet need to identify and characterize pts who rapidly progress on currently available therapies. Recent availability of linked clinico-genomic information offers an opportunity to characterize genetic profiles of rapid progressors to increase treatment options available to these patients. **Methods:** Pts diagnosed with NSCLC (n=2,139) within the Flatiron (FIH)-Foundation Medicine (FMI) linked database (Jan 2011–Dec 2016) were grouped by treatment class: cancer immunotherapy (CIT), targeted therapy (TKIs) or chemotherapy (CT). A composite real world endpoint of time to treatment failure (rwTTF) $<$2 months was created using the earliest of: a) time to next treatment, or b) real world progression (based on abstraction of clinician's assessment in electronic health records), or c) death within 60 days. A rwTTF $<$2 months was used to define rapid progressive (RPD). Baseline characteristics, overall survival (OS) and genetic profiles by NGS (using FMI) were analyzed for pts with RPD vs non rapid progressive disease (NRPD) by treatment class. **Results:** Baseline characteristics were mostly balanced. Median OS was substantially longer in pts with NRPD vs RPD across treatment classes confirming that the rwTTF definition can be used to identify RPD in real world databases. In CIT median OS was 4.4m (3.32–5.72) in the RPD vs 17.1m (14.26–NA) in the NPRD. In addition, higher tumor mutational burden (TMB) correlated with higher likelihood of response to CIT (median TMB was 9.9 (3.60–15.31) in NRPD patients vs. 5.4 (2.70–9.91) in RPD patients). This difference was not observed in the TKI or CT groups. In the CIT group, *HER2* and *EGFR* mutations were suggestive of an association with RPD status; however, *EGFR* and *BRAF* mutations were suggestive of an association with NRPD in the CT group. In the TKI group, CDKN2A/CDKN2B copy number variants were suggestive of an association with NRPD status. **Conclusions:** Applying a real world endpoint, we identified and characterized genetic profiles of pts with rapid progression. Rapid advances in data capture and linkage availability and quality can help with optimal management of patients at the point of care.

12007 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Liquid biopsy to predict benefit from rechallenge with cetuximab (cet) + irinotecan (iri) in RAS/BRAF wild-type metastatic colorectal cancer patients (pts) with acquired resistance to first-line cet+iri: Final results and translational analyses of the CRICKET study by GONO. *First Author: Daniele Rossini, Department of Translational Research and New Technologies in Medicine and Surgery, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana, Istituto Toscano Tumori, Pisa, Italy*

Background: CRICKET (NCT02296203) was designed to investigate the activity of the rechallenge with cet and iri as 3rd-line treatment in *RAS/BRAF* wild-type mCRC pts with acquired resistance to 1st-line cet- and iri-based therapy. The role of liquid biopsies as a tool to identify pts more likely to benefit from this strategy was investigated. **Methods:** Eligibility criteria included *RAS/BRAF* wild-type status on tissue samples; prior 1st-line iri-based, cet-containing regimen with at least RECIST partial response (PR), 1st-line PFS $\geq$6 months, and progression within 4 weeks after the last cet; prior 2nd-line oxaliplatin- and bevacizumab-based treatment. Pts received 3rd-line cet + iri until PD. The primary endpoint was response rate (RR) according to RECIST v1.1. With p0 = 5%, and p1 = 20%, 1-sided-α and β errors of 0.05 and 0.20, 27 pts were required. The null hypothesis can be rejected if responses are observed in $\geq$ 4 pts. Liquid biopsies were collected at the rechallenge baseline. ctDNA was analyzed with ddPCR for specific *RAS/BRAF* mutations (mut), and then by ultra-deep NGS with Ion Torrent S5 XL. **Results:** Between Jan 2015 and Jun 2017, 28 pts were enrolled in 9 centres. The primary endpoint was met. Six PRs (two unconfirmed) and 9 disease stabilizations (RR: 21%,95%CI: 10-40%, disease control rate: 54%,95%CI: 36-70%) were reported. *RAS* mut were found in liquid biopsies collected at the rechallenge baseline in 12 (48%) out of 25 evaluable pts (6 KRAS G12D, 5 KRAS G12V with 1 harboring also Q61H and 1 NRAS Q61L). No *RAS* mut were detected in samples from pts who achieved a confirmed PR. Pts with *RAS* wt ctDNA, had significantly longer PFS than those with *RAS* mut ctDNA (mPFS: 3.9 vs 1.9 mos; HR: 0.48 [95%CI 0.20-0.98], p = 0.048). No *BRAF* or *PIK3CA* mut were found. **Conclusions:** This is the first prospective demonstration of the activity of rechallenge with cet + iri in some mCRC pts initially sensitive and then resistant to first-line iri- and cet-based therapy, with no *RAS/BRAF* mut in pre-treatment liquid biopsies. Partially funded by Merck Serono SpA. Clinical trial information: NCT02296203.

12008 Oral Abstract Session, Tue, 8:00 AM-11:00 AM

Evolution of genomic instability in metastatic cancer. *First Author: Eric Yang Zhao, BC Cancer Agency, Vancouver, BC, Canada*

Background: Although metastasis underlies up to 90% of cancer-related mortality, genomic instability and mutation signatures are mostly studied in primary tumours. Mutation signatures are patterns of somatic mutation resulting from specific mutational processes (i.e. tobacco/UV exposure) and often evolve over time. Recent studies suggest that certain mutation signatures may predict chemotherapy response. Understanding mutational processes in metastatic cancers could uncover actionable targets and refine the understanding of progression and drug resistance. **Methods:** As part of the BC Cancer Agency Personalized Oncogenomics Project, mutation signatures were deciphered from 571 metastatic whole genomes from 12 cancer types totalling 13,249,678 somatic mutations. We created a novel Bayesian hiearchical model named SignIT (github.com/eyzhao/SignIT) to track temporal evolution of mutation signatures. Using real and simulated data, we showed that SignIT decomposes signatures and their temporal evolution more accurately than comparable methods. Previous chemotherapy treatments were catalogued for all patients by retrospective review. **Results:** We discovered 21 distinct mutation signatures, including 9 novel signatures (numbered M1-M9). Mutational processes associated with aging and cigarette smoke were early-arising. Signature 17 and M2 were consistently late-arising across cancer types and metastatic sites. Prior treatment with platinum-based chemotherapy was associated with depression of the homologous recombination deficiency signature 3 ($p = 0.03$). Platinum exposure was also associated with late elevation of signature 17. **Conclusions:** To date, this is the largest study of metastatic cancer whole genomes. Our findings revealed 9 novel mutation signatures, including potential markers of late disease and metastasis. We also observed temporal evolution of mutation signatures correlated with chemotherapy exposures. The association of decreasing signature 3 activity with platinum exposure suggests the restoration of homologous recombination as a resistance mechanism. These findings highlight the complexity of metastatic cancers, and the variety of factors which impact their mutagenesis.

12009 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

Characterisation of the TCR repertoire in NSCLC to reveal the relationship between TCR heterogeneity and genetic heterogeneity that is influenced by mutational load and is associated with disease recurrence. *First Author: Kroopa Joshi, Cancer Immunology Unit, University College London Cancer Institute, London, United Kingdom*

Background: The lung TRACERx study is a prospective study exploring the cancer genome evolution of NSCLC. Data analysis from the first 100 patients enrolled into the study has shown an increased risk of recurrence or death associated with intratumoural genomic heterogeneity. The importance of the phylogenetic clonality of cancer neoantigens in predicting overall survival in NSCLC and response to checkpoint blockade is previously reported. **Methods:** We hypothesised that mutational burden and genomic heterogeneity is reflected in the intra-tumoural T cell receptor (TCR) repertoire. We utilised quantitative high throughput sequencing of α and β chains to explore the TCR repertoire from multi-region tumour specimens, normal lung and PBMC samples from patients within the lung TRACERx study. **Results:** We observed that the TCR repertoire across multi-region tumour specimens was distinct to that observed in normal lung and PBMC. Intratumoural TCR repertoire heterogeneity was found to reflect genomic heterogeneity and was influenced by the tumour mutational load highlighting the potential importance of antigenic dosing in anti-tumour immunity. Moreover, we observed diversification of the TCR repertoire in late stage tumours and disease recurrence was associated with a heterogeneous intra-tumoural TCR response. Alpha and beta chain TCRs re-constructed from single cell RNA sequencing data obtained from T cells reactive to a truncal neoantigen were distributed across all regions of the tumour. **Conclusions:** Taken together, these findings demonstrate a heterogeneous spatial distribution of tumour infiltrating lymphocytes amongst patients with NSCLC. Moreover, our data suggest that TCR clones present across multiple regions of the tumour may expand in response to the presence of truncal neoantigens. The observations described are indicative of a dynamic intra-tumoural T cell response related to the diverse mutational landscape observed in NSCLC.

12010 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

NRG Oncology/NSABP B-31: Stromal tumor infiltrating lymphocytes (sTILs) and outcomes in early-stage HER2-positive breast cancer (BC). *First Author: Rim S. Kim, KU Leuven - University Hospitals Leuven, Leuven, Belgium*

Background: Stromal tumor infiltrating lymphocytes (sTILs) in HER2-positive and triple-negative breast cancer (BC) are associated with prognosis and treatment response. NSABP B-31 evaluated chemotherapy (C) *v* C + trastuzumab (CT) for early-stage HER2-positive BC. **Methods:** Based on International Immuno-Oncology Working Group (IIOWG) guidelines, sTILs were assessed by RSK in 1581/2016 eligible B-31 cases with available slides for H&E review, and as a semi-continuous variable (SCV) in 10% intervals. RSK and five pathologists from the IIOWG reviewed 100 of the cases as a consensus study. sTILs as an SCV and with a predefined lymphocyte-predominant BC (LPBC as $>$ 50% sTILs) were correlated with disease-free survival (DFS), the primary endpoint of B-31. sTILs were also correlated with clinicopathological characteristics, genotyping, intrinsic subtype, gene expression, and mutation profiling. Cox proportional hazard models were used, with p-values < 0.05 considered significant. **Results:** In both the C and CT arms, increases in sTILs, defined either as a SCV (combined arms HR 0.42, 95% CI 0.27-0.64, $p < 0.01$) or as LPBC (combined arms HR 0.65, 95% CI 0.49-0.86, $p = 0.003$), were significantly associated with improved DFS. However, there was no association of sTIL levels with degree of trastuzumab benefit (interaction $p = 0.556$). ER status by IHC was inversely associated with sTILs ($p < 0.01$). High sTILs were significantly associated with basal- and HER2- enriched intrinsic subtypes, and the high-benefit group by 8-gene expression model. None of the PIK3CA mutations or genotyping of Fc gamma receptors were associated with sTILs. The mean concordance between RSK and the other pathologists was 90.8%. **Conclusions:** sTILs were significantly associated with improved DFS in pts with early-stage HER2-positive BC treated with chemotherapy on B-31. However, sTILs were not associated with degree of trastuzumab benefit. sTILs may have utility as a prognostic biomarker to help to define pts with HER2-positive early BC, at low risk for recurrence. Pooled analysis in this clinical context is warranted. SUPPORT: U10CA180868, -180822, UG1-189867, U24-196067, PA DOH; Breast Cancer Research Foundation

12011 Clinical Science Symposium, Mon, 9:45 AM-11:15 AM

WINTHER: An international WIN Consortium precision medicine trial using genomic and transcriptomic analysis in patients with advanced malignancies. *First Author: Jordi Rodon, Vall d'Hebron Institute of Oncology, Barcelona, Spain*

Background: Precision medicine has focused mainly on matching drugs to tumor DNA alterations. However, not all individuals have tractable genomic alterations.We initiated the WINTHER trial to navigate patients to therapy based on either next generation sequencing (NGS) or transcriptomic analysis that compared tumor to normal tissue. **Methods:** Genomics (Arm A) was performed by NGS (N = 236 genes) (Foundation Medicine); transcriptomics (Arm B), by Agilent oligo-arrays (from fresh biopsies). A matching score was calculated for each patient (based on drugs received): for Arm A, number of alterations matched/total number of alterations; for RNA, by adding the reciprocals of the ranks of expression-matched drugs (using a transcriptomic algorithm). The clinical management committee (CMC) (lead investigators from the participating centers in 5 countries) suggested therapies, prioritizing genomic matches if available. The treating physician determined therapy given. **Results:** Overall, 303 patients consented; 107 (35%) received therapy consistent with CMC recommendations: 69 patients (64.5%) on Arm A (DNA-guided); 38 (35.5%), Arm B (RNA-guided). The median number of prior therapies was 3; median age = 59; median performance status = 1 (did not differ between arms). The most common diagnoses were colon, head/neck, and lung cancers. Adverse events after biopsy occurred in 1.2% of patients (1, (unrelated) convulsion; 2, pneumothorax). The rate of stable disease (SD) $\geq$ 6 months plus partial and complete response was 26.2%: Arm A, 23.2%; Arm B, 31.6%. Median progression-free survival (PFS) was 2.1 months (Arm A, 1.9; Arm B, 2.4). In multivariate analysis (hazard ratio (HR), 95% confidence interval (CI)), fewer prior therapies (0.63, 0.40-1.00, $p = 0.048$), better performance status (0.59, 0.37-0.92, $p = 0.020$) and a higher matching score (0.52, 0.33-0.82, $p = 0.005$) correlated with PFS. Higher matching score was also significantly associated with better overall survival (OS). ($p = 0.012$). **Conclusions:** Genomic and transcriptomic analysis were both useful for therapy selection. Higher degrees of DNA and RNA matching independently associated with longer PFS and OS. Clinical trial information: NCT01856296.

12012 Poster Discussion Session; Displayed in Poster Session (Board #125), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Association of loss of adaptive PD-L1 expression with upregulation of PBRM1 chromatin regulator in melanoma. *First Author: Daniel Sanghoon Shin, University of California Los Angeles Medical Center, Los Angeles, CA*

Background: Primary resistance to anti-PD-1 through genetic mechanisms is rare and may be mediated by loss-of-function (LoF) mutations in *JAK1/2* or antigen presentation. 3 out of 48 human melanoma cell lines with complete loss of adaptive PD-L1 expression upon interferon (IFN)-γ exposure, two harbored LoF mutations in *JAK1/2*. The third had intact IFN-γ signaling pathway without LoF mutations. We therefore sought to determine whether an epigenetic mechanism that may result in loss of adaptive PD-L1 expression in this cell line might be an underlying cause of primary resistance in some patients. **Methods:** Human melanoma cell lines that represent good, poorly and non-responding to IFN-γ were analyzed by flow cytometry, gene expression, ChIP-seq and ATAC-seq upon IFN-γ exposure. **Results:** The M412b human melanoma cell line showed no PD-L1 expression in response to IFN-γ exposure despite increased expression of IRF-1, STAT1 and STAT-3. ChIP-seq analysis for IRF-1 in M412B cell line showed no significant enrichment at the PD-L1 promoter compared to three others. ATAC-seq in M412b showed little signal at the PD-L1 promoter, suggesting that M412b cell line lost adaptive PD-L1 expression due to a promoter inaccessible to transcription factors. Peng et al (*Science*, 2018) demonstrated that the PBAF form of the SWI/SNF chromatin remodeling complex is associated with resistance to checkpoint blockade immunotherapy in the B16 murine melanoma model. Miao et al (*Science*, 2018) reported increased response to checkpoint blockade immunotherapy when patients with advanced renal cell carcinoma harbored LoF mutations in the PBRM1 gene. Consistently, M412b cell line displayed the highest PBRM1 and ARID2 expression among 48 human melanoma cell lines, suggesting that constitutive high expression of this chromatin remodeling complex may prevent access to PD-L1 promoter by transcription factors that would otherwise activate the gene in response to IFN-γ signaling. We are now testing this model. **Conclusions:** Lack of adaptive PD-L1 expression upon IFN-γ is associated with increased expression of the PBAF chromatin remodeling complex, which may be an epigenetic mechanism of primary or acquired resistance to anti-PD-1 therapy.

12013 Poster Discussion Session; Displayed in Poster Session (Board #126), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Role of CD4 cells in the complete anti-tumor response to PD1 blockade in a syngeneic murine melanoma model with activated WNT signaling. *First Author: Siwen Hu-Lieskovan, UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Recent data suggested a correlation of active WNT signaling and tumor T cell exclusion. We developed a syngeneic *BRAF^{V600E}/PTEN$^{-/-}$*melanoma model YUMM2.1 (Y2.1) that has partial response (PR) to anti-PD1 (Homet, 2016), and an inducible cre/lox system to stabilize ß catenin. We hypothesized that WNT activation would alter the efficacy of anti-PD1 therapy in this model. **Methods:** Y2.1 cells were treated with tamoxifen (4HT) *in vitro* and ß catenin stabilization was confirmed (Y2.1 4HT1). C57BL/6 mice were implanted Y2.1 4HT1 tumors sc, followed by ip anti-PD1 (RMP1-14) or Isotype q3d for 3wks when tumors reach 5-8mm. For *in vivo* depletion, antibodies (a) against CD4, CD8, NK1.1, CD40L was given starting 1d prior to anti-PD1 x2d then WKly x 3. Tumors were harvested for flow, RNAseq. **Results:** WNT activation rendered a partial response to anti-PD1 w Y2.1 to complete regression of Y2.1 4HT1 tumors by wk 8 in majority of treated mice (median vol 180 vs 48 mm3 in WK6, p = 0.02). This enhanced anti-tumor effect is seen in additional 4HT treated Y2.1 (Y2.1 4HT2-6), but not YUMM1.1 (resistant to anti-PD1), but is lost in Y2.1 4HT1 BCKO (ß catenin gene knocked out by CRISPR, median vol ISO 587 vs aPD 560 mm3 in WK6, p = 0.65). Depletion studies showed complete abrogation of anti-tumor response with CD4 depletion but only partial with CD8 depletion, aCD40L or in *IFNg-/-* mice (Table 1), and no effect w NK depletion. Flow Cytometry and RNAseq showed increased T cells, IFNg, granzyme B with anti-PD1 in Y2.1 4HT1 tumor. CD4 depleted tumors also have increased CD8 but w/o effector functionality, and a global downregulation of immune related genes by hierarchical clustering. **Conclusions:** WNT signaling activation results in complete response to anti-PD1 therapy, w increased T cell infiltration and CD4 cells being essential for this anti-PD1 mediated anti-tumor response.

Y2.1 4HT1 Tumors	ISO	aPD	ISO+ aCD4	aPD+ aCD4	ISO+ aCD8	aPD+aCD8	aPD+aCD40L
N.	6	5	5	5	5	5	5
Median (week 5)	226	86	900	950	285	264	488
95% CI							
Lower limit	111	56	429	857	162	48	182
Upper limit	416	136	1029	1150	725	416	850
Mann Whitney test		ISO vs aPD p = 0.009 **		aPD+aCD4 vs aPD p = 0.008 **		aPD+aCD8 vs aPD p = 0.45	aPD+aCD40L vs aPD p = 0.008 **

12014 Poster Discussion Session; Displayed in Poster Session (Board #127), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Facile single cell profiling and clonotype analysis of NSCLC immune microenvironments. *First Author: Ameen Abdulla Salahudeen, Stanford University, Stanford, CA*

Background: Immunotherapies acting upon tumor infiltrating lymphocytes (TILs) generate deep and durable responses in NSCLC patients. However, the clonality, cell phenotype, and signaling states of TILs remain poorly defined in clinical specimens. In addition, current in vitro model systems do not typically preserve both the tumor epithelium and microenvironment as an intact syngeneic unit thus hindering conceptual and therapeutic advances. **Methods:** We developed 3-dimensional organoid cultures of surgically resected NSCLC specimens that intrinsically retained diverse tumor microenvironmental cellular components without requiring reconstitution. We then profiled TIL clonotypes and gene expression phenotypes in varying histologies of NSCLC with a 5' based scRNA-seq platform capable of pairing alpha beta T cell receptor (TCR) sequence identity with 5' based transcriptomes. **Results:** Fresh clinical samples were viably dissociated into single cell suspensions and droplet based scRNA-seq was carried out in a rapid and reliable manner. Correct, full length, and paired TCRA/TCRB clonotypes were detected at expected ratios and demonstrated a detection sensitivity of clonal expansion with a sensitivity of 1% for 1000 cells observed. In addition, paired transcriptome analysis facilitated phenotypic categorization of each unique clonotype, including cytotoxic and helper T, B, Treg, as well as TIL exhaustion. Furthermore, examination of NSCLC tumor microenvironments with varying patient smoking history and tumor histology exhibited differences suggesting a potential link between immune microenvironments and cancer etiology. **Conclusions:** Organoid cultures faithfully recapitulate tumor microenvironment diversity within NSCLC histologic types, and scRNA-seq profiling of clonotype TIL dynamics may elucidate underlying immune microenvironment dynamics in NSCLC patients. Further studies in this human preclinical model coupled with scRNA-seq may advance our understanding of tumor immunology within NSCLC subtypes as well as facilitate the discovery of novel immunotherapies.

12015 Poster Discussion Session; Displayed in Poster Session (Board #128), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Expression and clinical significance of antigen presentation components beta-2 microglobulin, HLA class I heavy chains, and HLA class II in non-small cell lung cancer (NSCLC). *First Author: Ila Datar, Yale School of Medicine, New Haven, CT*

Background: Defective antigen presenting machinery (APM) limits tumor recognition by cognate T cells mediating resistance to immune checkpoint inhibitors (ICIs). The expression frequency, biological context and prognostic value of major APM components in NSCLC are poorly characterized. **Methods:** Using multiplexed quantitative immunofluorescence we measured levels of Beta-2 microglobulin (B2M, clone-D8P1H), HLA-B, C heavy chains (HLA-I, clone HC10), HLA Class-II (HLA-II, clone LGII-612.14) and pancytokeratin (CK, clone AE1/AE3) protein in 754 stage I-IV immunotherapy-naïve NSCLCs represented in tissue microarrays: Cohort#1 Yale (n = 423), Cohort#2 Greece (n = 284) and cohort# 3 Yale (n = 137) with molecularly annotated lung adenocarcinomas (ADCs). Targets were measured in tumor/stroma by fluorescence colocalization with tumor-specific CK. Associations with clinicopathological variables, T-cell infiltration, driver mutations and survival were studied. **Results:** B2M, HLA-I heavy chains (HCs) and HLA-II were expressed in tumor cells in 86.7%, 83.1% and 77.9% of NSCLCs, respectively. The markers showed significant positive association with each other in CK^- stromal cells (R^2= 0.27-0.33, $P < 0.05$) but not in CK^+ tumor cells (R^2= 0.002-0.14, $P > 0.05$). Tumors lacking B2M had significantly lower HLA-I, -II and $CD3^+$ infiltrating T cells than cases with B2M expression. No consistent association was seen between the targets and major clinicopathological variables across cohorts. Comparable levels of the markers were seen in KRAS/EGFR mutant and wild type lung ADCs. Tumor B2M downregulation was associated with worse outcome in both cohorts, but was significant only in cohort#1 and showed clear trend in #2. **Conclusions:** B2M, HLA-I HCs and HLA-II are downregulated in 12-22% of primary, immunotherapy-naïve NSCLCs. Reduced B2M expression associates with an immune "cold" phenotype characterized by low HLA-I, -II levels, low T cell infiltration and poor prognosis. Our results support an immunomodulatory role of APM downregulation in NSCLC and underscore its possible involvement in primary resistance to ICIs and potential as a biomarker.

12016 Poster Discussion Session; Displayed in Poster Session (Board #129), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Whole exome sequencing (WES) in hormone-receptor positive (HR+) metastatic breast cancer (MBC) to identify mediators of resistance to cyclin-dependent kinase 4/6 inhibitors (CDK4/6i). *First Author: Seth Andrew Wander, Dana-Farber Cancer Institute, Boston, MA*

Background: Combining CDK4/6i with endocrine therapy results in prolongation of disease control in HR+ MBC, though resistance invariably occurs. There is a critical need to understand mechanisms governing response and resistance to these agents. **Methods:** WES was performed on 51 baseline metastatic tumor biopsies obtained at treatment initiation with CDK4/6i in combination with various anti-estrogens. Tumor samples were classified as sensitive (S, from patients with clinical benefit) or intrinsically resistant (IR, from patients without clinical benefit). WES was also performed in 11 acquired resistance (AR) specimens obtained from responding patients after progression. In 6 patients, WES was performed on matched pre-treatment S and post-progression AR specimens. Putative resistance drivers were introduced into HR+/HER2- breast cancer cells (T47D, MCF7) via lentiviral infection or knockout via CRISPR. Sensitivity of the modified cell lines to anti-estrogens and CDK4/6i was characterized. **Results:** WES of 62 tumors revealed multiple potential mechanisms of resistance to CDK4/6i (Table), including biallelic *RB1* inactivation, *AKT1* mutation (mut) and/or amplification (amp), *RAS* mut, *AURKA* amp, *IGF1R* amp, *ERBB2* mut, and *FGFR2* mut and/or amp. Introduction of candidates into HR+ breast cancer cells conveyed resistance to CDK4/6i *in vitro*, including loss of Rb and overexpression of AKT1, AURKA, FGFR2, mut-KRAS, and mut-ERBB2. Additional sequencing efforts and characterization of variants is ongoing and will be presented. **Conclusions:** These results provide new insight into the diverse spectrum of genomic events driving resistance to CDK4/6i and set the stage for additional mechanistic studies. For patients with AKT1, RAS, AURKA, IGF1R, ERBB2, and FGFR2-dependent resistance, clinical trials incorporating novel combinations of targeted therapies could be designed to circumvent or overcome resistance.

Phenotype	S	IR	AR	IR+AR (%)
Tumor samples (n)	21	30	11	41
RB1 biallelic inactivation	0	3	1	4 (10)
IGF1R amp	0	2	1	3 (7)
RAS mut	0	2	1	3 (7)
AKT1 mut or amp	1	3	2	5 (12)
FGFR2 mut or amp	0	3	0	3 (7)
AURKA amp	0	7	4	11 (27)
HER2 mut	1	1	3	4 (10)

12017 Poster Discussion Session; Displayed in Poster Session (Board #130), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Analysis of tumor samples from SOLO2: Concordance of *BRCA* mutation (*BRCA*m) detection in tumor vs. blood and frequency of *BRCA*-specific loss of heterozygosity (LOH) and loss of function somatic mutations. *First Author: Darren R. Hodgson, AstraZeneca, Cambridge, United Kingdom*

Background: The PARP inhibitor olaparib is approved for maintenance treatment of platinum-sensitive relapsed ovarian cancer (PSR OC) in the USA based on pivotal studies (Study 19, SOLO2) that demonstrated a progression-free survival benefit of olaparib (Ledermann et al 2012, 2016; Pujade-Lauraine et al 2017). Patients (Pts) with *BRCA*m benefit most from olaparib, but questions remain on the functional equivalence of germline (g) and somatic *BRCA*m and the frequency and impact of *BRCA*-gene-specific LOH (Dougherty et al 2017; Maxwell et al 2017). **Methods:** Blood and tumor samples from 241 pts with g*BRCA*m in a Phase III trial of olaparib maintenance monotherapy (300 mg bid tablets; SOLO2; NCT01874353) were analyzed. A concordance analysis of g*BRCA*m and tumor *BRCA*m (t*BRCA*m) status was conducted; gene-specific LOH for *BRCA1* and *BRCA2* and assessment of homologous recombination deficiency (HRD) using Myriad HRD score (Tumor BRACAnalysis CDxTM test) was also determined. **Results:** t*BRCA*m testing was evaluable in 241/289 g*BRCA*m pts. There was 98% and 100% concordance between pts' *BRCA1*m and *BRCA2*m status, respectively, in t*BRCA*m vs g*BRCA*m. 13/241 (5.4%) of g*BRCA*m were due to large rearrangements (exonic insertions or deletions), of which 4 involving *BRCA1* were not detected in the tumor. A further deleterious somatic mutation in *BRCA1* was identified in 1/241 pts with g*BRCA*m tumors. This was a large rearrangement in *BRCA1*, causing an exon 1–22 deletion that likely constituted the second 'hit' in this tumor. Of 210 evaluable LOH samples, 144/144 (100%) g*BRCA1*m and 65/66 (99%) g*BRCA2*m tumors had gene-specific LOH. The pt without *BRCA2* LOH had an HRD score of 53, was progression-free for 911 days and remained on olaparib at data cut-off. **Conclusions:** Very high concordance between t*BRCA* and g*BRCA* testing is demonstrated, supporting wider implementation of t*BRCA* testing in addition to availability of g*BRCA* testing to determine *BRCA*m status in OC. Deleterious somatic *BRCA*m almost never arises in g*BRCA*m tumors, in keeping with *BRCA* loss being a driver of tumorigenesis in OC. In PSR g*BRCA*m pts, gene-specific LOH in tumors is almost universal. Clinical trial information: NCT01874353.

12018 Poster Discussion Session; Displayed in Poster Session (Board #131), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Mass spectrometry biomolecular omics profiling and imaging to dissect the initial emergence of molecular drug resistance in *ALK*-positive (ALK+) lung cancer. *First Author: Xiaoliang Wu, West Virginia University Cancer Institute, Morgantown, WV*

Background: ALK tyrosine kinase inhibitors (TKIs) yield a significant tumor response in advanced *ALK*+ non-small cell lung cancer (NSCLC), that is often rapid and remarkable. Nonetheless, acquired drug resistance invariably develops. Currently, the mechanisms for the initial emergence of molecular drug resistance in the responders are still not fully understood. **Methods:** *ALK*+ H3122 and Ma-ALK001.S (patient-derived cell line) lung adenocarcinoma in vivo xenograft models were investigated under drug treatment with/without ALK-TKI (TAE684 or Alectinib) for 0, 7 and 14 days. Mass spectrometry imaging (MSI) and biomolecular profiling were carried out on FFPE or fresh frozen tissues to compare peptide/lipid/metabolite profiles among the tumors using a histology-guided MS (HGMS) approach. Full section MSI was also performed to determine the intratumoral drug distribution. Cells were subjected to both Matrix Assisted Laser Desorption/Ionization (MALDI)-MS and Laser Ablation Electrospray Ionization (LAESI)-MS profiling. Statistical analyses were performed using SCiIS and MarkerLynx, respectively. **Results:** ALK-TKIs precision treatment engendered an early emergence of drug resistant escape in the ALK+ tumor cells within the initial 14 days of treatment. Direct MS/MS fragmentation verified that ALK-TKIs were detected within the drug-dosed tumors undergoing early drug-escape. We identified unique peptide landscape changes emerging under ALK-TKI treatment. Most significant peak differences were observed between day 0 and day 14 (677) in the H3122 group, and also between day 0 and day 14 (341) in the Ma-ALK001.S group. Interestingly, day 7 peptide signatures in these models were more similar to day 14 than to the day 0 control. Overall, biomolecular profiling (peptides, lipids and metabolites) of *ALK*+ lung tumor cells using combined MALDI and LAESI-MSI analysis was successful. **Conclusions:** MSI technology facilitates interrogation of the biomolecular changes occurring within drug persister tumor cells under precision treatment. An ALK drug resistant proteomics signature emerges as early as day 7 under precision inhibitor treatment.

12019 Poster Discussion Session; Displayed in Poster Session (Board #132), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Development of diagnostic method for bone and soft tissue sarcomas of various histological subtypes using serum microRNA profiles. *First Author: Naofumi Asano, Department of Orthopaedic Surgery School of Medicine, Keio University, Tokyo, Japan*

Background: Diagnosis of sarcomas is considered to be quite difficult because of the rarity and diversity of the disease. The development of a novel diagnostic test for sarcoma is eagerly awaited. The aim of this study is to address whether serum miRNA profiles can be used to detect only malignant cases (sarcomas) of bone and soft tissue tumors regardless of histological subtypes. **Methods:** The case-control study included 1,002 patients with bone and soft tissue tumors representing more than 43 histological subtypes, including sarcomas, intermediate, and benign tumors. As controls, 275 healthy and 240 patients with other cancers were enrolled. MiRNA levels were measured using microarray. Patients were divided into three cohorts: a discovery to identify differentially expressed miRNAs; a training to establish a diagnostic index; and a validation to validate the utility of the index. An exploratory cohort was used to evaluate the index in recurrent sarcomas, intermediate tumors, and other cancers. **Results:** Circulating serum miRNA profiles, determined by microarray analysis, in malignant cases of bone and sarcomas, were clearly distinct from those in benign and healthy controls. A promising molecular detector, diagnostic index II, was developed using the serum levels of three miRNAs. Diagnostic index II also clearly separated sarcomas from benign and healthy controls with remarkable high sensitivity (94%), specificity (90%), and accuracy (91%). **Conclusions:** Comprehensive analysis of serum miRNA profiles in approximately 1000 cases of bone and soft tissue tumors identified a promising classifier, diagnostic index II, calculated using the serum levels of three miRNAs with remarkable performance for the detection of sarcoma. The present data overcome a serious problem associated with sarcoma diagnosis and provide the basis for the development and implementation of miRNA-based strategies for diagnostic purposes in the clinic.

12020 Poster Discussion Session; Displayed in Poster Session (Board #133), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

PRC-2 epigenetic chromatin reprogramming in ALK-positive (ALK+) lung cancer initial emergence of precision drug resistance. *First Author: Patrick C. Ma, WVU Cancer Institute, West Virginia University, Morgantown, WV*

Background: Despite remarkable upfront response to ALK tyrosine kinase inhibitors (TKIs) in ALK+ lung cancer, acquired resistance eventually develops. Molecular mechanisms of the initial emergence of drug resistance are poorly understood. **Methods:** ALK+ H3122, H2228 and a patient-derived Ma-ALK001.S NSCLC cell lines were used in our study. In vitro MTS viability and murine in vivo xenograft assays were performed. siRNA knockdown and CRISPR/cas9 gene knockout were used for mechanistic studies. ChIP-qPCR was conducted to analyze HOXB3 epigenetic marks. RNA-seq was also performed for transcriptome analysis. Tumor microarray (TMA) biomarker study was adopted for outcome analysis of the polycomb repressive complex-2 (PRC-2) in NSCLC. **Results:** Our study revealed a rapid-onset emergence of adaptive drug-resistant ALK+ lung cancer cells within the first 14 days upon TKI treatment initiation. The expression of stem cell transcription factors, most notably HOXB3, was induced adaptively within the tumor cells undergoing drug escape. Similarly, tumoral TGFβ2 autocrine expression both at mRNA and protein levels were significantly elevated, and it regulated the downstream HOXB3 expression and mitochondrial prosurvival BCL-2/BCL-xL signaling, cancer stemness and EMT markers. RNA-seq revealed a rapid-onset adaptive global transcriptome reprogramming in the drug-escaping persister tumor cells. ChIP-qPCR showed resistance emerged via epigenetic regulation of the untreated bivalent HOXB3 promoter closed chromatin state transforming to stem-like open state during drug-escape, based on H3K4me3/H3K27me3 methylation mark balance. Findings were validated via CRISPR/cas9-EZH2 knockout studies. AQUA-TMA biomarker and survival outcome analysis confirmed the clinical relevance of EZH2/UTX of PRC-2. Finally, direct EZH2 inhibition or knock-out promoted ALK-TKI drug resistance, while UTX inhibition enhanced drug sensitivity. **Conclusions:** ALK+ lung cancer achieves initial rapid-onset emergence of adaptive drug escape through PRC-2 epigenetic chromatin reprogramming to regulate cancer plasticity-EMT/stemness interplay via the TGFβ2-EZH2/UTX-HOXB3-BCL-2/BCL-xL cascade.

12021 Poster Discussion Session; Displayed in Poster Session (Board #134), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Development of a comprehensive cell-free DNA (cfDNA) assay for early detection of multiple tumor types: The Circulating Cell-free Genome Atlas (CCGA) study. *First Author: Eric A. Klein, Cleveland Clinic Glickman Urology and Kidney Institute, Cleveland, OH*

Background: Globally most cancers are detected at advanced stages with high treatment burden and low cure rates. A noninvasive cfDNA blood test detecting multiple cancers at early stages when curative treatment is more likely to succeed is desirable. CCGA (NCT02889978) is a prospective multicenter observational study for development of a noninvasive cfDNA-based multi-cancer detection assay. **Methods:** Prospectively collected samples (N = 1627) from 749 controls (no cancer diagnosis, C) and 878 participants (pts) with newly diagnosed untreated cancer (20 tumor types, all stages) were analyzed in a preplanned substudy. 3 prototype sequencing assays were performed: paired cfDNA and white blood cell (WBC, 60,000X) targeted sequencing (507 genes) for single nucleotide variants/indels; paired cfDNA and WBC whole genome sequencing (WGS, 30X) for copy number variation; cfDNA whole genome bisulfite sequencing (WGBS, 30X) for methylation. For each assay a detection model was developed for all cancer pts; sensitivity was estimated at 95% specificity. **Results:** Pts w/cancer and C had similar age, smoking status and gender. WGBS had the highest sensitivity and is reported here; results were consistent across assays. Detected (sensitivity [95% CI]) cancers (stage I-III) included 28 colorectal (66% [48-84]), 19 esophageal (63% [38-84]), 5 head and neck (56% [21-86]), 5 hepatobiliary (80% [28-99]), 73 lung (59% [47-70]), 17 lymphoma (77% [50-93]), 11 multiple myeloma (73% [39-94]), 10 ovarian (90% [56-99]), and 10 pancreatic (80% [44-98]). Breast cancer-specific assay results are reported separately. Cancers with low signal ($<$ 10% sensitivity) include low gleason score prostate cancer, thyroid, uterine, melanoma, and renal. Comparison to tumor WGS and multi-assay classification will be reported. **Conclusions:** A cfDNA-based blood test detected multiple cancers at various stages with high specificity, indicating this approach is promising as a multi-cancer screening test, including for lethal unscreened cancers where stage shift can impact mortality. Further assay and clinical development of a multi-cancer cfDNA test in an asymptomatic population is ongoing. Clinical trial information: NCT02889978.

12022 Poster Discussion Session; Displayed in Poster Session (Board #135), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Cell-free circulating tumor DNA somatic alteration burden and its impact on survival in metastatic cancer. *First Author: Seyed Saeed Pairawan, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Prognostication has been a challenging subject in patients with metastatic disease. Physicians are expected to assess prognosis of patients with advanced disease both for determining suitability for clinical trials and for patient counseling. Increasingly, cell-free circulating tumor DNA (cfDNA) sequencing is being performed for clinical decision-making. We sought to determine whether somatic alteration burden (SAB) in cfDNA is associated with prognosis. **Methods:** We performed a retrospective analysis of 298 patients with metastatic disease who underwent clinical comprehensive cfDNA analysis at a single tertiary care institution. Our primary objective was to determine the influence of SAB (defined as maximum mutant allele frequency) on overall survival (OS). Secondary objectives included the association between the number of nonsynonymous mutations (NSM) and OS, and of site of primary malignancy on mutation detection and SAB. **Results:** CfDNA mutations were detected in 240 (80%) patients. SAB was classified by quartiles, Q1 lowest, Q4 highest SAB. Median follow-up was 8.4 months after cfDNA testing; we observed 116 deaths (39%) among 298 patients. Median OS was 11.5 months. Higher SAB levels had a statistically significant impact on overall survival in SAB Q3 (HR 2.3, p = 0.0069) and SAB Q4 (HR = 3.8, p $<$ 0.0001) on univariate analysis. On multivariate analysis, SAB Q4 (HR = 2.6, p = 0.0033), male sex (HR = 1.59, p = 0.0033) and albumin level $>$ 3.9 g/dl (HR = 0.40, p = 0.00011) were independent predictors of OS. CfDNA mutation detection, SAB, and number of NSM significantly differed between tumor types (p $<$ 0.0001, p = 0.0013, and p = 0.0001 respectively), being lowest in appendiceal cancer and highest in colon cancer. Having more than one NSM detected was associated with significantly worse overall survival (HR = 2.3, p $<$ 0.0001). **Conclusions:** Higher levels of cfDNA SAB and higher number of NSM were associated with worse OS in patients with metastatic disease. Further study is needed to determine optimal SAB thresholds for clinical decision-making and the utility of SAB across different tumor types.

12023 Poster Discussion Session; Displayed in Poster Session (Board #136), Mon, 1:15 PM-4:45 PM, Discussed in Poster Discussion Session, Mon, 4:45 PM-6:00 PM

Assessment of the genomic stability and molecular landscape of patient-derived xenograft (PDX) models from NCI's Patient-Derived Models Repository (PDMR). *First Author: Bishwajit Das, Frederick National Laboratory for Cancer Research, Frederick, MD*

Background: Patient-derived xenografts (PDXs) are a powerful tool for cancer translational research. However, it is unclear if early passage PDXs faithfully recapitulate the molecular profiles of the corresponding patient tumors. The National Cancer Institute (NCI) has developed a Patient-Derived Models Repository (PDMR; www.pdmr.cancer.gov) of PDXs with clinical annotation and comprehensive genomic data. We used this data set, which represents 13 broad categories of tumor types, to conduct an in-depth investigation of the genomic stability of PDXs with early passaging. **Methods:** Tumors (biopsy or resection), including some from metastatic sites, were used to establish 211 PDX models from 206 patients. Whole Exome Sequencing and RNA-Seq were performed on 2-9 mice per model. Passages represented include the original clinical sample, P0, P1, P2, and less frequently $>$ P2. **Results:** By several metrics, genomic profiles of a large majority of PDMR models were stable with early passaging: (1) transcriptome profiles of mice from different passages in a model were found to always cluster together; (2) 75% of PDXs maintained similar copy number alteration profiles compared with the original clinical sample, with no significant differences between passages; (3) the allele frequency (AF) of clinically relevant mutations remained consistent across passages, with only 20% of models having $>$ 15% AF range from the median. Moreover, genomic features of PDMR models were broadly comparable to those in large public patient data sets. For example, melanoma models had the highest tumor mutation burden and a 55% prevalence of BRAF V600X; 11% of colon adenocarcinoma models were MSI-H, with APC (65%), TP53 (59%) and KRAS (53%) being most frequently altered. **Conclusions:** In this large and histologically diverse PDMR data set, PDXs exhibited genomic stability with early passaging. The molecular landscape of PDMR models is faithfully comparable to large public patient data sets. As the PDMR collection expands additional in-depth analyses will be performed. The PDMR thus represents a valuable resource for researchers interested in pre-clinical drug or other studies.

12024 Poster Session (Board #137), Mon, 1:15 PM-4:45 PM

First-in-human phase I trial of BI 836880, a vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang-2)-blocking nanobody, given every 3 weeks (q3w) in patients (pts) with advanced/metastatic solid tumors. *First Author: Christophe Le Tourneau, Institut Curie, Paris, France*

Background: VEGF and Ang-2 inhibitors have demonstrated clinical activity in various tumor types. Given the overlap of the VEGF/VEGFR2 and Ang-2/Tie-2 signaling pathways there is a rationale for dual inhibition. BI 836880 is a humanized bispecific nanobody (engineered antibody fragment of variable antibody domains) that inhibits VEGF and Ang2 and has demonstrated preclinical activity in cancer models. **Methods:** Pts with solid tumors refractory after standard therapies/for whom no established treatment options were available received BI 836880 q3w (IV; starting dose 40 mg). Dose escalation followed a Bayesian logistic regression model with overdose control. The maximum-tolerated dose (MTD; primary endpoint) was evaluated based on dose-limiting toxicities (DLTs) in the first 21-day cycle. Treatment-related AEs (TRAEs) leading to dose reduction/discontinuation, exposure/disposition kinetic measures (both secondary endpoints) and best overall response were also assessed. **Results:** 29 pts were treated: median age 57 yrs (range 2879); 62% female. The MTD was determined as BI 836880 720 mg q3w (Table). All pts had at least 1 AE, most commonly (all grade/grade $\geq$3): hypertension 86%/34%, asthenia 48%/10%, nausea 45%/3% and vomiting 38%/3%. 23 (79%) pts had TRAEs; none led to dose reduction. One patient had a TRAE leading to discontinuation (pulmonary embolism DLT at 1000 mg). Two (7%) pts (nasopharyngeal [n = 1] and breast [n = 1] carcinoma) had a partial response and 9 (31%) pts had stable disease. PK/PD analysis of 14 evaluable pts showed dose-proportional plasma kinetics of BI 836880, complete peripheral target inhibition at doses $\geq$360 mg q3w and predicted required trough values at doses $\geq$720 mg q3w. Clinical trial information: NCT02674152. **Conclusions:** The MTD/recommended phase 2 dose of BI 836880 was determined as 720 mg q3w based on safety and PK/PD analyses. Early signs of antitumor activity were observed.

Dose, mg	Pts, n	Pts with DLT, n
40	3	0
120	2	0
360	2	0
720	17*	0
1000	5	1: G3 pulmonary embolism

*No DLT in first 2 pts; expanded to 7 after DLT at 1000 mg; 10 more patients enrolled after MTD determined at 720 mg.

12025 Poster Session (Board #138), Mon, 1:15 PM-4:45 PM

Monitoring microsatellite instability (MSI) in circulating tumor DNA by next-generation DNA-seq. *First Author: Adam Deng, Geneis(Beijing) Co.,Ltd., Beijing, China*

Background: Microsatellite instability (MSI) is a useful predictive biomarker for prognosis of patients with phase II colorectal cancer and clinical benefit from cancer immunotherapy. Conventional MSI testing is commonly performed with tumor tissues by a fluorescent multiplex PCR-based method, consisting of six mononucleotide microsatellite makers. Recently, next generation DNA sequencing (NGS) has been developed for detection of MSI status in tumor tissues. However, we are still curious about whether we could accurately monitor MSI in ctDNA by NGS to achieve the non-invasive diagnosis. **Methods:** We collected plasma, matched tumor tissue and blood samples from 200 cancer patients. ctDNAs extracted from plasma and genomic DNAs extracted from tumor tissue and blood were used to perform MSI testing by conventional PCR methodand amplicon-based NGS. Six regular mononucleotide microsatellite makers (NR-27, NR-21, BAT-26, BAT-25, NR-24, MONO-27) were analyzed in two methods, and blood was compared as the normal control for MSI evaluation. MSI-H or MSI-L/MSS patients were primarily distinguished by conventional PCR method. Further we performed MSI detection in plasma, matched tumor tissue and blood by NGS and designed an algorithm for evaluating MSI status. **Results:** In 200 cancer patients, we primarily identified 13 patients with MSI-H (6.5%) and the others with MSS by conventional PCR method. Interestingly, we found that MSI testing in plasma was not performed by conventional PCR assay, namely that MSI could not be precisely monitored by conventional method. However, both MSI testing in plasma and in tumor tissue could be performed well by NGS. Compared the results of MSI testing in tumor tissue by two methods, there was high consistency. Importantly, we found that all 13 MSI-H patients were correctly identified by MSI testing in circulating tumor DNA(ctDNA), in concordance with the results of MSI testing in tumor tissue. The sensitivity of MSI testing was 100%. **Conclusions:** In our study, the MSI status of cancer patients could be accurately monitored in circulating tumor DNA(ctDNA) by amplicon-based NGS. It provides the possibility of non-invasive MSI testing for cancer patients in clinical diagnosis.

12026 Poster Session (Board #139), Mon, 1:15 PM-4:45 PM

The prognostic and predictive value of AR-V7 quantification in mCRPC. *First Author: Adam Sharp, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Androgen receptor splice variant-7 (AR-V7) is associated with resistance to abiraterone/enzalutamide treatment in metastatic castration resistant prostate cancer (mCRPC). **Methods:** We determined CTC status and AR-V7 RNA quantification from mCRPC patient blood (Adnagen assay; AG). Reproducibility, clinical significance, and comparison to CellSearch CTC (CS_CTC) enumeration and biopsy AR-V7 protein quantification (Immunohistochemistry; IHC) was investigated. **Results:** To-date 218 blood samples from 130 patients have been analysed. AG reproducibility was determined from 84 samples run in triplicate with high concordance (70% of samples); poor concordance was seen in samples with low AR-V7 RNA expression supporting the identification of a cut-off for negative AR-V7 testing. CS_CTC enumeration was available for 109 samples; AG_CTC^{neg} samples had lower CS_CTC counts (p = 0.0001). AG_CTC^{pos}/AR-V7^{neg} samples had lower CS_CTC counts than AG_CTC^{pos}/AR-V7^{pos} samples (p = 0.006). CS_CTC counts in AG_CTC^{pos}/AR-V7^{pos} samples positively correlated with AR-V7 RNA expression (p = 0.0002). Contemporaneous mCRPC biopsies were available for 56 samples. All 25 AG_CTC^{pos}/AR-V7^{pos} samples, 12/16 AG_CTC^{pos}/AR-V7^{neg} samples and 9/15 AG_CTC^{neg} samples were AR-V7 IHC positive. Finally, AG_CTC^{pos}/AR-V7^{pos} patients had a worse prognosis than AG_CTC^{pos}/AR-V7^{neg} and AG_CTC^{neg} patients (median OS 6.9 vs 14.4 vs 30.8 mo; p $<$ 0.0001). In addition; only patients with AG_CTC^{pos}/AR-V7^{neg} (5/11) and AG_CTC^{neg} (1/5) samples, not AG_CTC^{pos}/AR-V7^{pos} (0/5) samples, before either enzalutamide/abiraterone therapy had a 50% PSA response. **Conclusions:** We confirm that AG_AR-V7 RNA analyses can be conducted as a continuous variable, and determine a cut-off for negative tests and show that this is prognostic and predictive. Furthermore, we show that AG_AR-V7 RNA expression may be associated with higher CS_CTC counts and more advanced disease. Finally, we demonstrate that patients with AG_CTC^{neg} and AG_CTC^{pos}/AR-V7^{neg} samples had mCRPC biopsies positive for AR-V7 protein expression; the clinical significance of this requires further interrogation to identify whether these patients derive less benefit from enzalutamide/abiraterone therapy.

12028 Poster Session (Board #141), Mon, 1:15 PM-4:45 PM

Re-visiting *EGFR* amplification as a target for anti-EGFR therapy: Analysis of cell-free circulating tumor DNA in patients with diverse cancers. *First Author: Shumei Kato, Moores Cancer Center, La Jolla, CA*

Background: To date, evidence for tissue *EGFR* amplification (amp)/overexpression as a biomarker for anti-EGFR efficacy has been weak. We investigated the relationship between elevated *EGFR* copy numbers in cell-free circulating tumor DNA (cfDNA) and the role of anti-EGFR drugs in achieving response. **Methods:** We evaluated *EGFR* amp status amongst 1,435 patients with diverse cancers using clinical-grade next generation sequencing (NGS) of cfDNA (Guardant Health) (detects single nucleotide variants [54-73 genes], amp, fusions and indels in selected genes) and analyzed treatments used (NCT02478931). **Results:** Overall, 6.0% of patients (86/1,435) had *EGFR* amp on initial cfDNA evaluation (copy numbers, 1+: 2.13-2.39 [N = 40], 2+: 2.40-3.99 [N = 40], 3+: $>$ 4.00 [N = 6]). *EGFR* amp was most frequent among small cell lung (30.0% [3/10]), breast (11.9% [13/109]) and colorectal cancer (11.0% [14/127]). All patients had co-existing alterations, most commonly in other tyrosine kinase family genes (70.9% [61/86]), MAPK signaling pathway (59.3% [51/86]) or cell cycle-associated genes (53.5% [46/86]). Nine evaluable patients with *EGFR* amp were treated with anti-EGFR-based regimens. Fifty-six percent (5/9) achieved partial responses, including 2 patients treated with dual anti-EGFR agents (small molecule inhibitor plus antibody) (adenocarcinoma of unknown primary [-44%, 4 months] and gastroesophageal cancer [-70%, 17+ months]. Responses were seen across different degrees of *EGFR* amp (1+ [N = 1], 2+ [N = 2], 3+ [N = 2]) and included patients with colorectal cancer. Two of 5 responders had tissue NGS showing *EGFR* amp; 1 of 3 non-responders with tissue NGS showed EGFR amp. Two-month landmark analysis showed median PFS of 3.9 versus 0.57 months among responders versus non-responders (P = 0.11); overall survival, 4.8 versus 0.6 months (P = 0.04). **Conclusions:** *EGFR* amp was detected in cfDNA among 6.0% of diverse cancers. Most patients had co-existing alterations. Responses were observed in 5 of 9 patients who received EGFR inhibitors, including 3 who were negative for *EGFR* amp in tissue. Incorporating EGFR inhibitors in regimens given to patients with *EGFR* amp in cfDNA merits further study. Clinical trial information: NCT02478931.

12029 Poster Session (Board #142), Mon, 1:15 PM-4:45 PM

Correlation between natural killer cell activity and treatment effect in patients with disseminated cancer. *First Author: Torben Hansen, Department of Oncology, Vejle Hospital, Institute of Regional Health Research, University of Southern Denmark, Vejle, Denmark*

Background: Prediction of treatment effect remains an unsolved problem in patients with malignant tumors. The aim of the present study was to analyze the possible correlation between Natural Killer (NK) cell activity as measured by the NK Vue assay and treatment effect in patients with different tumors. **Methods:** The study included four different trials encompassing palliative treatment to patients with prostate, ovarian and colorectal cancer. The current results are based on 93 patients with mature data on treatment effect. Blood samples were collected at baseline and prior to each treatment cycle into NK Vue Promoca tubes and placed in an incubator at 37°C within 15 minutes of sampling. Following 24 hours of stimulation the level of interferon-gamma (IFNγ) in the plasma was measured by ELISA (NK Vue Gold) as a surrogate for NK cell activity. Response rates (RR) and progression free survival (PFS) were endpoints. **Results:** The relationship between NK cell activity and treatment response was similar across tumor types and treatment, and data were consequently pooled for analyses. The outcome suggested a classification into three groups. During the first two months of treatment the IFNγ dropped to an abnormal level (< 200 pg/mL) in group 1 or remained at an abnormal level (n = 35). In group 2 (n = 30) the level remained within a normal range (> 500 pg/mL), while in group 3 (n = 28) it increased from an abnormal to a normal level. The RR were 29%, 47%, and 82%, respectively, p = 0.0001. The median PFS was 2.6 months (95% confidence interval (CI) 2.1-3.9), 10.0 months (95% CI 6.5-11.1), and 8.3 months (95% CI 6.5-8.7), respectively, $p < 0.0001$ (log-rank). **Conclusions:** The results suggest a correlation between NK cell activity and treatment effect across different tumor types and treatments. Patients lacking the ability to mount an immune response during the first two months of treatment have a very poor prognosis and clinical benefit of the treatment is questionable.

12030 Poster Session (Board #143), Mon, 1:15 PM-4:45 PM

Extracellular matrix (ECM) circulating peptide biomarkers as potential predictors of survival in patients (pts) with untreated metastatic pancreatic ductal adenocarcinoma (mPDA) receiving pegvorhyaluronidase alfa (PEGPH20), nab-paclitaxel (A), and gemcitabine (G). *First Author: Song Wang, Halozyme Therapeutics, Inc., San Diego, CA*

Background: Hyaluronan (HA) and collagens are major constituents of the ECM. HA accumulation in the tumor microenvironment may result in elevated interstitial fluid pressure, vascular compression, and reduced drug delivery and immune cell access. PEGPH20 degrades HA, increasing tumoral access for therapeutics and immune cells. Liquid biopsies reflecting ECM remodeling may provide a non-invasive approach to identify pts most likely to benefit from PEGPH20 therapy. **Methods:** Peptide markers of ECM remodeling (C3M, PRO-C3, PRO-C6, and VCANM) were measured using baseline plasma samples from Stage 1 (n=94) and Stage 2 (n=95) of HALO-109-202 (NCT01453153), a Phase 2, open-label, randomized study of PEGPH20 + A + G (PAG) *vs* AG in previously untreated pts with Stage IV PDAC. Univariate and ratio analyses were conducted to correlate biomarker levels with survival outcomes (PFS, OS). **Results:** The ratio of C3M (MMP degradation fragment of type-III collagen) *vs* PRO-C3 (N-terminal pro-peptide of type-III collagen) predicted for PFS benefit in PEGPH20-treated pts in Stage 1. The predictive value of this ratio for PFS and OS of PEGPH20-treated pts was further validated in Stage 2. **Conclusions:** This supports development of a liquid biopsy-based companion diagnostic for selecting pts that may benefit from PEGPH20.

Biomarker levels and survival outcome.

			PFS								
			Median (mths)		Log-rank, P	HR (95% CI)					
	Measurement cut-off		AG	PAG							
Stage 1 (Discovery cohort)	C3M/PRO-C3 ratio (0.550, 50th percentile)	Ratio-high pts (≥0.550)	5.3	8.0	0.026	0.40 (0.17–0.92)					
		Ratio-low pts (<0.550)	5.2	3.0	0.810	1.09 (0.55–2.18)					
			PFS				OS				
	Measurement cut-off		Median (mths)		Log-rank, P	HR (95% CI)	Median (mths)		Log-rank, P	HR (95% CI)	
			AG	PAG			AG	PAG			
Stage 2 (Validation Cohort)	C3M/PRO-C3 ratio (0.550, stage-1 cut-off)	Ratio-high pts (≥0.550)	3.4	8.8	0.039	0.46 (0.21–0.99)	8.5	13.8	0.006	0.35 (0.16–0.77)	
		Ratio-low pts (<0.550)	5.8	5.3	0.560	1.30 (0.54–3.16)	9.0	7.9	0.523	0.80 (0.41–1.57)	

12031 Poster Session (Board #144), Mon, 1:15 PM-4:45 PM

Role of serum thymidine kinase-1 (TK1) activity in patients (pts) with hormone receptor positive (HR+) advanced breast cancer (ABC) treated with endocrine therapy (ET) in the EFECT trial. *First Author: Luca Malorni, Sandro Pitigliani Medical Oncology Department, Hospital of Prato, Prato, Italy*

Background: TK1 plays a critical role in DNA synthesis and cell proliferation. The DiviTum assay measures serum TK1 activity (sTKa), reflecting cancer cell proliferation. Recent studies suggest this assay may provide real time prognostic information in ABC. However, its role in HR+ ABC needs further validation. **Methods:** EFECT (n = 693) was a double-blind, randomized trial of fulvestrant 250mg versus exemestane after progression on nonsteroidal aromatase inhibitor therapy for ABC. 58% of pts had received > 1 prior ET for ABC. sTKa was retrospectively assessed with DiviTum on serum samples from pts in the EFECT cohort. Samples were collected before start of ET (T0), after 3 (T3) and 6 (T6) months of ET, and at disease progression (PD). Pts were categorized as High/Low sTKa at T0 based on the median value. On-treatment sTKa changes were calculated from T0 to the next available time-point within 3 months from randomization (T3, or PD for those pts with early progression - ePD), accounting for a coefficient of variation of 10%, and defined as follows: Drop (T3 or ePD $<$ T0); Increase (T3 or ePD $>$ T0); No change (T3 or ePD = T0). Analyses were conducted regardless of study arms. **Results:** All available samples were successfully tested for sTKa (586 samples from 244 consenting pts). Median sTKa at T0 (n = 227), T3 (n = 135), T6 (n = 80) and PD (n = 137) was 97, 57, 57.5 and 132 Du/L, respectively. Median time to progression (mTTP) for pts with Low T0 sTKa (n = 111) was 5.03 months (m) (95% CI 3.91-5.89) vs 2.57 (95% CI 2.04-3.52) for pts with High T0 sTKa (n = 110) ($p < 0.001$). On-treatment sTKa changes from T0 were analysed in 159 pts (T3 = 116; ePD = 43). mTTP in pts with TK1 Drop (n = 53) was 5.4 m (95% CI 3.7-7.7) vs 3.4 (95% CI 2.1-4.1) in pts with Increase (n = 68) ($p < 0.018$). mTTP in pts with No change (n = 38) was similar to those with Drop. After adjustment for major prognostic factors, sTKa remained an independent marker. **Conclusions:** sTKa is a potential circulating prognostic marker in pts with ABC treated with ET, and may represent a tool for upfront identification of ET-resistant pts, and non-invasive monitoring of response to ET. Independent validation of these results is warranted.

12032 Poster Session (Board #145), Mon, 1:15 PM-4:45 PM

Combining circulating tumor cells and circulating cancer associated macrophage-like cells for accurately predicting responsiveness of new line therapies in late stage cancers. *First Author: Daniel Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: The discovery of cancer associated macrophage like cells (CAMLs) as independent prognostic indicators of survival has highlighted the need for more in depth analysis of blood based diagnostics. As CTCs & CAMLs are isolated in parallel from a single blood sample and both are prognostic for therapy response, we hypothesized that monitoring CTCs & CAMLs before and after initiation of therapy might increase their prognostic value in a large array of cancer subtypes. **Methods:** A prospective 2 year blind multi-institutional study was undertaken to evaluate CTCs & CAMLs before, and after, induction of a new line therapy. Patients with breast (n = 12), esophageal (n = 20), NSCLC (n = 23), prostate (n = 12), and SCLC (n = 7) in Stage III (n = 45) or Stage IV (n = 30) disease were recruited. A baseline (BL) blood sample was taken prior to induction of a new therapy and a 2nd sample (T1) taken after initiation of systemic therapy (~30 days). Blood was filtered by CellSieve filtration. The quantities and subtypes of CTCs & CAMLs were analyzed based on OS hazard ratios (HRs) by censored univariate & multivariate analysis. **Results:** CTCs were identified in 16% of patients at BL, with a single CTC being prognostic for OS (HR = 4.8 95%CI1.5-14.9, p = 0.018). Further, CTCs were found in 19% of samples at T1 and also prognostic for OS (HR = 4.3 95%CI1.7-10.7, p = 0.005). However, CTCs were rare in lung (7%), esophageal (5%) and prostate cancers (17%), but common in breast (58%). In contrast, CAMLs were found in 97% of BL, with $\geq 50\mu$m CAMLs being a prognostic for OS (HR = 2.8, 95% CI 1.3-5.9, p = 0.011). At T1, the OS prognostic value of $\geq 50\mu$m CAMLs increased (HR = 3.1 95% CI 1.5-6.6, p = 0.005). Further, after induction of systemic therapy, the presence of both, > 5 CTCs or a $\geq 50\mu$m CAML was 92% accurate at predicting survival of patients within 24 months, with OS HR = 3.4 95%CI1.6-7.2, p = 0.002. **Conclusions:** Our data suggests that simultaneous measurement of both CTCs and CAMLs may increase the prognostic value of blood based diagnostics and may be predictive of benefit of subsequent therapies.

12033 Poster Session (Board #146), Mon, 1:15 PM-4:45 PM

Dynamic change of PD-L1 expression on circulating tumor cells in advanced gastrointestinal tumor patients undergoing PD-1 blockade therapy. *First Author: Chunyan Yue, National Center for Nanoscience and Technology of China, Beijing, China*

Background: Tumor PD-L1 levels have predictive value in PD-1/PD-L1 checkpoint blockade therapies, yet biopsies can only provide baseline information. Whether PD-L1 expression on circulating tumor cells (CTCs) could serve as an alternative biomarker is of great interest. **Methods:** We established an immunofluorescence assay for semi-quantitative assessment of the PD-L1 expression levels on CTCs with four categories (PD-L1^{negative}, PD-L1^{low}, PD-L1^{medium} and PD-L1^{high}). 35 patients with advanced gastrointestinal tumors were enrolled in a phase 1 trial of a PD-1 inhibitor, IBI308. The CTC numeration and the PD-L1 expression levels were analyzed prior the treatment and at the time of therapeutic evaluation. **Results:** Prior the treatment of PD-1 inhibitor, 97% (34/35) patients had CTCs, ranging from1 to 70 (median 7). 74% (26/35) had PD-L1^{positive} CTCs, and 60% (21/35) had at least one PD-L1^{high} CTCs. The disease control (DC) rate in PD-L1^{high} patients (48%) is much higher than the others (14%). The group with at least 20% abundance of PD-L1^{high} CTCs had even higher DC rate of 64% (9/14), with only 14% DC rate for the rest (3/21). We also observed that the count changes of total CTC, PD-L1^{postive} CTC and PD-L1^{high} CTC correlate quite well with disease outcome ($P < 0.001$, $P = 0.002$ and 0.007, respectively). In addition, the abundance of PD-L1^{high} CTCs at baseline had predicative significance for progression free survival (PFS). **Conclusions:** We revealed that the abundance of PD-L1^{high} CTCs at baseline might serve as a predictor to screen patients for PD-1/PD-L1 blockade therapies and measuring the dynamic changes of CTC could indicate the therapeutic response at early time. Clinical trial information: NCT02937116.

12034 Poster Session (Board #147), Mon, 1:15 PM-4:45 PM

Theoretical model and clinical validation of blood tumor mutation burden (bTMB) detection for cancer immunotherapy. *First Author: Jianchun Duan, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Tumor mutational burden(TMB) measured by whole exome sequencing (WES) or cancer gene panel (CGP) sequencing, has been identified to be associated with clinical outcome to anti-PD1/PDL1 treatment. However, a considerable proportion of patients(pts) with advanced lung cancer cannot acquire enough tumor tissue for TMB detection. Here, we defined an optimal gene panel for TMB estimation and validated the availability of blood TMB (bTMB) from circulating tumor DNA (ctDNA) in predicting therapeutic efficacy of anti-PD1/PDL1. **Methods:** A theoretical model of measuring TMB by CGP was established including 9205 WES-measured samples of 33 tumor types based on TCGA database. We further designed a panel (CT150) including 62 hotspot genes and 88 lung-cancer related genes, and built a robust bTMB detection pipeline. Correlation of CT150-measured bTMB and WES-measured TMB from paired tumor tissue in 30 NSCLC patients was analyzed to validate our model. Public clinical dataset and an independent clinical cohort were used to evaluate the association of bTMB with the efficacy of anti-PD1/PDL1 treatment. **Results:** Our model demonstrated that at least 100 genes need to be included in CGP when estimating WES based TMB, which was identified being influenced by the choice of hotspot genes, the weight of nonsynonymous mutations and the sequencing depth. In most tumor types, the CT150-measured TMB is highly correlated with WES-measured TMB. The bTMB and WES-based tumor TMB (tTMB) in 30 NSCLC patients is highly correlated. pts with high TMB estimated by CT150 had a significantly longer median progression free survival (mPFS) (14.5 vs 4.1 months, $p = 0.01$) than those with low TMB in the published Rizvi cohort ($N = 34$) . In a pilot study of 12 NSCLC pts treated with PD1/PDL1 inhibitors, pts with bTMB-high (designated as≥8 muts) had higher durable clinical benefit (DCB) rate and longer mPFS than those of bTMB-low (DCB %: 100% vs 42.9%, mPFS: 9.9 vs 2.9 months, $p = 0.03$). **Conclusions:** The designed CT150 panel can be utilized to estimate the TMB in the majority of cancer types. The bTMB estimated by this panel might provide a noninvasive biomarker assay to identify NSCLC pts benefitting from PD1/PDL1 inhibitors.

12035 Poster Session (Board #148), Mon, 1:15 PM-4:45 PM

Correlation of peripheral T cell receptor repertoire with response to neoadjuvant chemotherapy plus trastuzumab in early-stage HER2-positive breast cancer. *First Author: Wenna Wang, Department of Medical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CAMS & PUMC), Beijing, China*

Background: The immune microenvironment of tumor is now emerging as an indicator of responses to anticancer treatment in HER2-positive breast cancer. However, the peripheral blood (PB) TCR repertoire and its interaction with early-stage HER2-positive breast cancer patients treated with chemotherapy plus trastuzumab have not been systemically studied. **Methods:** We investigated the TCR repertoire using next-generation deep sequencing of the complementarity determining region 3 (CDR3) of the TCR β chain in the PB samples from 26 treatment-naïve hormonal receptor (HR)-negative HER2-positive breast cancer patients before and after 2 cycles of chemotherapy plus trastuzumab and 26 age- and gender-matched healthy volunteers. The patient population was obtained from a single-center prospective study between January 2014 and June 2017 (ClinicalTrials.gov, NCT02041338). **Results:** The TCR repertoire in the pre-treatment PB of patients was markedly different from that of healthy volunteers, exhibiting higher TCR density ($P = 0.0001$) and lower evenness ($P = 0.01$). Patients who achieved a pCR ($n = 11$) had a lower TCR density in their pre-treatment PB ($P = 0.0147$) and a higher degree of overlap between the pre- and post-treatment PB TCR repertoires ($P = 0.0488$) than patients who achieved a non-pCR ($n = 15$). The sequences of V segments of the TCR β chain demonstrated significantly lower frequencies of TCR β variable (TRBV) 3-1, TRBV4-2, TRBV12-3, TRBV12-5, TRBV15, TRBV6-2, and TRBV7-7 genes in the pre-treatment PB samples of the pCR group than in the non-pCR group. There were no significant differences in TCR density, diversity, clonality or evenness between pre- and post-treatment PB samples. **Conclusions:** Based on the current study, the TCR repertoire in pre-treatment PB may be used as a predictor of response to neoadjuvant chemotherapy plus trastuzumab in HR-negative HER2-positive breast cancer patients and as a new approach to select patients who will benefit from neoadjuvant therapy.

12036 Poster Session (Board #149), Mon, 1:15 PM-4:45 PM

Circulating tumor DNA as a potential indicator of tumor load during interventional therapy of unresectable hepatocellular carcinoma. *First Author: Yong Li, Center of Intervention radiology, Zhuhai Precision Medicine Center, Zhuhai People's Hospital,Jinan University, Zhuhai,Guangdong 519000, P.R. China, Guangdong, China*

Background: Hepatocellular carcinoma (HCC) is a common malignant tumor, causing high morbidity and mortality. Interventional treatments have improved survival in unresectable hepatocellular carcinoma. Imageology and serologic biomarkers are major methods to evaluate therapeutic efficacy but limited in radiation exposure and accuracy. This study aims to assess feasibility of ctDNA as a potential biomarker to monitor therapeutic response during interventional treatments of HCC. **Methods:** We enrolled 30 HCC patients from 2016 to 2017. Tumor biopsies and matched pretreatment peripheral blood samples were collected. We implemented target capture NGS to identify somatic variants with a panel of 1021 cancer related genes. Blood tumor mutation burden (bTMB) analysis interrogated single nucleotide variants, small insertion and deletion, with VAF ≥0.5 %. **Results:** Somatic genomic alterations were identified in 29 of 30 tumour biopsies (96.7%). TP53 (%), TERT (37.9%), CTNNB1 (13.8%) mutated most frequently in this cohort. Mutations in TP53 was commonly detected at codon 249(R249S). In matched plasma samples, we identified 28 of 30 (93.3%) patients to be positive before interventional treatment. A consistence of detected mutation between ctDNA and tumors is 90% and presented positive relation with tumour load (Pearson $r = 0.48$, $p = 0.01$). Compared with AFP, ctDNA abundance showed a positive correlation with tumour load ($r = 0.61$, $p = 0.0005$). In addition, TP53-mutated samples showed higher bTMB than TP53-wild samples (5.5 vs 2.4 mut/Mb, $p = 0.03$), suggesting a potential better effect when received treatment of immune checkpoint inhibitors. **Conclusions:** Liquid biopsy can reveal the mutation profile of patients of HCC. CtDNA can be used as a potential tool to reflect the tumor load and guide more precise interventional treatments.

12037 Poster Session (Board #150), Mon, 1:15 PM-4:45 PM

Correlation of expression of TK1 in plasma-derived exosomes with clinical response to CDK4/6 inhibitors in breast cancer. *First Author: Marzia Del Re, Clinical Pharmacology and Pharmacogenetics Unit, Department of Clinical and Experimental Medicine, Pisa, Italy*

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) improve PFS in patients with hormone receptor positive (HR+) advanced breast cancer (1). In order to better characterize the response to these agents and increase our knowledge on the pharmacogenetic profile of CDK4/6i, the aim of this study was to analyse the expression of targets relevant to the activity of CDK4/6i in plasma-derived exosomes. **Methods:** Blood samples were collected from patients affected by HR+, HER2- advanced breast cancer receiving a palbociclib in association with hormonal therapy. Three ml of plasma were taken at the beginning of treatment (baseline) and at the first clinical evaluation (after 3 months). Objective responses were defined following the RECIST criteria v.1.1. RNA from plasma-derived exosomes was extracted by the ExoRNeasy kit (Qiagen) and analysed for the expression of thymidine kinase 1 (TK1), CDK 4, 6 and 9 by digital droplet PCR (BioRad). Mann-Whitney test was applied. **Results:** Thirty-eight metastatic breast cancer patients were prospectively enrolled in this study. The comparison of mRNA levels of TK1, CDK4, 6 and 9 between baseline and the first clinical evaluation was available in 5 patients treated with letrozole + palbociclib and 11 patients given fulvestrant + palbociclib. Eight patients had newly diagnosed advanced breast cancer while 9 patients received $>=1$ line of treatment. Objective responses were: 2 (12%) PR, 12 (70%) SD and 3 (18%) PD. The comparison of the expression between TK1, CDK 4, 6 and 9 at baseline and at first evaluation was statistically significant for TK1 (PR+SD vs PD $p = 0.048$). No association was found between the baseline levels of TK1, CDK 4, 6 and 9 and best response or number of disease sites. **Conclusions:** Exosomal TK1 expression may be useful to early identify patients who are likely to respond to CDK4/6i. **Reference:** Finn RS, et al. New England Journal of Medicine. 2016;375(20):1925-36.

12038 Poster Session (Board #151), Mon, 1:15 PM-4:45 PM

Analysis of single circulating tumor cells (CTCs) to identify resistance mutations to ALK-inhibitors in both ALK-gene and bypass oncogenic pathways. *First Author: Emma Pailler, Gustave Roussy, Université Paris-Saclay, "Circulating Tumor Cells" Translational Platform, CNRS UMS3655 – INSERM US23 AMMICA, Villejuif, France*

Background: Non-invasive methods including CTCs are crucial to develop for the implementation of precision medicine in the treatment of NSCLC. *ALK*-rearranged NSCLC patients develop resistance to ALK-inhibitors which manifest by genetic alterations either in the *ALK*-gene itself or in by-pass signaling pathways. Here, we evaluated whether resistance mutations to first-generation ALK-inhibitor crizotinib and third-generation lorlatinib could be identified using individual CTCs. **Methods:** The study included 17 patients at resistance to crizotinib or lorlatinib. Matched tumor-biopsies were available for 3. Two CTC isolation strategies were used. A process including Ampli1 whole-genome amplification, quality controls, multiplex PCR with two panels (Ampli1 CHPCustomBeta cancer panel and a home-made panel targeting the 13 known *ALK* mutations) and Ion Torrent next-generation sequencing was established. Single CTCs or pools of 2-10 CTCs and one $CD45^+$ cell pool were analyzed for each patient. A specific bioinformatic workflow was developed to identify somatic variants including determination of positive predicted value (PPV), allele drop-out (ADO), false-positive rate (FPR). **Results:** PPV, ADO and FPR means were respectively $> 95\%$, 19% and 6.10^{-4} in the seven first patients. A limited number of shared mutations between CTCs and matched tumor-biopsies were identified. Several CTC-private (exclusively present in CTCs and not in matched biopsies) hotspots mutations were identified including in *ALK*-gene such as the F1174L, F1174C or G1202R. Potential by-pass signaling pathways in other oncogenic drivers such *TP53, PIK3CA* and *BRAF* genes were also identified. A much higher degree of mutational diversity was observed in CTCs compared to tumor-biopsies. **Conclusions:** Using a rigorously qualified workflow, we report for the first time that resistance mutations to ALK-inhibitors can be identified in individually isolated CTCs of *ALK*-rearranged patients. Our data demonstrate that both "on-target" and "off-target" resistance mechanisms can be detected in individual CTCs highlighting their important mutational diversity in *ALK*-rearranged patients.

12039 Poster Session (Board #152), Mon, 1:15 PM-4:45 PM

Integration of lymphocyte ratios (LRs) and circulating tumor cells (CTCs) characterization: The interplay between immunity and metastatic breast cancer (MBC). *First Author: Lorenzo Gerratana, Department of Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine; Department of Oncology, University Hospital of Udine, Udine, Italy*

Background: The detection of CTCs in MBC is associated with worse prognosis and metastases development. We evaluated the integration of immunity biomarkers such as monocyte, neutrophil and platelets LRs (MLR, NLR, PLR) with CTCs data to identify new clues about the interaction between MBC and the immune system. **Methods:** The study enrolled 44 MBC patients (pts) at the University Hospital of Udine, Italy, between 2013 and 2015, regardless of the line of treatment. $CD45^{neg}$ circulating cells (CC) were sorted through the DEPArray microfluidic system, based on a multiparametric fluorescence analysis. The $CD45^{neg}$ CC phenotypes were defined as epithelial (E CTC), mesenchymal (MES) and transitional (EM CTC). MLR, NLR and PLR cut-offs were previously obtained through ROC analysis using propensity score-matched healthy controls (Gerratana et al 2018). The association between LRs and $CD45^{neg}$ CC was explored through Kruskal Wallis test. CC subtypes were analyzed both as a percentage of total $CD45^{neg}$ CCs and as absolute values. **Results:** In luminal-like MBC pts, both NLR and PLR were significantly associated with EM CTC ($P = 0.016$), while a trend was observed in respect to MLR. In pts with HER2 positive MBC, PLR was significantly associated with E CTC ($P = 0.042$). Notably, only MLR was associated with EM CTC in the total population ($P = 0.02$). Pts with visceral involvement had higher EM CTC and E CTC when MLR^{high} ($P = 0.036$ and $P = 0.031$, respectively) and E CTC when PLR^{high} ($P = 0.025$), while MES was significantly lower when MLR^{high} ($P = 0.001$). In particular, in case of liver localizations, the MLR^{high} subgroup showed higher E CTC ($P = 0.022$) and lower MES ($P < 0.001$). Pts with bone localizations had lower MES when MLR^{high} ($P = 0.004$). Interestingly, MLR^{high} pts with 2 or more sites of distant involvement, had higher EM CTC and lower MES ($P = 0.015$ and $P < 0.001$, respectively). **Conclusions:** MLR is associated with $CD45^{neg}$ CC subtypes proportions. Particularly intriguing is the direct correlation with EM CTCs suggesting an interlink between CTC and immunity in MBC pathogenesis and progression. Moreover, these findings highlight the need to explore more granular classifications for $CD45^{neg}$ CC.

12040 Poster Session (Board #153), Mon, 1:15 PM-4:45 PM

Circulating tumor cells enumeration (CTCs) and circulating tumor DNA (ctDNA): Clinical and molecular features of "rapidly progressing" stage IV disease (Stage IV_{prog}). *First Author: Lorenzo Gerratana, Department of Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine; Department of Oncology, University Hospital of Udine, Chicago, IL*

Background: Liquid biopsy technologies, including CTCs and ctDNA, have a growingly paramount role in the management of advanced breast cancer (ABC) and are potentially capable to convey different types of information. **Methods:** This retrospective study analyzed 62 ABC patients (pts), characterized with paired CTCs and ctDNA assessments. CTCs were isolated through CellSearch and ctDNA was analyzed using the Guardant360 NGS assay. The previously reported cut-off of 5.7 was used for ctDNA percentage (%ctDNA) (Gerratana et al 2018), while 5 count was used for CTCs. Matched pairs variations in %ctDNA and CTCs at baseline (BL), at the 1st evaluation (E1) and at progression (PD) were tested through Wilcoxon test and associations with clinical variables were tested through Kruskal-Wallis test. Their prognostic impact was explored through Cox regression for progression-free survival (PFS), overall survival (OS) and PFS after E1 (E1_PFS). **Results:** CTCs and %ctDNA were comparable in respect to age at BL, while CTCs were marginally higher in luminal ABC ($P = 0.07$). Pairwise %ctDNA varied significantly between BL and E1 ($P = 0.0012$) and E1 and PD ($P = 0.0016$), but not between BL and PD. No significant variations were observed regarding CTCs, apart from triple negative ABC ($P = 0.035$). Both BL %ctDNA and CTCs had an impact in terms of PFS (HR 1.9, $P = 0.02$ and HR 3.4, $P = 0.003$ respectively) and OS (HR 3.5, $P = 0.021$ and HR 16.6, $P = 0.011$; respectively) but only BL CTCs retained its impact on E1_PFS (HR 3.5, $P = 0.015$). On the other hand, both E1 %ctDNA and CTCs had a prognostic impact on E1_PFS (HR 3.2, $P = 0.009$ and HR 3.2, $P = 0.012$; respectively). Pts with an increased ≥ 5.7 %ctDNA or stable ≥ 5.7 %ctDNA between BL and E1, experienced a worse E1_PFS in respect to pts with stable %ctDNA < 5.7 (HR 9, $P = 0.009$ and HR 3.1, $P = 0.043$; respectively); with a median time to progression after E1 of 22 days and 2.53 months each. **Conclusions:** The study suggests that both CTCs and ctDNA provide non-overlapping information about prognosis and treatment benefit. CTCs describes the underlying metastatic biology, while ctDNA gives a more, quantitative, *real-time* assessment of tumor burden and treatment benefit.

12041 Poster Session (Board #154), Mon, 1:15 PM-4:45 PM

Landscape of kinase rearrangements (kRE) detected in circulating tumor DNA (ctDNA). *First Author: Ben C. Creelan, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: kRE are established oncogenic drivers and therapeutic targets across advanced cancers. Increasingly, clinical activity targeting kRE across tumor types has been reported, largely based on tissue analysis. We sought to describe the pan-cancer landscape of predicted driver kRE identified in ctDNA. **Methods:** Blood samples from 8,567 cancer patients underwent hybrid capture-based genomic profiling of ctDNA. We evaluated rearrangements in 6 genes (*ALK, EGFR, FGFR3, PDGFRA, RET, ROS1)* for which selected introns are baited, and 7 others (*BRAF, ERBB2, FGFR1, FGFR2, MET, PDGFRB, RAF1).* Only samples with detectable ctDNA were included in analysis (N = 6,571). **Results:** kRE were observed in 4.9% of lung cancer (LC) cases (N = 2,709) and 2.4% of non-lung (nLC) (N = 3,862), including 223 unique cases (3.4% overall) with 254 kRE events (Table). The most commonly rearranged kinases were *ALK (45%), RET (15%), ROS1* (15%), *FGFR3 (8%), FGFR2* (5%), and *EGFR (4%).* The frequency of kinases altered by kRE varied by anatomic origin, with *FGFR2* events identified only outside lung cancer ($p < 0.001$) (Table 1). Top recurrent kRE were *EML4-ALK* (61 LC + 7 nLC), *FGFR3-TACC3* (7 + 11), *KIF5B-RET* (9 + 2), *CD74-ROS1* (9 + 1), and *CCDC6-RET* (5 + 3). Comparison with > 70,000 tissue genomic profiles analyzed over the same time period showed *ALK*, *RET*, or *ROS1* kRE in 4.3% of ctDNA and 4.9% of tissue LC samples, and 1.3% of nLC ctDNA and 0.4% of tissue nLC. 65% of kRE detected in ctDNA were also detected in paired tissue samples (N = 43), including 9 of 11 collected < 30 days apart. **Conclusions:** Kinase fusions and rearrangements exist across tumor types and can be detected by liquid biopsy. Comparison of genomic profiles of ctDNA to tissue suggest similar frequencies of *ALK*, *RET* or *ROS1* kRE in lung, but a higher frequency of kRE in non-lung samples by ctDNA vs tissue, perhaps reflecting greater heterogeneity.

ctDNA-detected kRE across solid tumors.

Cancer	Total N	N with kRE	%	*ALK*	*RET*	*ROS1*	*FGFR2*	*FGFR3*	*EGFR*
Lung	2709	134	4.9%	78	20	19		7	4
Non-lung	3862	93	2.4%	20	16	14	12	13	6
Breast	933	16	1.7%	3	4		2	3	2
Unknown primary	618	19	3.1%	4	2	6	4	2	1
Prostate	390	8	2.1%	3	1	2		2	
Colorectal	500	18	3.6%	5	3	3	2		1
Pancreas	332	9	2.7%	1	3	1	1		
Liver	120	5	4.2%	1			3		
Ovarian	181	1	0.6%		1				
Bladder	57	3	5.3%		1			2	
Esophagus	56	2	3.6%					1	1

12042 Poster Session (Board #155), Mon, 1:15 PM-4:45 PM

Circulating tumor DNA as biomarker in mutant malignant melanoma. *First Author: Jan Braune, Department of Hematology and Oncology, University Medical Center, Freiburg, Germany*

Background: Available biomarkers LDH and S100B possess limited sensitivity and specificity to predict outcome in melanoma. In this pilot study we evaluated the use of circulating tumor (ct)DNA harboring BRAF and NRAS mutations as a predictive biomarker for treatment response and progression-free survival (PFS) in patients with locally advanced or metastatic melanoma. **Methods:** We analyzed 168 retrospective plasma samples from 40 unselected pts, and 311 samples from 33 pts included in a prospective trial (DRKS00009507). We included stage III disease with planned resection or stage IV disease before initiation or change of medical treatment. Blood samples were taken at baseline at d +8, d +28, and thereafter at 3 months intervals for up to two years. We developed hydrolysis probe based, Locked Nucleic Acid assays to detect BRAF, NRAS and wild type ctDNA by droplet digital PCR. Results were correlated with LDH, S100B and PFS. **Results:** Sensitivity of the specific assays was 0.01% with a limit of Blank of 0.28 copies/well. Of 37 stage IV pts with retrospective samples, 29 were positive for ctDNA at least once (78%). Out of eight negative pts, three were in CR, three had SD, and two were negative despite measurable disease. Positive pts had a mean of 9 (range: 1-17) and 283 (range: 0.1-16,388) ctDNA copies/mL for stage III and stage IV respectively. The presence of ctDNA one month after therapy initiation indicated poor PFS (hazard ratio [HR] 1.9, 95% CI 0.85-4.44). No measureable increase in ctDNA was a favorable prognostic factor for PFS for all therapies (hazard ratio [HR] 0.30, 95% CI 0.05-2.56) with a median PFS of 4.5 vs. 3.1 months (range 0.9-17.5 vs. 1.5-9.1) and particularly for those receiving Immunotherapy (hazard ratio [HR] 0.07, 95%CI 0.007-0.68) with a median PFS of 8.8 vs. 2.6 (range 1.8-17.5 vs 1.5-3.1). Based on 290 measurement pairs, ctDNA strongly correlated with S100 (r = 0.73) and LDH (r = 0.52). **Conclusions:** Residual ctDNA early after change or institution of treatment predicted tumor progression at first clinical response assessment. A positive to negative conversion or a decrease indicated a more favorable course especially for those receiving immunotherapy. These data support the use of ctDNA as an early predictive marker for treatment response. Clinical trial information: DRKS00009507.

12043 Poster Session (Board #156), Mon, 1:15 PM-4:45 PM

Predictive tools for bevacizumab therapy in patients with aggressive HER 2-negative metastatic breast cancer: 2-years results from an observational study. *First Author: Encarnación González Flores, H. Virgen de las Nieves, Granada, Spain*

Background: The determination of monitoring Circulating Tumor Cells (CTC) in patients (pts) with metastatic breast cancer (MBC) is a well-established prognostic marker of efficacy/tolerance. We aimed to determine the predictive value of the normalization of CTC in terms of clinical benefit. **Methods:** Multicenter, prospective, observational study in pts with aggressive HER2-negative MBC amenable to receive first-line treatment with chemotherapy plus bevacizumab. A 18-month follow-up is planned. CTC levels were determinated in baseline (BL) and after the first cycle. The Spearman correlation coefficient was calculated to CTC and biomarkers. Interim analysis of 2-years with data on the correlation and progression free survival (PFS). **Results:** At database cut, 111 evaluable pts were enrolled: median (range) age 54.1 (46.4-61.3) years; ECOG 0/1: 50.5/39.6%. Median (range) time from diagnosis was 2.9 (0.8-7.2) years, and 28.8% of pts were "di novo" MBC. Neoadjuvant and/or adjuvant therapy was received by 70.3% pts and 73.0% underwent surgery. Histological grade III found in 49.3% of pts; ER-positive in 74.6% and PR-positive in 50.8%. Metastases were mainly located in liver (62.2%), bone (57.7%) and lung (40.5%). Mean (SD) CTC levels: 83.4 (333.8)/7.5 mL BL and 3.6(10.3)/7.5 mL after first cycle. According to this change, 89.5% were sensitive. Discontinuation in 28 pts (75.0% exitus; 3.6% progression). A 3.5% had complete response, 50.6% partial response and 25.9% stable disease. Median follow-up was 8.2 (5.3-12.9) months. The median PFS was 11.0 (6.6-15.4) months. Median overall survival was not reached. BL CTC levels had a significant correlation with CEA ($p < 0.05$) and CA 15.3 ($p < 0.001$). Overall, 79.3% pts presented at least one toxicity. Most common grade III/IV toxicities were hypertension (8.1%), peripheral neuropathy (3.6%), neurotoxicity (3.6%) and neutropenia (2.7%). Two grade V toxicities reported abdominal sepsis and pain upper. **Conclusions:** The preliminary data shows a correlation with CTC levels and other tested biomarkers. No safety concerns were addressed.

12044 Poster Session (Board #157), Mon, 1:15 PM-4:45 PM

A priori filtering of post-operative (post-op) circulating tumor DNA (ctDNA) to predict recurrence in post-metastasectomy colorectal cancer patients (CRC pts) without knowledge of tumor genotype. *First Author: Michael J. Overman, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ctDNA in post-op CRC pts correlates with molecular residual disease and may be useful to guide adjuvant therapy. However, initial studies employed clinically impractical assays indexed to individual pt-specific tumor tissue-defined mutations or were confounded by non-tumor-associated somatic alterations, including variants related to clonal hematopoiesis. **Methods:** 51 CRC pts undergoing curative intent metastasectomy were prospectively recruited at a single institution. Pre and post-op (1-17 days) plasma was sequenced to high depth using a 23-gene NGS panel with 96% theoretical sensitivity for CRC. Tumor tissue was sequenced using this panel or local testing. ctDNA profiles from 4000 CRC pts (Guardant Health) were used to train a variant classifier to predict truncal CRC mutations. **Results:** At median follow up of 10 months (range 1.2-57.7), 37 of 51 pts recurred (median 7.8 months, range 1.2-34.5). Based on post-op mutation detection alone, ctDNA was identified in 31 of 36 recurrent (sensitivity 86% [71-96%]) and 9 of 15 non-recurrent pts (specificity 60% [32-84%]). When restricted to variants detected in tumor tissue, ctDNA was identified in 14 of 31 recurrent (sensitivity 38% [27-64%]) and 0 of 10 non-recurrent pts (specificity 100% [69-100%]). When filtered by the variant classifier, post-op ctDNA was found in 18 of 36 (sensitivity 50% [33-67%]) recurrent pts and 0 of 15 non-recurrent pts (specificity 100% [78-100%]). Median somatic allelic fraction was similar after tumor tissue- and classifier-based filtering (median 0.48% vs. 0.65%, range 0.02-20.0%). **Conclusions:** Recurrence prediction using post-op somatic variant detection alone is fraught by a high clinical false positive rate. Filtering using tumor tissue is effective but reduces sensitivity substantially and is clinically impractical. However, filtering using a variant classifier without knowledge of tumor genotype eliminated false positives and maintained clinical sensitivity in this cohort. *A priori* variant classification may enable clinically feasible ctDNA diagnostics for adjuvant decision making in early-stage disease.

12045 Poster Session (Board #158), Mon, 1:15 PM-4:45 PM

Mutation count, a potential surrogate for tumor mutation load, of circulating tumor DNA (ctDNA) using targeted panel sequencing correlates with clinical outcomes in late stage lung adenocarcinoma and small cell lung cancer. *First Author: Stephanie Yaung, Roche Sequencing Solutions, Pleasanton, CA*

Background: Studies show that mutation count can be used as a biomarker to predict whether or not a patient may respond to immunotherapy or chemoradiation therapy. However, mutation count is usually determined by whole exome sequencing or large targeted panel sequencing of tumor tissue DNA. Tissue biopsy is often inaccessible for many late stage lung cancer patients. **Methods:** We assessed mutation count using the AVENIO ctDNA Surveillance Kit, a targeted next-generation sequencing panel of 198 kilobases, on pre-treatment plasma samples from a prospective, observational study, where 43 late stage lung adenocarcinoma and 72 late stage small cell lung cancers (SCLC) treated with first-line chemo or chemoradiation therapies were initially assessed. Synonymous and prevalent driver mutations were filtered out from the detected somatic mutations prior to calculating a mutation count per megabase. Subjects were classified as high mutation count if the filtered somatic mutation count was above the bottom tertile of their cancer type. **Results:** We detected somatic variants in all 43 lung adenocarcinoma and 72 SCLC subjects with a median mutation count of 9 and 14, respectively. Lung adenocarcinoma subjects with low mutation count showed better survival in terms of overall survival (OS) (18.3 vs 7.8 mo, HR 0.41, p = 0.026) and progression free survival (PFS) (6.2 vs 4.3 mo, HR 0.51, p = 0.042). SCLC subjects with low mutation count had shorter OS (9.3 vs 14.1 mo, HR 1.75, p = 0.034) and a similar trend in PFS. **Conclusions:** We were able to derive a ctDNA-based mutation count from a panel the size of one-fifth of a megabase and identified an association between low mutation count and better prognosis in subjects with late stage lung adenocarcinoma treated with chemo or chemoradiation therapy. In late stage SCLC, however, high mutation count correlated with better prognosis. Our findings suggest differences in lung cancer histology are key to understanding measurements of mutation count and their potential to predict outcome on chemotherapy. Studies to further validate these results are ongoing.

12046 Poster Session (Board #159), Mon, 1:15 PM-4:45 PM

Use of cell-free DNA for management of breast and lung cancer by academic and community providers. *First Author: Roby Antony Thomas, University of Pittsburgh Medical Center, Pittsburgh, PA*

Background: Next-generation sequencing of cell-free DNA (cfDNA) can assess presence of somatic genomic alterations in patients with cancer without an invasive biopsy. Results may guide therapeutic decision-making. We evaluated use of cfDNA test results for management of breast and lung cancer in a major healthcare system with academic and community-based practices. **Methods:** Retrospective review of cfDNA tests (Guardant360) ordered for patients with breast or lung cancer at the University of Pittsburgh Medical Center between 8/2014 and 3/2017 was performed. For patients with actionable results (lung: alterations with FDA-approved or NCCN-recommended targeted therapy; breast: ERBB2, ESR1 or PIK3CA alterations), information on clinical care was abstracted. Differences in clinical use of test results were evaluated between academic and community providers. **Results:** In total, 230 tests were ordered for 218 subjects; 128 by academic and 102 by community providers. Community providers ordered significantly ($P < 0.05$) more tests for lung cancer patients than academic providers (78% vs. 47%) and their patients were older (mean age: 65.5 vs. 60.3 yrs.). Actionable alterations were identified in 82 subjects (38%; 48 breast, 34 lung). Six were excluded from further analyses because their mutations had been known previously. For 32 (42%) of the remaining 76 subjects, actionable results led to a change in therapy, for the other 44 it did not. Reasons for not changing therapy included: patient died or lost to follow up, palliative care elected, treatment targeted a different molecular finding, targeted therapy recommended but cost prohibitive, and patient currently stable but results could guide therapy at progression. Actionable results significantly more often resulted in a management change for lung cancer than breast cancer (63% vs. 28%). Use of test results differed significantly between academic and community providers (result led to change: 31% vs. 61%) **Conclusions:** Results of cfDNA tests were used to guide therapy changes, especially for patients with lung cancer. Community practice-based providers appear to act on actionable results more often than academic center-based providers in this health care system.

12047 Poster Session (Board #160), Mon, 1:15 PM-4:45 PM

Liquid biopsies (LB) across treatment of 29 metastatic colorectal cancer (mCRC) patients (pts) to reveal driver mutations and tumor evolution with anti-EGFR therapy: Experience in a GI oncology clinic at Fox Chase Cancer Center. *First Author: Pooja Ghatalia, Fox Chase Cancer Center, Philadelphia, PA*

Background: LB captures dynamic genomic alterations (alts) across mCRC therapy and may complement tissue biopsy (TB). We sought to describe the utility of LB and better understand mCRC biology. **Methods:** We identified 29 pts with mCRC who underwent LB (Guardant360; 2016-17). We used non-parametric methods to measure correlations between alts, highest allelic fraction (maxpct) and clinical variables. We used Kendall's tau to describe correlations. **Results:** Of 29 pts, 14 (48.2%) were women; 17 (58.6%) had colon and the rest rectal cancer. Pts received a median of 2 (range 0-7) lines of therapy before LB. 15 pts had limited testing on TB (*RAS/RAF/TP53/APC*), 11 had extended NGS and 2 no TB. Of 3 pts with 0 alts in LB, only 1 had NED on CT. LB was performed due to inability to get TB in 5 pts and to assess mutation load or targetable alterations in 24 pts. Median maxpct was 11% (range 0-83.9%). Median number of alts was 5 (range 0-43). One pt with MSI-H on TB had LB 11 alts while a pt with 27 alts was MSS. MSI status was not done in 1 pt with 43 LB alts. Maxpct and alts correlated with CEA ($p = 0.002$, $p < 0.001$, respectively). In 3/5 pts with serial LB, CEA correlated with maxpct trend and CT tumor burden. In 6 pts mutant *RAS* was seen in LB only; 5/6 had received anti-EGFR therapy prior to LB, suggesting *RAS* alts developed post-therapy. In 2 pts *RAS*-mutated by TB, no *RAS* alts were detected on LB, due to low disease burden on CT at time of LB that also did not reveal *APC* or *TP53* alts. In 1 pt with serial LB, a *KRAS* alt was found in TB and the first LB but subsequent LB showed no *KRAS* alts post-treatment. Mean number of alts was higher post anti-EGFR LB (n = 12) vs anti-EGFR naïve LB (n = 24) (10.6 vs 5.3, p = 0.009). More alts were also noted in post anti-EGFR therapy LB vs *KRAS* wt anti-EGFR-naïve LB (n = 8) (10.6 vs 4.9, p = 0.055) and *KRAS* mutant anti-EGFR-naïve LB (n = 16) (11.6 vs 5.6, p = 0.056). 1 pt had LB pre- and post-anti-EGFR therapy but alts remained the same. **Conclusions:** LB across mCRC therapy detects driver mutations, monitors disease burden, and identifies sub-clonal alts that reflect drug resistance, tumor evolution and heterogeneity.

12048 Poster Session (Board #161), Mon, 1:15 PM-4:45 PM

Duvelisib inhibition of chemokines in patients with CLL (DUO study) and iNHL (DYNAMO study). *First Author: David T. Weaver, Verastem, Inc., Needham, MA*

Background: Duvelisib (IPI-145) (DUV) is an oral dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ being developed to treat B-cell malignancies. PI3K-δ inhibition directly targets proliferation and survival of malignant leukemia and lymphoma cells, while PI3K-γ inhibition modulates the tumor microenvironment (TME) through key support cells, including tumor-associated macrophages, nurse-like stroma and T cells, and via soluble factors stimulating tumor growth, survival and migration. The Phase 3 DUO study in relapsed/refractory (RR) CLL/SLL and the Phase 2 DYNAMO study in RR iNHL both met their primary endpoints (Flinn, ASH 2017; Zinzani EHA 2017). **Methods:** DUO (NCT02004522) pts were randomized to DUV (n = 160) or ofatumumab (OFA) (n = 159). DYNAMO (NCT01882803) pts (n = 129) received DUV. Serum from baseline and C2D1 was used for correlative studies of 24 chemokines, cytokines and serum factors. Bonferroni-Holm adjustment for multiple comparisons was applied. **Results:** In DUO, CCL1, CCL17, CXCL9, CXCL10, CXCL11, and IL-10 were reduced in pts treated with DUV (median % inhibition = 43.8%) but not in those treated with OFA ($p \leq 0.0009$). Eight chemokines were reduced in both treatment arms, but the level of reduction was significantly greater for DUV pts (median % inhibition, DUV 64.6% vs OFA 26.8%; $p \leq 0.001$). Many of the chemokines inhibited following DUV treatment are associated with the TME, including TNFα, IL-10, IL2Rα, IL12P40, CCL1, CCL17, CCL19, CXCL9, CXCL10, CXCL11, and CXCL13. In DYNAMO, 13 corresponding chemokines were also inhibited ($p \leq 0.008$), including TME factors. Reductions occurred rapidly (by C2D1) in both studies. In DUO, there was a correlation between duration of response and reduction (highest quartile) of the following chemokines: CCL17 (19.4 mo. Q4 vs 10.4 mo. Q1-3), CXCL11 (14.9 mo. Q4 vs 10.9 mo. Q1-3) IL-6 (16.6 mo. Q4 vs 10.9 mo. Q1-3), TRAIL (24 mo. Q4 vs 10.3 mo. Q1-3), VEGF_D (24 mo. Q4 vs 10.9 mo. Q1-3), TPO (14.9 mo. Q4 vs 10.9 mo. Q1-3). **Conclusions:** Pts with CLL and iNHL treated with DUV monotherapy showed significant reduction of chemokines potentially derived from the tumor cells and TME. Further investigation of the effects of DUV on TME pharmacodynamic markers is warranted. Clinical trial information: NCT02004522; NCT01882803.

12049 Poster Session (Board #162), Mon, 1:15 PM-4:45 PM

Immunoprofiling in intrahepatic cholangiocarcinoma (IHCC). *First Author: Roberto Carmagnani Pestana, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Molecular profiling has become important in directing therapy for IHCC, while not much has been described about the immune environment of this disease. Understanding the immune milieu could highlight potential options for immunotherapy (IT). **Methods:** We performed a retrospective institutional review of 99 surgically resected IHCC from February 2007 to November 2016. Immunohistochemistry was performed using 13 immune antibodies including CD3, CD4, TIM-3, PD-1, and ICOS. Overall survival (OS) was defined as the time from surgery to death date or last follow-up (f/u). OS was estimated by Kaplan-Meier method, and differences were assessed by two-sided log-rank tests. Cox proportional hazards regression models were used to assess association between pt characteristics and OS. **Results:** Median age: 62 yrs (range, 24-83), females (61%), T stage (T1/T2; 75%), w/o metastasis (90%), and w/o neoadjuvant chemotherapy (NACT) (73%). Median f/u among survivors :3.0 yrs (range 0.04 to 9.1). Median OS was 6.3 yrs (95% CI: 3.6 – NE). Among B- and T-lymphoid cells, $CD3^+$ T-cells represented the dominant population and were predominantly located in the invasive margin (IM). Positivity for PD-1 was seen in 4.7 centrally located, tumor infiltrative lymphocytes (CL-TI)/mm^2 and 14.2 CL-TI/mm^2 were positive for TIM-3. Univariate Cox analysis revealed that longer OS was significantly associated w/ a high number of CL-TI CD3+ (HR 0.78; p=.044) and CD4+ (HR 0.76; p=.05) immune cells, and lower CL-TI TIM-3+ cells (HR 0.87; p=.01). *Multivariate Cox analysis* demonstrated *that* lower number of CL-TI TIM-3+ cells (HR 0.87; p=.01) was an independent predictor of improved OS. Expression of CL-TI TIM-3+ cell was significantly associated with higher CL-TI CD3+ ($p<.001$), CD4+(p=.003), and PD1+ ($p<.001$) immune cells. Expression of a membrane-bound form of B7-H4 was significantly increased in pt that received NACT (p=.013). **Conclusions:** Our findings identify CL-TI CD3+/CD4+ and TIM-3 expression as independent prognostic factors following surgical resection in IHCC and shed light on changes in immune markers with NACT. This study represents one of the largest analyses of the immune environment of IHCC and suggests potential targets for drug development with IT in this disease.

12050 Poster Session (Board #163), Mon, 1:15 PM-4:45 PM

Immunologic and clinical implications of CD73 expression in non-small cell lung cancer (NSCLC). *First Author: Lee Chun Park, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: CD73, known as ecto-5'-nucleotidase and encoded by the *NT5E* gene, is a pivotal enzyme that converts extracellular adenosine monophosphate (AMP) into adenosine, which promotes tumor growth by impairing anti-tumor T cell immunity. Several preclinical studies noted that the pharmacologic inhibition of CD73 led to improved immune response and thus highlighted the value of CD73 as a therapeutic target for cancer immunotherapy. **Methods:** CD73 expression was explored from The Cancer Genome Atlas (TCGA) database including patients with adenocarcinoma (n = 517) and squamous cell carcinoma (n = 501) of the lung. We stratified samples based on mRNA expression level (low, low-intermediate, intermediate-high, high). Immune profiling (immune cell infiltration, immune checkpoints, and cytokines), tumor mutational burden (TMB), neoantigen burden, and survival outcome were analyzed between the CD73 high group (CD73-H) and CD73 low group (CD73-L). The tumor immune landscape was analyzed using the signatures derived from 812 'immune metagenes' that predict the immune infiltration of 31 distinct immune cells for each tumor sample (Angelova, M. *et al*, 2015). **Results:** In NSCLC, CD73-H showed significantly lower infiltration of activated CD4 and CD8 T cells compared with CD73-L (41% vs 20%, $P< 0.01$; 47% vs 28%, $P< 0.01$ respectively). In addition, PD-L1 (*CD274*), *ICOS*, *TGFB1*, and *IL1B* expression positively correlated with CD73 expression. However, TMB and neoantigen burden demonstrated no significant differences between the two groups. CD73-H had significantly shorter overall survival (OS) and disease free survival (DFS) compared with CD73-L (OS median 62 vs 44 months, $P< 0.01$; DFS median 83 vs 34 months, $P< 0.01$). Additionally, CD73 expression was significantly increased in samples with EGFR mutations when compared with wild type (mean z-score 0.77 vs -0.06, $P= 0.03$). **Conclusions:** This is the first report to illustrate an inverse association between CD73 expression and tumor infiltration of activated CD4 and CD8 T cells, as analyzed in over 1,000 human lung cancer samples. In addition, CD73-H demonstrated unfavorable survival outcome compared with CD73-L. CD73 remains a promising target for cancer immune modulation.

12052 Poster Session (Board #165), Mon, 1:15 PM-4:45 PM

TP53 mutations and programmed cell death ligand-1 expression in solid tumors: Associations with clinical factors and outcomes. *First Author: Ed Kheder, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The regulation of Programmed cell death ligand-1 (PD-L1) expression remains poorly understood. Preclinical data suggest that TP53, via microRNA-34, regulates PD-L1 expression in lung adenocarcinoma cell-line. We aimed to estimate the correlation between TP53 mutations and PD-L1 expression in solid tumors. **Methods:** We reviewed pathology, immunohistochemical (IHC) and mutational analysis reports of patients who were diagnosed with advanced solid tumors and treated at MD Anderson Cancer Center. We used Kaplan-Meier, logistic regression, and Cox PH regression, for statistical analysis. Survival was computed from date of biopsy used for mutational analysis. **Results:** We analyzed data from 302 patients [136(45%) female, 163 (55%) male; median age: 57 years, range (16-83); median OS: 43 month]. One hundred and three (34%) patients had TP53 mutations, 105 (35%) patients had PD-L1 $\geq$ 1%, and 50 (18%) had both. Tumor types (%): GI 41 (14%); GU 36 (12%); non-small cell lung cancer (NSCLC) 54 (18%); melanoma 40 (13%); sarcoma 27 (9%); head and neck (HNC) 21 (7%); others 83 (27%). The association between TP53 mutations and tumoral PD-L1 expression was significant across all patients [OR: 2.47, 95%CI (1.5-4.07). p = 0.0003], but changed significantly with tumor type (p = 0.021): OR: 5.3 sarcoma; 5.2 "other"; 3.6 NSCLC; 1.4 melanoma; 1.1 GU; 0.7 GI. The odds of PD-L1 expression increased with age [30 year increase OR: 1.84, 95%CI (1.01, 3.38). p = 0.044], but not sex [OR: 1.0, 95%CI (0.6, 1.7). p = 0.87]. TP53 mutation was associated with worse OS [HR = 1.6, 95% CI (1.1, 2.2). p = 0.010] and PD-L1+ with better OS [HR = 0.6, 95% CI (0.4, 0.8). p = 0.0042]. The effect of PD-L1 on OS did not depend on TP53 mutation status (p = 0.37). Among PD-L1+ and PD-L1- patients, OS was related to tumor type ($p < 0.004$). One-year survival rate of patients treated with PD-1 or PD-L1 inhibitors in phase I trials was independent of PD-L1/TP53 status (p = 0.53). **Conclusions:** PD-L1 expression is multifactorial. TP53 mutations are highly associated with PD-L1 expression across solid tumors but association significantly varies among tumor types.

12053 Poster Session (Board #166), Mon, 1:15 PM-4:45 PM

GBR1302: Effect of CD3-HER2, a bispecific T cell engager antibody, in trastuzumab-resistant cancers. *First Author: Jonathan Back, Glenmark Pharmaceuticals SA, La Chaux-De-Fonds, Switzerland*

Background: Current therapies targeting HER2 overexpressing cancers, such as Herceptin (trastuzumab) and Kadcyla (T-DM1), have proven beneficial but therapeutic benefit is limited by many resistance mechanisms. Checkpoint inhibition therapies demonstrate the potential of mobilizing T cell activities to elicit anti-tumor responses, but these T cell tumor-specific immune responses are highly immune contexture-dependent. Using Glenmark's BEAT platform, we developed GBR 1302, a T cell redirecting antibody targeting CD3 and HER2, as an alternative way of leveraging T cell potency against tumor cells, independently of existing tumor immune response. **Methods:** In vitro cytotoxic assays. In vivo tumor models. Ex vivo assay recreating native TME, including immune compartment, stroma and vasculature. **Results:** Preclinical pharmacology studies demonstrated that GBR 1302 can trigger a potent killing of HER2 positive (IHC3+) as well as HER2 equivocal (IHC2+) cancer cells while maintaining an acceptable therapeutic window on cells expressing normal levels of HER2. In vitro assays, as well as in vivo tumor models comparing the potency of GBR 1302 to trastuzumab or T-DM1 demonstrated a superior cytotoxic potential for GBR 1302 against a variety of tumor cells and that GBR1302 is effective in trastuzumab resistant tumors in vitro and in vivo. To further translate these observations into a clinically relevant human context, we studied the effects of GBR1302, as a single agent and combination partner, in a patient derived tumor microenvironment matched ex vivo assay with co-culture of autologous immune system and tumor tissue from 50 subjects with varying levels of HER2 expression ranging from 3+ to 1+. GBR 1302 treatment arm was compared to trastuzumab and to a combination of GBR 1302 + a PD-1 inhibitor on metastatic breast, gastric and gastro-esophageal cancers. GBR 1302 is currently in a phase 1 dose escalation clinical trial in HER2 positive and equivocal cancers. Preliminary data from peripheral blood biomarkers indicate that GBR 1302 triggers relevant T cell activation and cytokine production.

12054 Poster Session (Board #167), Mon, 1:15 PM-4:45 PM

Isolation of CD4$^+$ T cells specific for neoantigens created by recurrent driver mutations in non-small cell lung cancer (NSCLC) and melanoma. *First Author: Joshua Veatch, Hutchinson Cancer Rsrch Ctr, Seattle, WA*

Background: T cells specific for neoantigens encoded by mutated genes are increasingly recognized as mediators of tumor destruction after immune checkpoint inhibitor therapy or adoptive cell transfer. Unfortunately, almost all neoantigens result from random mutations that are patient-specific. Here, we describe CD4$^+$ T cell responses one melanoma patient and two NSCLC patients that are specific for recurrent driver mutations in their cancers. **Methods:** Neoantigen-reactive T cells were expanded and cloned by peptide stimulation of the peripheral blood from cancer patients. **Results:** The melanoma patient had a CD4$^+$ T cell response to the peptide encoded by the BRAF V600E mutation found in 40% of melanoma, and obtained a complete response following adoptive transfer of tumor infiltrating lymphocytes (TIL). The BRAF V600E specific cells showed a Th1 memory phenotype, were preferentially localized to the tumor at the time of resection, and expanded and persisted in blood greater than 2 years after TIL therapy. Gene transfer of the BRAF V600E-specific T cell receptor (TCR) conferred recognition of class II MHC positive cells expressing the BRAF mutation. A CD4$^+$ T cell response specific for KRAS G12V that is present in 5% of NSCLC and 10% of colon cancer was detected in one NSCLC patient. A second NSCLC patient had a CD4$^+$ T cell response specific for the Her2 internal tandem duplication (ITD) found in 4% of NSCLC, and deep sequencing of TCR genes showed the mutation-specific T cell clone was enriched in a tumor resection sample, relative to the non-adjacent lung. The CD4$^+$ T cells specific for the BRAF V600E, KRAS G12V, and Her2 ITD epitopes only recognized the mutant and not the wild-type peptide and were restricted by common class II HLA alleles found in 10-25% of the population. The neoantigen reactive Her2 and KRAS reactive TCRs are currently being cloned. **Conclusions:** This study greatly expands the number of driver mutations with known T cell responses, and suggests that adoptive transfer or vaccination strategies targeting recurrent driver mutations could help interrogate the role of CD4$^+$ T cells in human anti-tumor immunity, and could have clinical activity across multiple patients.

12055 Poster Session (Board #168), Mon, 1:15 PM-4:45 PM

Synergy of TLR4 agonist GSK1795091, an innate immune activator, with agonistic antibody against co-stimulatory immune checkpoint molecule OX40 in cancer immunotherapy. *First Author: Hua-Xin Gao, GSK, Collegeville, PA*

Background: GSK1795091 (aka, GSK'091) is a synthetic glycolipid toll-like receptor 4 (TLR4) agonist. TLR4 is a Pattern Recognition Receptor for host defense against bacterial infection, expressed on innate immune cells monocytes, macrophages, dendritic cells. GSK'091 is a potent and selective TLR4 agonist and is being evaluated for use in combination with other immunotherapies to treat cancer **Methods:** To understand the antitumor activity and pharmacologic effects of intravenously administered GSK'091, *in vivo* studies were performed in murine syngeneic tumor models. Pharmacodynamic (PD) effects of GSK'091 was examined in peripheral and tumor infiltrating lymphocytes (TILs) using multicolor flow cytometry assays. Additionally, TCRβ sequencing, Nano string and multiplex cytokine assays were employed to understand the molecular and cellular mechanisms induced by this molecule **Results:** GSK'091 potently activated the immune system and modulated the tumor microenvironment by inducing an array of proinflammatory cytokines, enhancing antigen presentation, activating T cells, and reducing T regulatory cells. At doses sufficient to induce systemic cytokines in mice, GSK'091 inhibited tumor growth and resulted in long term survival in tumor model. When administrated with OX86, a murine surrogate OX40 agonist monoclonal antibody (mAb), the combination induced a robust PD response as demonstrated by a significant increase in Th1 cytokines, expression of interferon regulated genes, higher tumor infiltration by leucocytes, increase in T cell activation , proliferation and increase in the CD8: Treg ratio. Additionally, GSK'091 when combined with anti-OX40 induced clonal expansion of T-cells and drove synergistic interferon and T-cell dependent anti-tumor response **Conclusions:** The current study demonstrated that GSK'091 activates key initiating immune pathways and can induce robust anti-tumor efficacy when combined with agonistic antibodies directed against the OX40 receptor. This novel combination provides a strong rationale and supports evaluation of GSK'091 in combination with immuno-oncology agents in clinical trials

12056 Poster Session (Board #169), Mon, 1:15 PM-4:45 PM

Dependency of radiotherapy and combinatorial radio-immunotherapy responses on the systemic t cell immune response. *First Author: Kevin Lee Min Chua, National Cancer Centre Singapore, Singapore, Singapore*

Background: Combinatorial immune checkpoint blockade (ICB) with radiotherapy (RT) potentiates anti-tumour response via modulation of the immune microenvironment. However, detailed host-specific mechanisms underpinning dramatic clinical responses of RT-ICB are poorly understood. Here, we performed deep characterization of the systemic immune response in circulating T cells following treatment with RT and RT-ICB. **Methods:** We recruited a cohort of 29 patients with biopsy-proven metastatic cancers (10 prostate, 10 EBV+ nasopharynx, 9 others) who underwent RT (N = 13) or RT-ICB (N = 16; anti-PD1/-PDL1/-CTLA4), under a prospective observational study protocol. All patients received ablative RT (8-50 Gy in 1-5 fractions). Patient blood samples were longitudinally collected at following timepoints: baseline, 2 d, 7 d, and 14 d post-RT/RT-ICB. Circulating T cells were profiled by a customized CyTOF panel of 41 T cell surface markers, and analyzed using the t-SNE method (ACCENSE v3.0). **Results:** Median follow-up was 3.6 mo (0.5–8 mo). At time of reporting, 26 of 29 patients had evaluable lesions; response of any kind was observed in 9 of 12 cases in the RT cohort and 12 of 14 cases in the RT-ICB cohort. However, we observed increased complete response rates at 1 mo in the RT-ICB than RT group (50% vs 8%). Additionally, we observed abscopal responses in 2 of 14 RT-ICB cases. We detected significant shifts in the CD8+ and CD4+ T cells that peaked 7 d post-RT ($P < 0.001$). Interestingly, the majority of responses (67%) involved the expansion of a distinct immunophenotype of elevated Tbet^{Dim}CD28^{high} effector memory CD8+ and CD4+ T cells post-RT. These responses were reproduced in the RT-ICB cohort; in particular, CD28^{high}CD27^{high} CD4+ T cells were increased in the exceptional responders ($P = 0.027$). Lastly, for a patient with abscopal response, this was associated with a 25% reduction of TH2 CD4+ T cells. **Conclusions:** Here, we characterized the systemic immune repertoire of circulating CD8+ and CD4+ T cells in response to RT, either alone or in combination with immunotherapy. Our data suggests that expansion of a distinct CD28^{high}CD27^{high} CD4+ T cell population may account for the dramatic responses to RT-immunotherapy.

12057 Poster Session (Board #170), Mon, 1:15 PM-4:45 PM

Association of Akt inhibition with change in immunophenotype of tumor microenvironment (TME) in breast cancer (BC). *First Author: Douglas Kanter Marks, Columbia University Medical Center, New York, NY*

Background: The PI3K/Akt/mTOR pathway is a known regulator of oncogenic growth in BC. In addition, this pathway also modulates host immune function and may indirectly affect tumorigenesis. Clinicopathologic studies have demonstrated that tumor infiltrating lymphocyte density is predictive of chemosensitivity and improved prognosis in BC, while myeloid infiltration has been hypothesized to play a deleterious role. To define the impact of Akt inhibition on the TME, we analyzed tumor tissue from patients (pts) with early-stage BC treated with MK-2206, an Akt inhibitor, as part of a pre-surgical trial (NCT01319539). **Methods:** Transcriptomic analysis was performed on surgical specimens to assess if differences exist in mRNA expression of tumor-associated and immune genes between pts treated with MK-2206 (n = 6) and untreated matched controls (n = 5) (nanoString). Quantitative immunofluorescence (qmIF) was performed for CD3, CD8, CD4, FOXP3, CD68, Pancytokeratin on 4uM sections from biopsy and surgical specimens of both groups. Images acquired using Vectra (PerkinElmer), allowing for multiparameter phenotyping. Statistical analysis performed using t-Test and Z- test. **Results:** mRNA expression supports in vivo activity of MK-2206 with decreased expression of cell cycle, proliferation and antiapoptotic genes (CTNNB1, CCND2, BAX, $p < 0.05$) and a numerical decrease in FasL ($p = 0.12$) in MK-2206 treated pts. Additionally, MK-2206 was associated with marked decrease of expression of myeloid markers (CSF1R, CD163, TGFBR2, CLEC7A) in post-treatment tissue ($p < 0.05$). On qmIF analysis, MK-2206 treated pts exhibited a significant increase in median CD3+CD8+ cell (CTL) density between pretreatment biopsy and surgical excision specimens, as compared to the control pts (87% vs.0.2%, $p < 0.05$). **Conclusions:** Combined mRNA and qmIF analysis suggest that Akt inhibition, may decrease myeloid infiltration and increase recruitment of CTLs. Thus, Akt inhibition may promote a favorable TME. At present, there are both FDA approved and investigational agents that target the PI3K pathway. Further investigation is warranted to understand the impact of Akt inhibition on the TME and its potential therapeutic implication.

12058 Poster Session (Board #171), Mon, 1:15 PM-4:45 PM

Tumor PD-L1 heterogeneity in non-small cell lung cancer: Does biopsy size and volume matter? *First Author: Monica Khunger, Cleveland Clinic, Cleveland, OH*

Background: Although patients with high tumor programmed death ligand-1 (PD-L1) expression benefit from PD-1/PD-L1 axis inhibitors, many studies have highlighted that a fraction of patients respond to these agents despite lacking detectable PD-L1 expression. Heterogeneity of tumor PD-L1 expression within the tumor has been postulated to be contributing to the limited performance of PD-L1 as a predictive biomarker. We evaluated the PD-L1 expression heterogeneity by comparing the percentage of PD-L1 positive tumor cells as a measure of tumor PD-L1 proportion scores (TPS) using fluorescence immunohistochemistry in paired whole tissue sections (WTS) and tissue microarray (TMA) cores from surgical non-small cell lung cancer (NSCLC) specimens. **Methods:** WTS and two 0.6mm TMA cores localized at least 3mm apart from each other were prepared from each formalin-fixed, paraffin-embedded surgically resected tumor specimens of 451 patients with stage I-III NSCLC. Using quantitative immunofluorescence with the E1L3N anti-PD-L1 antibody, TPS were generated in TMA and corresponding WTS and classified as 0%, 1-49% and ≥50%. **Results:** There was a high discordance between the TPS scores of PD-L1 expression among the WTS and TMA cores (discordance rate = 40.6%, 95% CI, 35.4%-45.9%; k = 0.26). Moderate discordance was observed between the TPS of PD-L1 expression among the two TMA cores (discordance rate = 10.2%, 95% CI, 7.6%-13.5%; k = 0.609). **Conclusions:** Discrepancies among the PD-L1 expression between WTS and TMA core as well as between TMA cores themselves represents intratumoral heterogeneity of PD-L1. Small needle aspirations or biopsies during endobronchial or CT-guided biopsy, which can be equated to TMA core, may not be representative of the true tumor PD-L1 expression. It is imperative to obtain bigger or multiple needle biopsies to identify patients with true positive tumor PD-L1 expression and maximize the number of patients who could benefit from PD-1/PD-L1 axis inhibitors.

12059 Poster Session (Board #172), Mon, 1:15 PM-4:45 PM

PD-1/PD-L1 interaction and CD25/FOXP3+ t cells to predict survival benefit from adjuvant chemotherapy in early stage non–small-cell lung cancer (ES-NSCLC). *First Author: Jennifer Bordeaux, Navigate BioPharma Services, Inc, Carlsbad, CA*

Background: Adjuvant chemotherapy (ACT) for ES-NSCLC provides only a modest improvement in survival and is associated with serious adverse effects. Thus, identifying subgroups of ES-NSCLC patients who will benefit from ACT is of high clinical relevance. Utilizing novel digital pathology algorithms, we evaluated relationship between pre-treatment tumor immune microenvironment and survival benefit from ACT in ES-NSCLC patients. **Methods:** 451 tissue sections of formalin-fixed, paraffin embedded surgical resection specimens from ES-NSCLC patients with/without ACT were tested with multiplexed fluorescence immunohistochemistry assays designed to detect key immune cell markers such as PD-1, PD-L1, CD4, CD8, CD25, FOXP3 and Ki67. Fluorescence Images were acquired on the Vectra platform (Perkin Elmer) and analyzed with novel AQUA algorithms designed to accurately measure the co-localization of PD-1 and PD-L1 (the Interaction Score), regulatory (CD25+/FOXP3+) and activated (Ki67+) T cell subsets. **Results:** High PD-1/PD-L1 Interaction Scores (≥ 643) and regulatory T cell burden (≥ 1%) in pre-treatment tumors exhibited significant correlations with improved recurrence free ($p = 0.003$) and overall survival ($p = 0.004$) in patients receiving ACT after surgery, whereas no difference in survival was observed for patients who received surgery alone ($p > 0.5$). Median RFS was not reached in signature positive patients vs 93.2 months in signature negative patients. Interestingly, the levels of PD-1 or PD-L1 alone did not predict survival for surgery + ACT or surgery alone patient populations. **Conclusions:** PD-1/PD-L1 Interaction Score and CD25/FOXP3 positive T cells are predictive of benefit from ACT in patients with ES-NSCLC. Future studies will determine if these biomarker signatures can be used to select patients that may be spared chemotherapy without compromising outcome.

12060 Poster Session (Board #173), Mon, 1:15 PM-4:45 PM

Exploring effects of MEK inhibition in tumor microenvironment in non-small cell lung cancer (NSCLC) pre-clinical models. *First Author: Tarik Silk, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NSCLCs often harbor mutations in the KRAS oncogene and require improved treatment to provide durable disease control. Targeted therapy via MEK inhibition shows promising but temporary control of tumor growth but ultimately fails with a quick rebound of tumor growth. As the RAS-RAF-MEK-ERK pathway is evolutionarily conserved in most cells, MEK inhibition may cause broader effects in the tumor microenvironment. **Methods:** We examined the effect of novel pulsatile versus standard continuous MEK inhibition on lymphocytes and myeloid cells. KRAS tumor bearing mice were treated with selumetinib and T cells were analyzed for phenotypic changes. Tumor progression and survival with and without the addition of checkpoint blockade therapy was also monitored. In vitro experiments were also conducted with murine bone marrow-derived macrophages subsequently exposed to pulsatile or continuous selumetinib treatment. **Results:** MEK inhibition in T cells shows significant effects on T cell activation and proliferation. CD8+ T cell phenotypes increased CTLA-4, Ki67 and 4-1BB expression when treated with pulsatile compared to continuous MEK inhibitor, suggesting greater activation and proliferation status. Pulsatile MEK inhibitor therapy with CTLA-4 checkpoint blockade showed improved overall survival compared to continuous treatment in a mouse model of Kras mutant lung cancer. We extended our investigation to other tumor microenvironment components particularly myeloid cells. In vitro experiments revealed that pulsatile versus continuous treatment with the clinical MEK1/2 inhibitor selumetinib differentially effects macrophage viability and pro-inflammatory cytokine production. **Conclusions:** Pulsatile MEK inhibition improves T cell activation and prolongs survival in combination with anti-CTLA-4, compared with continuous treatment. It also has a modulating effect on myeloid cells compared to the standard continuous dosing. Optimizing MEK inhibition scheduling to target cancer cells and activate immune infiltrates will provide the best therapy for KRAS mutant NSCLC. These data will contribute to informing design immune modulation with targeted therapies in patients.

12061 Poster Session (Board #174), Mon, 1:15 PM-4:45 PM

Computer extracted features of cancer nuclei from H&E stained tissues of tumor predicts response to nivolumab in non-small cell lung cancer. *First Author: Xiangxue Wang, Case Western Reserve University, Cleveland, OH*

Background: Immune checkpoint inhibitors have recently been FDA-approved for use in advanced stage non-small cell lung cancer (NSCLC). These drugs target the PD-1 receptor or its ligand PD-L1, but treated patients only have a response rate of about 20%. It is thus crucial to identify which patients will derive maximal benefit from such treatments, especially since the current gold standard biomarker, detection of tissue-based PD-L1 expression, has been shown to be inadequate. Previous studies have shown that computer extracted features of nuclear shape and texture are predictive of recurrence in early stage NSCLC. The goal of this work is to evaluate the role of features of nuclei shape and arrangement in the tumor in predicting response to Nivolumab for NSCLC. **Methods:** The study included 56 patients with NSCLC from two different institutions who had had pre-treatment tumor biopsies and were treated with Nivolumab. The patients were split into two categories, responders and non-responders, that were determined by clinical improvement and radiologic assessment through RECIST criteria. The 245 features from tumor nuclei included standard measures used to characterize shape and texture of nuclei as well graph based features that capture the distinct spatial arrangement of the nuclei. Features were extracted from tumor regions manually annotated on digitized H&E images by two expert pathologists. **Results:** A statistical feature selection method determined the top five tumor nuclear features from the training set. These features included the spatial arrangement of nuclei and variance in nuclear shape and chromatin structure. A machine learning classifier trained with these top five features yielded an AUC = 0.65 on the training set (n = 32) and an AUC = 0.6 on the independent validation set from a separate institution. (n = 24). **Conclusions:** Computer extracted features of cancer nuclei were found to distinguish between patients who did and did not respond to Nivolumab immunotherapy. Validation is needed on larger cohorts from multiple different sites.

12062 Poster Session (Board #175), Mon, 1:15 PM-4:45 PM

Upfront next generation sequencing in NSCLC: A publicly funded perspective. *First Author: Kirstin Perdrizet, University of Toronto, Toronto, ON, Canada*

Background: A growing number of actionable targets in non small cell lung cancer (NSCLC) have led to the need for molecular profiling beyond the standard of care (SOC) *EGFR/ALK*. Here we present actionable targets, impact on patient treatment, clinical trial opportunities and costs using the Illumina TruSight Tumour 15 panel (TST15) for NSCLC samples. **Methods:** In addition to immunohistochemistry for ALK and PDL-1, tissue-based next generation sequencing using the TST15 was reflexively performed on all new non-squamous NSCLC specimens at the University Health Network (Toronto, Canada) between February and December 2017. The panel identifies hot spot mutations in *KRAS*, *EGFR*, *TP53*, *PIK3CA*, *BRAF*, *ERBB2*, *FOXL2*, *GNA11*, *GNAQ*, *KIT*, *NRAS*, *PDGFRA*, *RET*, *AKT1* and *MET*, but not fusions, copy number variations (CNV) nor *MET* exon 14 skipping mutations. Patient age, stage, pathologic subtype and genotyping results were collected prospectively. Treatment changes as a result of TST15 and clinical trial opportunities (using clinicaltrials.gov) were identified. Incremental testing costs were based on direct laboratory costs, but not personnel and administration costs. **Results:** Testing included 284 samples from 282 patients. The TST15 panel identified 343 mutations from 284 samples. Sample demographics include: male/female 53/47%, stage 1/2/3/4 33/7/16/44%. Incremental actionable targets beyond *EGFR* and *ALK* were identified in 2.6% of specimens (*ERBB2* 1.7%, *BRAF* V600E 0.9%). Most mutations occurred in *TP53* (43%), *EGFR* (25%) and *KRAS* (24%), with co-mutations in 31% (*TP53*, *KRAS*, *EGFR*). To date, one patient has had a treatment change as a result of TST15 beyond targeting *EGFR*. Above SOC clinical trial options were identified for 73% of stage IV and 25% of stage III patients. 3.6 samples were needed to identify one actionable mutation, predominantly in *EGFR*, at an estimated cost of $1919 CAD per target. **Conclusions:** Extended genotyping with TST15 in NSCLC identifies many actionable mutations and improves clinical trial options for patients. Despite this, impact on patient treatment beyond targeting *EGFR* is minimal. To enhance the number of targets and minimize costs, population-based comprehensive testing with a panel that includes fusions/CNV is needed.

12063 Poster Session (Board #176), Mon, 1:15 PM-4:45 PM

The role of dynamic susceptibility contrast perfusion- weighted MRI in the estimation of IDH mutation in gliomas. *First Author: Sotirios Bisdas, University College London, London, United Kingdom*

Background: The presence of mutation in the encoding gene of isocitrate-dehydrogenase (IDH) has been defined as a molecular biomarker in the diagnosis and differentiation of gliomas. Dynamic Susceptibility Contrast Perfusion- Weighted Imaging (DSC - PWI) is a relatively recently established technique for gliomas staging and its diagnostic accuracy may benefit when using sophisticated image analysis algorithms. In this study, we aimed to investigate whether DSC - PWI, enhanced by texture analysis and machine learning, can stratify gliomas according to their IDH mutation status. **Methods:** 208 patients (F/ M : 84 / 119, median age : 47 [range 21-81 years]) from a multicenter setting, who have have been immunohistopathologically diagnosed with gliomas (IDH positive / negative: 98 / 105) were prospectively included in our study. The raw data from DSC - PWI was processed on a dedicated workstation, using a fully adaptive Bayesian method, to create leakage-corrected relative cerebral blood volume (rCBV) maps. Tumours were manually segmented and registered to rCBV maps. rCBV maps were used to generate distribution and rotational invariant Haralick texture features over the tumour mask. The predictive power of the extracted features in differentiating between IDH status was assessed in a 2-fold cross-validation setting of 1000 iterations using support vector machine and multinomial ordinal regression, respectively. **Results:** Overall sensitivity and specificity rates for the rCBV for IDH stratification were 68% and 81%, respectively. All except one of the ten classical histogram statistics and 12 texture features appeared significantly different across mutation status ($p < 0.05$) when using non parametric Wilcoxon test. In the case of the classification across grading, the same features led to a distance error (difference between the real and predicted grade) inferior or equal to 1 in 88.6 % of the cases and an exact prediction in 57.2% of cases. **Conclusions:** Preliminary results are promising in the differentiation of gliomas with DSC- PWI on the basis of IDH mutation status, especially regarding the high specificity rates obtained using features from rCBV data.

12064 Poster Session (Board #177), Mon, 1:15 PM-4:45 PM

Resolving diagnostic uncertainty in bone-predominant metastases in cancer of unknown primary (CUP) using the 92-gene assay. *First Author: Kanwal Pratap Singh Raghav, Department of GI Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Bone-predominant metastases in patients (pts) with CUP pose diagnostic challenges in pathologic analyses, which may delay optimal therapy. The 92-gene assay is a validated gene expression profiling (GEP)–based cancer classifier with high accuracy in limited tissue. This study evaluated performance and clinical utility of the 92-gene assay in bone biopsies from bone-predominant CUP. **Methods:** A correlative database integrating 92-gene assay (CancerTYPE ID) results and de-identified patient data was developed under an IRB-approved protocol for 26,594 cases where the assay was performed in routine care. Database was queried using biopsy site of bone/skeletal designation (rib, pelvis, vertebrae, sacrum, femur). Descriptive statistics and Chi-square analyses were used. **Results:** 7% (n = 1834) of cases were bone specimens. With an analytical success rate of 70%, a molecular diagnosis was made in 94% cases, among which pancreaticobiliary (Pb; 19%), NSCLC (14%), and kidney (8.3%) were most frequently classified tumors. Kidney, sarcoma, liver, salivary gland, and thyroid were more prevalent with bone biopsies (all $p < 0.05$), while neuroendocrine, intestine, ovary, and endometrium were more frequent with non-bone cases (all $p < 0.05$). In Pb subtypes, gallbladder showed a higher proportion of bone cases ($p < 0.001$) compared to cholangiocarcinoma and pancreas. Higher frequency of immune-responsive tumor types was observed in bone vs non-bone biopsies (44% vs 35%), with kidney and liver predictions 2-3x more frequent in bone samples ($p < 0.0001$). **Conclusions:** The 92-gene assay is effective for molecular diagnosis in bone-predominant CUP. In this large cohort of bone biopsies, tumor type results matched previously reported frequencies of CUP putative primaries. A notable subset of bone-predominant CUP was identified as having a molecular diagnosis with an FDA-approved indication for immunotherapy. These results indicate a promising avenue for a GEP classifier to identify immune-responsive CUP subsets. Given the limited nature of bone samples, tissue-sparing GEP assay should be considered early in the diagnostic workup to direct biomarker testing and treatment selection.

12065 Poster Session (Board #178), Mon, 1:15 PM-4:45 PM

Whole genome sequencing in metastatic breast cancer: Lessons learned from the BC Cancer personalized oncogenomics program. *First Author: Nathalie LeVasseur, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: The emerging interest in precision medicine has lead to the genomic profiling of breast cancer, with the intent of identifying therapeutically targetable alterations. The clinical relevance of whole genome sequencing (WGS) and RNA-sequencing as compared to targeted next generation sequencing (NGS) remains uncertain. Moreover refined data is needed to identify which patients benefit most from molecular profiling. **Methods:** Informative and actionable findings from WGS in metastatic breast cancer patients between 2012-2017 were reviewed and compared to FoundationOne and MSKCC-IMPACT targeted panels. The data providing rationale for informative and actionable findings was compiled using an RNA/DNA heatmap. Comparison of signal nucleotide variants (SNVs) mutation signatures and mutational burden was compared across histological and molecular subtypes and between aging-driven and non-aging driven tumours. **Results:** WGS of 139 metastatic breast cancer patients revealed that 77% of actionable items arose from expression data, 60% from mutations, 45% from copy number changes, 28% from mutation signature, mutation burden, or homologous recombination deficiency (HRD) and 5% from structural variants (SV). The majority (7616/7998, 95%) of mutations were only detected by WGS, representing mostly passenger mutations, whereas driver mutations were also identified with the genes included in the FoundationOne (339/7998, 4%) and MSKCC-IMPACT panels (201/7998, 3%). No significant differences in mutation burden were identified among subtypes, although tumors whose somatic mutagenesis was driven predominantly by aging-related processes displayed lower mutation burdens. More frequent elevation of HRD-associated mutation signatures of SNV/SV were identified in triple-negative/basal-like tumors. **Conclusions:** While most actionable mutations were covered by pre-existing targeted panels, expression data represents a significant proportion of actionable information obtained from WGS. Mutational burden did not vary significantly among subtypes. Signature properties and their relation to molecular subtypes remains an interesting arena for clinical application.

12066 Poster Session (Board #179), Mon, 1:15 PM-4:45 PM

Clinical significance of enterocyte-specific gene polymorphisms as candidate marker of oxaliplatin-based treatment for metastatic colorectal cancer. *First Author: Mitsukuni Suenaga, USC Keck School of Medicine Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: An enterocyte subtype of the Colorectal Cancer (CRC) Assigner classifier has shown to confer benefit from oxaliplatin in adjuvant treatment for stage III CRC. *MS4A12* belongs to the enterocyte subtype-specific gene, whose expression is regulated by endogenous CDX2. We tested whether single nucleotide polymorphisms (SNPs) in enterocyte-related genes predict oxaliplatin efficacy in first-line treatment for metastatic CRC (mCRC). **Methods:** Three different cohorts of mCRC patients (pts) (total 603) were included in this study: discovery cohort receiving FOLFOX ± bevacizumab (BV) (n = 146, median age = 61, median follow-up = 45.0 mos); validation cohort receiving FOLFOXIRI + BV (n = 230, TRIBE arm B, median age = 60, median follow-up = 46.5 mos); and control cohort receiving FOLFIRI + BV (n = 228, TRIBE arm A, median age = 60, median follow-up = 49.3 mos). SNPs were analyzed by PCR-based direct sequencing. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier curves, log-rank test, and Cox proportional hazards regression. **Results:** Among the SNPs tested in the discovery cohort, *MS4A12* rs4939378 and *CDX2* rs3812863 were extracted as potential markers of efficacy. In the validation cohort, any G allele in *MS4A12* rs4939378 was associated with longer PFS than the A/A variant in univariate analysis (12.4 vs. 10.9 mos, HR 0.70, 95% CI: 0.49-0.99, *P*= 0.033) and multivariable analysis (HR 0.65, 95%CI: 0.44-0.97, *P*= 0.035). The findings were more evident in the *KRAS* mutant than *KRAS* wild-type pts. In contrast, *KRAS* wild-type mCRC pts with the G/G variant in *CDX2* rs3812863 had a longer PFS than those with any A allele (32.3 vs. 10.3 mos, HR 0.39, 95%CI: 0.19-0.81, *P*= 0.004), and the trend remained in multivariable analysis though without statistical significance (HR 0.48, 95%CI: 0.21-1.09, *P*= 0.08). These findings were not confirmed in the control cohort. **Conclusions:** The enterocyte subtype might affect the antitumor activity of oxaliplatin in not only early stage but also metastatic disease in CRC. Genetic variants in *MS4A12* and *CDX2* gene polymorphisms may serve as potential predictive marker of oxaliplatin-based treatment in mCRC pts.

12067 Poster Session (Board #180), Mon, 1:15 PM-4:45 PM

Poly-ligand profiling (PLP) to differentiate pancreatic cancer patients who benefit from gemcitabine+evofosfamide versus gemcitabine+placebo treatment. *First Author: Valeriy Domenyuk, Caris Life Sciences, Phoenix, AZ*

Background: The MAESTRO trial randomized 693 locally advanced or metastatic pancreatic cancer patients to gemcitabine (G) + placebo vs G + evofosfamide (GE). OS hazard ratio (HR) was 0.84; p = 0.059. We developed a PLP assay that identifies patients most likely to benefit from GE vs G alone. By capitalizing on ssDNA aptamer binding properties, PLP measures network changes in tumors, including those that predict drug response. **Methods:** FFPE tissues of pancreatic cancer patients from the MAESTRO trial with good (OS > 13 mos) or poor (OS < 7 mos) outcome from GE were used for PLP assay development. Assay cut-points were determined using a training set (n = 12) and performance metrics were then determined using an independent blinded test set (n = 172). The study population enrolled in MAESTRO was divided into four cohorts based on treatment and benefit (cut-point = 240 days). The assay performance from the blinded test set was used to generate 1000 different possible patient subsets. Each simulation represents one possible trial outcome if the PLP assay had been used to enroll patients. We used the average value of the simulated median increase in OS from the 1000 random selections to estimate the impact the PLP assay would have had on MAESTRO. **Results:** 97% of the simulations yielded log-rank p < 0.05. Compared to MAESTRO, the average median OS increase for GE improved by 116±38% (simulation s.d.) with an average HR of 0.72±0.04. Moreover, the sample size in the simulations was 49% smaller compared to the original study, reflecting the percentage of test positive patients in the blinded test set. When only data from primary tumors were used, 100% of the permutations yielded log-rank p < 0.05 with an average median OS increase of 216±36% compared to MAESTRO and an average HR of 0.63±0.03. **Conclusions:** This retrospective study demonstrates that PLP, if prospectively applied, likely would have resulted in a successful study comparing GE to G pancreatic cancer patients. PLP is a powerful, flexible and facile platform warrants further study of additional therapies and in prospective trials.

12068 Poster Session (Board #181), Mon, 1:15 PM-4:45 PM

Identification of clonal hematopoiesis mutations in solid tumor patients undergoing unpaired commercial next-generation sequencing assays. *First Author: Catherine Callaghan Coombs, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Precision medicine is increasingly utilized for both prognostication and application of targeted therapies for oncologic patients (pts). Results from next-generation sequencing (NGS) assays ideally should reflect the burden of somatic tumor mutations (muts), yet challenges can arise from differentiation of germline muts and from contamination of biopsies by non-tumor tissue. Clonal hematopoiesis (CH), defined by the presence of somatic muts typically in leukemia-associated genes in hematopoietic cells, occurs in aging individuals, with an increased risk for hematologic cancers and shorter survival in pts with solid tumors (ST). Here we examine the prevalence of CH leading to false positive (FP) calls on commercial NGS assays. **Methods:** This is a multi-institution, retrospective cohort study of pts undergoing NGS of ST. All pts undergoing commercial NGS (Foundation Medicine) testing were examined (N = 768 at UNC and 989 at MCC). For a subset of pts (N = 64 at UNC and 30 at MCC), NGS of paired blood samples was performed to examine the prevalence of true CH events, defined as a variant allele frequency (VAF) in the blood exceeding the VAF in the tumor tissue. Germline events were defined by VAF > 35% in both tumor and blood. **Results:** Muts in genes that are frequently altered in CH (*DNMT3A*, *TET2*, *ASXL1*, *TP53*, *ATM*, *CHEK2*, *SF3B1*, *CBL*, *JAK2*) were identified in 65% of pts; excluding *TP53*, often mutated in ST, these events were seen in 35% of pts. A bimodal distribution of VAFs was seen for CH genes, with low VAF events most suggestive of true CH events. Using paired blood samples, we confirmed such muts as true CH events in 9.4% of ST pts in the UNC cohort. Across all genes, germline events were reported in 23% of UNC pts, of which 33% were known or likely pathogenic variants. MCC samples were enriched for pts with reported muts in CH genes; 33% of which (10/30) were confirmed as true CH events. The majority of *DNMT3A* muts (64%, 7/11) were CH; the minority of *TP53* muts (4%, 2/50) were CH. **Conclusions:** Muts in CH genes are commonly reported on unpaired clinical NGS testing of ST; some are true CH events as opposed to TS events. It is important to recognize CH as a possible FP when applying NGS results to pt care.

12069 Poster Session (Board #182), Mon, 1:15 PM-4:45 PM

Molecular subtypes of triple-negative breast cancer (TNBC) tumor samples obtained before and after neoadjuvant systemic therapy (NST) and relationship between immunomodulatory (IM) gene signature and intensity of tumor-infiltrating lymphocytes (TILs). *First Author: Hiroko Masuda, Department of Surgical oncology, Showa University, Tokyo, Japan*

Background: Lehmann et al have identified 4 molecular subtypes of TNBC [basal-like (BL) 1, BL2, mesenchymal (M), and luminal androgen receptor (LAR)] and an IM gene expression signature. Our group previously showed that response of TNBC to NST differs by molecular subtype, but whether NST affects TNBC subtype has not been studied. We hypothesized that certain TNBC subtypes change after NST. We also tested whether IM signature correlates with the intensity of TILs. **Methods:** From the World TNBC Consortium dataset, which contains TNBC samples from 4 institutions from 4 countries, we examined 68 formalin-fixed, paraffin-embedded tumor samples from patients treated with NST: 27 pairs of matched pre-NST and post-NST samples and 14 pre-NST samples. TNBC classification was performed with the Insight TNBCtype assay. We compared the molecular subtypes of TNBC samples obtained before and after NST. We used the Spearman correlation test to investigate the association between IM status and percentage of TILs in all 68 samples. **Results:** The distribution of TNBC subtypes before and after NST is shown in the Table. Of the 27 matched pairs, 14 (52%) showed a change in TNBC subtype after NST. Among the 14 matched pairs with a subtype change, all 7 cases of BL1 subtype before NST changed to M, and 4 of 5 cases of LAR subtype before NST converted to BL2 (one LAR changed to unclarified). As expected, a low residual cancer burden (RCB 1) was more common in patients with (4/14 [29%]) than in patients without subtype change (1/13 [8%]); however, subtype change and amount of residual cancer were not related statistically (p = 0.32), most likely due to the small sample size. There was a strong positive correlation (rho 0.95, p = 0.0008) between TIL intensity and IM gene signature positivity. **Conclusions:** TNBC molecular subtype frequently changed after NST. TIL intensity positively correlated with IM signature. We will validate our findings in a larger group of samples in the World TNBC Consortium dataset. Subtype Distribution

Subtype	Pre-NST (%)	Post-NST(%)
BL1	37	11
BL2	11	22
LAR	37	22
M	15	37
Unstable	—	8

12070 Poster Session (Board #183), Mon, 1:15 PM-4:45 PM

Novel platform for monitoring bladder cancer recurrence using expression analysis of small non-coding RNAs. *First Author: Ilija Aleksic, Albany Medical College, Albany, NY*

Background: Bladder cancer patients are routinely monitored after treatment by cystoscopy due to a high rate of recurrence. In the absence of an accurate non-invasive screening test to monitor recurrence, bladder cancer will remain the most expensive malignancy to manage. We have developed a non-invasive test that interrogates small non-coding RNAs (sncRNAs) present in urinary exosomes. Analyzing the urine exosome data with a novel statistical classification algorithm provides a platform that unequivocally differentiates between patients with no evidence of disease and those with recurrence. **Methods:** Urine samples were collected from patients previously treated for bladder cancer (n = 82) who are currently under routine surveillance cystoscopy. Patients without bladder cancer or without evidence of recurrent disease served as the control cohort. A Sentinel sncRNA signature specific for bladder cancer was generated by interrogation of urine exosomal RNAs on Affymetrix 4.0 arrays that probes for > 6600 sncRNAs. A customized platform to interrogate the most informative (~120) Sentinel sncRNAs, was then used to screen urine exosomal RNA derived from patients at risk for recurrent disease. Data were then analyzed using a statistical classification algorithm that provides the miR-BCPx (bladder cancer progression score). This novel analytical approach requires no *a priori* knowledge of the sncRNA function to generate an unbiased classification into those with stable disease versus those with recurrent tumor. **Results:** Bladder cancer patients have significantly elevated levels of exosomal RNA relative to control cohort. In a small blinded testing male cohort, comparison of the miR-BCPx score generated to the disease status demonstrates that the miR-BCPx identifies patients with recurrent tumor with 100% sensitivity (59/59) and 96% specificity (22/23). **Conclusions:** Implementation of the miR-BCPx as a surveillance screen for bladder cancer patients provides an affordable, non-invasive alternative to cystoscopy for monitoring disease stability, and can readily be deployed in the clinic to reduce the number of screening cystoscopies needed.

12071 Poster Session (Board #184), Mon, 1:15 PM-4:45 PM

Survival of patients treated by a Precision Oncology approach is determined by performance status and lines of therapy. *First Author: Bat-Ami Gordon, Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Academic Medical Centers (AMC) and community practices are implementing Molecular Tumor Boards (MTB) to interpret next-generation sequencing (NGS) results and develop clinical guidelines for utilizing NGS results. Reports of MTB experiences from cancer centers nationally vary in their abilities to translate molecular test results to actionable recommendations for their patients. In these efforts, there is not yet a definition for parameters of patients who would benefit most from a Precision Oncology approach. **Methods:** Defining Platforms for Individualized Cancer Treatment (DePICT) is an IRB approved registry trial designed to monitor outcomes of Broward County, FL residents with late-stage refractory cancer (ECOG ≤2) who undergo NGS. After consent, the MTB used NGS results to match patients to targeted clinical trials and therapies. The patients are followed at 12 week intervals. DePICT has consented 141 patients, out of which 111 have had at least one follow up. We analyzed these cases to identify key characteristics of patients that benefit most from NGS testing and MTB review. Groups were defined as those who pursued targeted therapies versus those who pursued standard of care or palliative regimens. Kaplan Meier survival analyses were done in R 3.4.3. **Results:** Patients with ≤3 previous lines of therapy were more likely to pursue targeted therapy than patients with ≥4 lines of therapy (32% vs. 17%, p = 0.045). Only patients with an ECOG score 0 or 1 pursued targeted therapy. An analysis of this population (ECOG < 2, ≤3 lines of therapy) revealed that patients on targeted therapy performed better than their palliative care counterparts. Median overall survival (mOS) for patients who received targeted therapy is 84 weeks (95% CI 36-Not Reached (NR)) and the mOS for patients who did not undergo targeted therapies was 36 weeks (95% CI 36-NR). **Conclusions:** This analysis identifies patients who may benefit most from NGS testing. Patients with ECOG scores of 0 or 1 and 3 or fewer lines of therapy were more likely to go on targeted therapy, and have better outcomes. Patients should be evaluated by precision oncology approaches earlier in their cancer care continuum.

12072 Poster Session (Board #185), Mon, 1:15 PM-4:45 PM

A cell cycle-related RNA expression signature of neoantigen burden in lung adenocarcinoma. *First Author: Michael F Sharpnack, The Ohio State University, Columbus, OH*

Background: Tumor somatic mutation burden (TMB) and neoantigen burden (NB), are emerging therapeutic biomarkers for immune checkpoint blockade in NSCLC; however, these biomarkers are costly and require extensive expertise to measure. Cheaper, simpler surrogate biomarkers are necessary to keep up with current translational research findings. **Methods:** We curated RNAseq, NB, and clinical data from The Cancer Genome Atlas (TCGA) for lung adenocarcinoma (LUAD, n = 461) tumors. Gene-level RNAseq data was correlated with TMB and NB, and ontological enrichment of genes associated with these quantities are discovered using the enrichR tool. In addition, RNA expression and TMB data from lung adenocarcinoma cell lines were curated from the Cancer Cell Line Encyclopedia. Neural network and penalized linear regression methods were used to create and test RNA expression signatures of somatic mutation and neoantigen burden. The code for these methods was implemented in R. **Results:** 5199 genes' RNA expression are significantly correlated with NB (Spearman correlation, Benjamin hochberg q-value < 0.01). Genes positively associated with NB are highly enriched in cell cycle related genes (pathway database, corrected p-value < 0.01). Further, we correlated RNA expression with mutation burden in lung adenocarcinoma cell lines and found a similar enrichment of cell cycle related genes. We created RNA expression signatures of NB using two separate methods and tested their performance on TCGA LUAD tumors using a random cross validation approach. Neural network and penalized linear regression cross-validation experiments had mean AUCs of 0.74 and 0.68, respectively. The final signatures were selected based on consistent and accurate performance on LUAD tumors. 50 genes were selected for the final signature, including *YBX2*, *TDRKH*, *HDGF* and others. **Conclusions:** Cell cycle-related RNA abundances are strongly associated with NB in LUAD. We show that these genes can be incorporated into a biomarker of NB. We are in the process of validating this RNA signature's ability to predict NB with a NanoString RNA panel on a separate LUAD cohort and investigating its implication in lung cancer immunotherapy.

12073 Poster Session (Board #186), Mon, 1:15 PM-4:45 PM

Plasma sequencing of ctDNA in early stage breast cancer as part of the screening process. *First Author: Begona Jimenez Rodriguez, Unidad de Gestión Clínica Intercentros de Oncología, Hospitales Universitarios Regional y Virgen de la Victoria de Málaga, Malaga, Spain*

Background: Mammography is the current standard of care for breast cancer (BC) screening. However, not all cancers are detectable on mammography and not all mammographic findings represent cancer, moreover, the confirmatory biopsy is not always 100% informative due to the intrinsic intratumor heterogeneity. The aim of this study was to investigate the power of ctDNA to both confirm and interrogate disease status beyond mammography findings by comparing ctDNA mutation results to those obtained by tissue sequencing. **Methods:** Matched blood and fresh tissue biopsies were collected from 56 patients with BIRADS 4c/5 mammography findings and subsequent diagnosis of primary BC. The blood draw was performed immediately before the tissue biopsy. The NGS study on fresh frozen tissue samples was performed using a customized design of TruSeq Custom Amplicon Low Input Panel (Illumina), which includes the full region of PIK3CA, TP53, CDH1, GATA3, PIK3R1 and MAP2K4 genes (most commonly mutated ganes in early stage BC according to TCGA). Plasma sequencing was performed using Plasma SafeSeq (PSS). **Results:** At the time of this analysis, 29 matched samples were analyzed for TP53 and PIK3CA mutations. Median age was 64y(44-92), 56% of patients has mammographic lesions greater than 2cm, 35% of patients had grade 3 tumors and % of IHQ tumor subtypes was 52% LumA, 30.5% LumB, 13% TNBC and 4.5% Her2-enriched. At least 1 mutation was detected in each patient in the tissue analysis, with 10 *TP53* and 24 *PIK3CA* different mutations detected overall. PSS detected TP53 and PIK3CA mutations in 10 of these 29 patients. Concordance of plasma and tumor mutations was observed in 8 of 29 patients (27.6%) [3 TP53 (c.637C > T, c.398T > A,c.587G > C); 4 PIK3CA (c.3140A > G, c.1633G > A,C.1624G > A, C.3145G > C), 1 with both mutations (TP53 c.743G > T, PIK3CAC.3140A > T)]. Additionally, PSS revealed 4 plasma mutations that were not identified in the tissue (3 TP53, 1 PIK3CA). **Conclusions:** Mutations in ctDNA can be readily detected using a highly sensitive plasma sequencing method in early-stage breast cancer patients. These findings suggest that early ctDNA testing can provide critical clinical information that may improve patient diagnosis.

12074 Poster Session (Board #187), Mon, 1:15 PM-4:45 PM

Comparison of the prognostic performance between OncoMasTR and OncotypeDX multigene signatures in hormone receptor-positive, HER2-negative, lymph node-negative breast cancer. *First Author: Catherine Margaret Kelly, Mater Misericordiae University Hospital, Dublin, Ireland*

Background: Multigene prognostic signatures (MGPS) enable identification of early stage breast cancer (BC) patients requiring less aggressive treatment. OncoMasTR is a new MGPS found via a novel transcriptional network analysis method that identified genes – Master Transcription Regulators (MTRs) – that regulate previously identified prognostic biomarkers. The optimised OncoMasTR signature consisting of just 3 MTRs (OM) and incorporating clinicopathological information (OMclinical) has been clinically validated. We examined OncoMasTR's prognostic performance alone and in comparison to OncotypeDX. **Methods:** We measured MTR expression levels by RT-qPCR in tissue from Irish patients (n = 367) enrolled in the Trial Assigning Individualized Options for Treatment (TAILORx) study through Cancer Trials Ireland. OM and OMclinical numeric risk scores and risk category (high or low) were blindly calculated using the OncoMasTR algorithm. OncoMasTR scores and OncotypeDX recurrence scores (RS) were independently compared on measures of risk classification, BC recurrence (all, local and distant), correlation and concordance over 9 years of follow-up. **Results:** OM ($LR\chi^2$= 12.92, p = 0.0003) and OMclinical ($LR\chi^2$= 17.21, $p < 0.0001$) provided more prognostic information than RS ($LR\chi^2$= 4.74, p = 0.0294). OM classified 39% of samples as low risk (no local or distant recurrence, 0.0% recurrence) and 61% as high risk (9.0% recurrence; 4.5% local, 4.5% distant). OncotypeDX classified 17.3% of samples as low risk (1.9% recurrence; 1.9% local, 0% distant), 63.3% as intermediate risk (7.0% recurrence; 3.5% local, 3.5% distant), and 19.4% as high risk (8.0% recurrence; 3.2% local, 4.8% distant). There was moderate correlation between OM and RS numeric risk scores (r = 0.46, $p < 0.0001$) and low concordance between the OM and RS risk categories. Higher correlation and concordance were observed among high risk samples. **Conclusions:** OM, OMclinical and RS were significantly prognostic for recurrence in TAILORx samples. OM and OMclinical demonstrated exceptional sensitivity by classifying all patients who had any recurrence to the high risk category.

12075 Poster Session (Board #188), Mon, 1:15 PM-4:45 PM

Computer-extracted stromal features of African-Americans versus Caucasians from H&E slides and impact on prognosis of biochemical recurrence. *First Author: Hersh Kumar Bhargava, University of California, Berkeley, Department of Molecular and Cell Biology, Berkeley, CA*

Background: There has been recent interest in investigating differences in the prostate cancer (PCa) phenotype between African-Americans (AA) and Caucasian-Americans (CA). Separately, there is evidence that stromal morphology may be predictive of cancer aggressiveness. The objective of this work was to evaluate whether computer extracted measurements of stromal nuclei in PCa histology (1) were significantly different between AA and CA populations and (2) could be used to create more accurate, population-specific prognostic models for biochemical recurrence (BCR) following surgery. **Methods:** Radical prostatectomy specimens from 200 patients (93 AA, 93 CA, 73 BCR, 113 non-BCR) were reviewed (ethnicity self-declared). Patients were randomly partitioned into training (n = 124) and validation sets (n = 62). Image features from stromal nuclei were computed from scanned H&E slides and used with 3 machine learning (ML) models (random forest, top 4 features by t-test) to predict BCR in each population subset. We validated these models against the independent validation cohort and compared them with extant clinical recurrence risk prediction nomograms (KATTAN, CAPRA-S). **Results:** 23 stromal features had significantly differing distributions between the BCR and non-BCR cohorts ($p < 0.05$). These included descriptors of nuclear shape and arrangement. 31 features were significant in the AA cohort while only 4 were in the CA cohort. Our ML models based on these features significantly (log-rank $p < .005$) outperformed existing nomograms for AA patients and had an AUC of 0.82. **Conclusions:** Stromal nuclear features were predictive of PCa BCR in AA patients. Taking into account population-specific information significantly improves accuracy of computational pathology based prognostic models for AA PCa patients.

Comparison of our model with nomograms for AA validation cohort.

Classifier	Features	Statistics
Random Forest	4 descriptors of nuclear shape.	AUC: 0.82 Logf-rank p = 0.0046 Hazard ratio: 19.95
CAPRA-S	Clinical variables (PSA, grade, stage, age, etc.).	AUC: 0.61 Log-rank p = 0.4265 Hazard ratio = 0.5514
KATTAN	AUC: 0.64 Log-rank p = 0.3385 Hazard ratio = 0.54	

12076 Poster Session (Board #189), Mon, 1:15 PM-4:45 PM

Comprehensive detection of targetable fusions in lung adenocarcinomas by complementary targeted DNAseq and RNAseq assays. *First Author: Ryma Benayed, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While *ALK*, *ROS1*, *RET* fusions, and *MET* exon 14 (*MET*ex14) alterations are routinely detected by hybridization capture-based DNASeq assays such as MSK-IMPACT, a genomic DNA-based approach may not identify all patients with such events. We evaluated the utility of targeted RNAseq for the identification of these alterations in MSK-IMPACT driver-negative lung cancers. **Methods:** MSK-IMPACT driver-negative tumors (defined in Jordan E *et al*, 2017, PMID 28336552), underwent further molecular profiling with the MSK-Fusion Solid panel, a custom RNAseq panel based on the Archer FusionPlex technology designed to detect fusions involving 62 cancer genes and *MET*ex14 skipping. Low tumor mutation burden (TMB) was assessed as a potential prioritization criterion for targeted RNAseq. **Results:** Between 01/01/2014 and 12/31/2017, 2502 lung adenocarcinomas were profiled using MSK-IMPACT; 201 (8%) gene fusions and 119 (5%) *MET* exon 14 alterations were identified (table). Among 276 driver-negative cases, 255 (92%) with available tissue were subjected to targeted RNAseq. A previously undetected alteration was identified in 36 of 255 (14%) cases by the MSK-Fusion Solid panel, 33 of which were actionable (27 in-frame gene fusions, 6 *MET*ex14 skipping events; table). Of these 33 patients, 11 were eligible for matched targeted therapies (the rest had early-stage disease or low KPS, or were on alternate therapies, on active observation, or deceased). All 11 patients received targeted therapy, 8 of whom (72%) derived clinical benefit. In the subset of 63/255 MSK-IMPACT driver-negative cases with low TMB (0-5 mt/Mb), 19 (30%) were positive for previously undetected gene fusions. **Conclusions:** Our results emphasize the importance of complementary targeted DNAseq and RNAseq assays to ensure robust and comprehensive detection of actionable gene fusions and *MET*ex14 alterations in clinical samples. Furthermore, we observed enrichment for gene fusions in driver-negative samples with low TMB, supporting the prioritization of such cases for complementary RNAseq analysis.

Gene	*ALK*	*RET*	*ROS1*	*BRAF*	*NRG1*	*NTRK1*	*NTRK2*	*NTRK3*	*FGFR1*	*FGFR2*	*FGFR3*	*METex14*
DNASeq (n = 2502)	86	44	50	7	3	4	0	0	1	1	5	119
RNASeq (n = 255)	4	3	10	1	5	0	1	2	0	1	0	6

12077 Poster Session (Board #190), Mon, 1:15 PM-4:45 PM

Longitudinal ctDNA analysis to enable early assessment of prognosis in lung adenocarcinoma in the absence of matched tissue biopsy. *First Author: Xiaoju Max Ma, Roche Molecular Syst, Pleasanton, CA*

Background: Longitudinal ctDNA monitoring using variants identified in tissue biopsies is an emerging method for disease management. However, tissue biopsy is often inaccessible for many late stage lung cancer patients. We hypothesized that variants found in baseline plasma ctDNA can also be used for monitoring, and that an early response assessed by changes in the level of ctDNA could predict treatment effect. **Methods:** We employed a 197-gene NGS assay, the AVENIO ctDNA Surveillance Kit, which allowed us to perform longitudinal ctDNA analysis and measure changes in the allele frequency (AF) of the variants identified in baseline plasma. Using this tissue-independent method, we evaluated the association between change in ctDNA levels and survival of advanced lung adenocarcinoma subjects treated with first-line chemo or chemoradiation therapies. Post-treatment AF values were compared with the lowest AF value (nadir) of all previous timepoints, including baseline. New variants were included if the AF was above the mean AF at baseline (b0). The algorithm was tested in a training cohort (44 subjects) and validated in an independent cohort from a prospective, observational study (40 subjects, all stage IV lung adenocarcinoma). **Results:** At b0, we identified variants in all subjects to enable ctDNA monitoring. From the training cohort, we defined the post-second treatment cycle (p2) as 30 to 60 days post-start of first treatment and compared AF value of each variant with the nadir value. Good responders at p2 were defined as having no significant increase in AF from the nadir. Applying this algorithm to the validation cohort, good early responders with samples collected within p2, 24/40 (60%), were associated with better progression-free survival (PFS) (6.1 vs. 3.8 mo, P = 0.0145; HR 0.43; 95% CI 0.21, 0.86) and overall survival (OS) (15.0 vs. 6.8 mo, P = 0.0032; HR 0.31; 95% CI 0.14, 0.70). **Conclusions:** Longitudinal ctDNA analysis in the absence of matched tissue biopsy may be feasible. No significant increase in post-treatment ctDNA levels measured by NGS was associated with better prognosis in advanced lung adenocarcinoma treated with first-line chemo or chemoradiation therapy.

12078 Poster Session (Board #191), Mon, 1:15 PM-4:45 PM

Cancer genomics-based screening of new therapeutic targets and biomarkers for lung cancer. *First Author: Yataro Daigo, Research Hospital, Institute of Medical Science, The University of Tokyo, Tokyo, Japan*

Background: As the number of lung cancer patients who show objective response to standard therapies is still small, development of new anti-cancer drugs with minimum risk of adverse events and highly sensitive and specific cancer biomarkers is urgently awaited. **Methods:** We have been screening new molecular therapeutic targets and their companion biomarkers for lung cancer as follows; i) To identify up-regulated genes in lung cancers by the gene expression microarray, ii) To verify the candidate genes for their low expression in normal tissues, iii) To validate the clinicopathological significance of their protein expression by tissue microarray covering 385 lung cancers, and iv) To verify their function for the growth/survival/invasion of cancer cells by siRNAs. **Results:** We identified various candidate oncoproteins and selected a serine/threonine phosphatase *LAPP1* (lung cancer-associated protein phosphatase 1). Immunohistochemical analysis revealed that LAPP1 was expressed in 253 of 385 (65.7%) lung cancer tissues but not in healthy lung epithelia. LAPP1 expression was significantly associated with poor prognosis for lung cancer patients ($P < 0.0001$), and multivariate analysis confirmed its independent prognostic value. Further analysis identified EF1D (a cadmium-responsive proto-oncogene) as a LAPP1-interacting protein that was highly expressed in lung cancers. Suppression of LAPP1 or EF1D expression by siRNAs inhibited cell growth, whereas exogenous expression of LAPP1 in EF1D(+) cells elevated the dephosphorylation of EF1D(+), and subsequent increase of active phospho-AKT. Blocking this interaction by a cell-permeable peptide corresponding to a leucine zipper motif in EF1D destabilized EF1D protein and inhibited cancer cell growth and invasion. **Conclusions:** Cancer genomics approach could facilitate the development of diagnostic and prognostic biomarkers as well as therapeutic targets for small molecules, monoclonal antibodies, nucleic acid drugs, and cancer vaccines.

12079 Poster Session (Board #192), Mon, 1:15 PM-4:45 PM

Chimeric antigen receptor T cells targeting the lambda light chain of human immunoglobulin as a viable target for B cell non-Hodgkin lymphoma. *First Author: Raghuveer Ranganathan, University of North Carolina-Chapel Hill, Chapel Hill, NC*

Background: Mantle Cell Lymphoma (MCL) is an uncommon and clinically aggressive subtype of B cell derived non-Hodgkin lymphomas (B-NHL) which continues to have poor outcomes of all B-NHLs. Chemotherapy plus CD20-targeting antibodies make remission possible, with fit patients consolidated with autologous stem cell transplant but effects are invariably short-lived and MCL continues to principally be incurable. Adoptive chimeric antigen receptor T cells targeting CD19 (CD19.CAR-T) has shown therapeutic promise for B-NHL. Targeting this antigen, however, does not distinguish between normal and malignant B cells and causes profound B-cell aplasia since CD19.CAR-T can persist long-term. MCL, along with many diffuse large B cell lymphoma (DLBCL) subsets, expresses surface immunoglobulin (Ig) that carries the lambda light chain. We explored targeting Ig-lambda with CAR-T, which would possibly spare B lymphocytes expressing the reciprocal kappa light chain, and consequently reduce the impairment of humoral immunity. **Methods:** We genetically modified CAR-T cells to target the tumor-associated immunoglobulin lambda light chain (CAR.λ). We conducted in vitro trials with B-NHL derived tumor cell lines expressing the lambda light chain, and in vivo experiments using a NOD-*scid* xenograft murine model injected with these same tumor cell lines. We also established a murine model that reconstituted human B lymphocytes within immunosuppressed NSG mice using CD34+ umbilical cord blood cells. We then measured the selective ability of CAR.λ cells to eliminate normal human B-lymphocytes. **Results:** We found that the CAR.λ showed high cytotoxic activity against Ig-lambda+ B-cell tumor cell lines in vitro and in vivo within the NOD-*scid* xenograft murine model. We also demonstrated the selective elimination by the CAR.λ of lambda light chain-expressing B lymphocytes, with sparing of kappa chain-expressing B lymphocytes, in a humanized murine model. **Conclusions:** Adoptive transfer of CAR-T targeting the lambda light chain can be a very useful immunotherapy approach to treating both MCL and DLBCL clinically, without entirely compromising humoral immunity.

12080 Poster Session (Board #193), Mon, 1:15 PM-4:45 PM

Successful generation of patient derived xenografts and patient derived 3D cultures as preclinical models for breast cancer. *First Author: Verena Imke Isabel Kiver, Charite Comprehensive Cancer Center and Department of Gynecology and Breast Center Charité Universitätsmedizin Berlin Campus Mitte, Berlin, Germany*

Background: The establishment of patient-derived preclinical models in breast cancer has been a challenge for many years. We report our successful experience in establishing breast cancer patient derived xenografts (PDX) and patient derived 3D cultures (PD3D). **Methods:** Tumor tissue samples (twice 3mm diameter) from breast cancer patients undergoing surgery were collected by a team of gynecologists and pathologists. Ischemia time was minimized. Small tumor fragments were transplanted to immunodeficient NOG mice. The other part was used to establish a cell culture on serum free organoid media in the presence of growth hormones and, in case of hormone receptor positive breast cancer, estradiol supplementation. To address the question whether the genetics features of the model have changed during the process of engraftment and expansion the established models are currently undergoing molecular profiling. **Results:** Since May 2017 28 breast cancer samples have been processed. The sample characteristics are summarized in the table. Currently we have one PDX established, 18 in passage and 9 have not engrafted. Breast cancer PD3D organoids had a take rate of 56% under our culture conditions. Moreover, hormone receptor positive breast cancer PD3D models were successfully established as PD3D with a take rate of 37.5%. **Conclusions:** A high take rate under improved culture conditions provided a versatile method of patient-derived preclinical model generation.

Take rates and distribution of breast cancer subtypes.

	Samples	Her2 -, HR- (TNBC)	Her2-, HR+,	Her2+, HR -	Her2+, HR+
PDX N	28	11	15	1	1
PDX established	1	1	N/A	N/A	N/A
PDX eliminated	9	5	3	1	N/A
Take rate	9.9%	9.9%	N/A	N/A	N/A
PDX in passage	18	5	12	N/A	1
PD3D N	24	8	14	1	1
PD3D established	9	3	4	1	N/A
PD3D eliminated	7	5	1	N/A	1
Take rate	56.3%	37.5%	80%	100%	0
PD3D in culture	9	N/A	9	N/A	N/A

12081 Poster Session (Board #194), Mon, 1:15 PM-4:45 PM

Role of PD-L1 expression in triple-negative breast cancer stem cells. *First Author: Massimo A. Di Nicola, Fondazione IRCCS Insituto Nazionale Tumori, Milan, Italy*

Background: Triple negative breast cancer (TNBC) is characterized by poor prognosis, lack of specific-targeted agents and is in need of new therapeutics. Immune checkpoint blockers have shown significant efficacy against various tumors, including TNBC. Recent evidences suggested that PD-L1 expression on cancer stem cells (CSCs) might induce immune evasion. We have investigated the role of PD-L1 expression on TNBC stem cells (TNBCSCs). **Methods:** Formalin-fixed, paraffin embedded (FFPE) samples from TNBC patients treated at our Institution and at Fundación Mexicana de Fomento para la Prevención Oportuna del Cáncer de Mama, were analyzed for PD-L1 and immune gene pathways expression and for cancer stemness features. TNBC cell lines (MDAMB231, MDAMB468, SUM149, SUM159, and BT549) and syngeneic high-grade mammary murine models (SN25A) were used to elucidate the mechanisms behind PD-L1 implication in TNBC stemness. **Results:** FFPE tumor samples from a total of 158 TNBC patients were sorted according to the high (79 cases; 50%) and low (79 cases; 50%) median level of PD-L1 transcript. In our series, PD-L1 expression was associated with the stemness-score ($p = 0.026$) and with the up-regulation of CSC-related WNT signaling pathway. Digital fluorescence microscopy analyses revealed a preferential PD-L1 expression in $ALDH^+$ and $CD44^+$ cells. This data was confirmed *in vitro*, being the significant and constitutive higher expression of PD-L1 associated with $ALDH^+$ and CD44-high TNBCSC subsets but not with their neg/low expressing counterparts. Also, $PD\text{-}L1^+$ TNBC cells had a significantly higher mammosphere-forming efficiency than $PD\text{-}L1^-$ TNBC cells. On the same line, XAV-939, a specific inhibitor of WNT, significantly impaired PD-L1 expression indicating their active cross-talk in sustaining stemness feature. *In vivo*, we observed that in syngeneic murine high grade mammary tumor models, Sca^+ and $PD\text{-}L1^{High}$ tumor elements took close contact with CD8 and CD3 T cells suggesting a direct interaction between CSCs and lymphoid cells. **Conclusions:** Our study shows that TNBCSCs up-regulate PD-L1 through the activation of the WNT pathway. Unveiling this new mechanism of TNBC immune modulation, we suggest of targeting the WNT pathway to overcome TNBC immune-evasion.

12082 Poster Session (Board #195), Mon, 1:15 PM-4:45 PM

Local drug activation technology to make cytotoxics safer for localized solid tumors. *First Author: Sangeetha Srinivasan, Shasqi Inc., San Francisco, CA*

Background: Only 1-2% of systemic chemotherapies actually reaches a localized tumor while the rest can result in severe off-target effects. There is a critical need to safely deliver cytotoxics directly to the tumor. **Methods:** Shasqi's Therapy (Shasqi Tx) is a bioorthogonal chemistry-based approach consisting of 1) a drug-activating gel and 2) a systemic prodrug. The biocompatible tetrazine (Tz)-modified gel is injected at tumor site and a *trans*-cyclooctene (TCO)-modified prodrug of a cytotoxic agent such as doxorubicin (Dox), with attenuated activity is given systemically. The prodrug concentrates through a covalent reaction between TCO and the Tz located at the gel. The active drug is spontaneously released over multiple days, directly in the tumor compartment. Remaining prodrug is rapidly cleared by systemic routes, minimizing off-target effects. This technology is reloadable and independent of biological processes. The attenuation of prodrug activity enables an increase in therapeutic index while reducing systemic side effects, as the active drug predominantly localizes to the gel site. **Results:** NSG-H mice injected with Tz-modified alginate gel and systemic TCO-doxorubicin (TCO-Dox; prodrug of Dox). The maximum tolerable dose (MTD) of single dose of TCO-Dox was >12x and as 5 daily doses was >38x of single MTD of Dox (control), without any adverse effects. Preliminary bioanalysis provides a basis for the improved safety of Shasqi Tx over traditional chemotherapy. Gel-injected BALB/c mice received TCO-Dox IV. In serum 5 min after injection > 90% of the circulating anthracycline remained as intact prodrug while ~7% was converted to Dox. Finally, we tested Shasqi Tx's safety in a pilot dog study with spontaneous local adenocarcinoma. Standard Dox therapy led to disease progression with a drastic drop in body weight. Then, multiple cycles of Shasqi Tx given at > 11x the lifetime MTD of Dox, reduced tumor size and led to stable disease for > 430d, body wt. gain without major side effects. **Conclusions:** Shasqi Tx enhances delivery of toxic drugs to a target site while limiting exposure in off-target tissues in small and large animals. Further, the increase in therapeutic index allows greater doses of cytotoxics to be delivered safely.

12083 Poster Session (Board #196), Mon, 1:15 PM-4:45 PM

Clinicopathologic characteristics and molecular features of BRG1-deficient non-small cell lung cancer (NSCLC). *First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA*

Background: Genomic alterations (GA) in *SMARCA4*, the gene encoding the SWI/SNF complex subunit BRG1, have been observed in 10% of NSCLC. RNA-based analyses suggest that loss of BRG1 expression is frequently associated with frameshift/nonsense (F/N) *SMARCA4* GA. In preclinical studies, BRG1 deficiency sensitizes to enhancer zeste homolog 2 (EZH2) inhibition combined with chemotherapy (PMID: 25629630). To characterize the subset with *SMARCA4* GA, we reviewed 2 independent NSCLC datasets and analyzed BRG1 protein expression in cases with available tissue. **Methods:** To identify cases with *SMARCA4* GA, we examined the molecular profiles of 27,281 NSCLCs sequenced at Foundation Medicine (FM) and a separate cohort of 820 consecutive NSCLCs sequenced at Massachusetts General Hospital (MGH). We performed immunohistochemistry (IHC) using the Abcam rabbit BRG1 antibody (EPR3912) to assess BRG1 expression in NSCLCs with *SMARCA4* GA. **Results:** We detected *SMARCA4* GA in 73 (9%) and 3,188 (11%) patients (pts) in the MGH and FM datasets, respectively. *SMARCA4* GA were distributed throughout all protein domains. F/N GA comprised approximately one-third of *SMARCA4* GA in both groups (MGH: 32% and FM:36%). 40 pts (15 with F/N GA) in the MGH group had available tissue for IHC. Thirteen specimens—all from smokers with F/N *SMARCA4* GA— had loss of BRG1 expression. Median age of pts with absent BRG1 expression was 69.2 years. Loss of BRG1 expression was observed in 9 adenocarcinomas as well as 2 poorly-differentiated,1 sarcomatoid, and 1 neuroendocrine carcinoma(s). Ten of the 13 pts with BRG1-deficient NSCLC underwent PD-L1 testing. Eight tumors had no PD-L1 expression and one had ≥50% expression. With the exception of 5 (38%) pts with concurrent *KRAS* GA, we did not find driver GA in the BRG1-deficient specimens. As BRG1 loss was limited to F/N GA, we queried the FM dataset to identify genes frequently co-altered with F/N *SMARCA4* GA. F/N *SMARCA4* GA commonly co-occurred with *TP53* (74%), *CDKN2A* (38%), *STK11* (34%), and *KRAS* (26%) GA. **Conclusions:** *SMARCA4* GA are present in approximately 10% of NSCLC, but our data suggest that F/N GA may disproportionately lead to BRG1 loss. F/N *SMARCA4* GA occur in 3-4% of NSCLC and overlap with *KRAS* GA.

12084 Poster Session (Board #197), Mon, 1:15 PM-4:45 PM

Incidence of *Neuregulin1* (*NRG1*) gene fusions across tumor types. *First Author: Stephen V. Liu, Georgetown University Medical Center, Washington, DC*

Background: *NRG1* gene fusions are an emerging potential therapeutic target in non-small cell lung cancer (NSCLC). NRG1 is a ligand for the HER3 tyrosine kinase and *NRG1* fusions can activate oncogenic HER2/HER3 and PI3K-AKT signaling. The pan-ErbB inhibitor afatinib has been associated with durable response in patients with *NRG1*+ lung adenocarcinoma. *NRG1* fusions and the specific fusion partners have not been well characterized across different tumor types. **Methods:** Tumor samples submitted for profiling between 01/16 - 01/18 at a CLIA-certified genomics laboratory (Caris Life Sciences, Phoenix, AZ) were assayed with anchored multiplex PCR for targeted RNA sequencing with the ArcherDX fusion assay (Boulder, CO). Novel isoforms and fusions with high reads (defined as > 10% of total reads), high confidence after bioinformatics filtering and considered in-frame are included in this analysis. **Results:** In a cohort of 14,150 tumors successfully assayed, 31 cases (0.2%) harbored an *NRG1* fusion. The incidence of *NRG1* fusions varied by tumor type: 0.9% thyroid (1/116), 0.5% ovary (3/574), 0.5% cholangiocarcinoma (1/194), 0.4% pancreas(2/510), 0.3% NSCLC (20/5869), 0.2% breast (2/927), 0.2% sarcoma (1/475), and 1 case in sinonasal teratocarcinoma (SNTC). One of the 20 NSCLC cases (NRG1- SDC4) had squamous histology, the remaining were adenocarcinoma. No *NRG1* fusions were detected in colorectal cancer (0/1382) or glioblastoma multiforme (0/1200). In NSCLC, *NRG1* fusions were mutually exclusive with oncogenic alterations in *EGFR*, *ALK*, *ROS1*, *RET*, and *KRAS* with the exception of one case that co-occurred with a *KRAS* G12C mutation. Fusion partners are shown below. **Conclusions:** Gene fusions in *NRG1* can be identified in various tumor types though the highest number of events was in NSCLC. Consistent detection of *NRG1* fusions will need to account for multiple fusion partners. The optimal treatment of tumors harboring *NRG1* fusions needs to be established.

Tumor Type	NRG1 fusion partners
NSCLC	CD74 (n = 8), SDC4 (n = 3), ATPB1, DPYSL2, MRPL13, OAS2, PARP8, ROCK1, SLCA3, TNC, WRN (n = 1, each)
Ovary	ZMYM2, SETD4, TSHZ2 (n = 1, each)
Pancreas	CDH1, VTCN1 (n = 1, each)
Breast	ADAM9, COX10-AS1 (n = 1, each)
Thyroid	TRAF3IP2
Cholangiocarcinoma	NOTCH2
Sarcoma	WHSC1L1
SNTC	HMBOX1

12085 Poster Session (Board #198), Mon, 1:15 PM-4:45 PM

Effect of anti-PD-1 and anti-Id-1 combo on tumor response and survival in lung cancer. *First Author: Iosune Baraibar, Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain*

Background: PD-1/PDL-1 inhibitors are approved in advanced non-small cell lung cancer (NSCLC). Long-term survivals associated to PD-1/PDL-1 blockade have changed treatment paradigm. However, many patients do not benefit from PD-1/PDL-1 blockade. New therapeutic combinations are under investigation. Id1 is involved in proliferation, angiogenesis and immunosuppression. We described Id1 as a prognostic factor in NSCLC (Ponz-Sarvise, Clin Cancer Res 2011) and more recently showed Id1's role in lung cancer metastasis (Castanon, Cancer Letters 2017). Here we test a combined therapeutic strategy targeting PD-1 and Id1 in a murine lung cancer model. **Methods:** Three *in vivo* studies evaluated the impact of *Id1* inhibition in tumor cells, tumor microenvironment and in both, on tumor volumes and mice survival. A syngeneic tumor model using C57BL/6 and *Id1-/- Id3+/-* mice was created by subcutaneous injection of Lewis Lung Carcinoma (3LL) cells and *Id1* silenced 3LL (*Id1Sh*) cells. After injection, mice were treated with an anti-PD-1 (RMP-1-14) monoclonal antibody or PBS. Tumor volumes according to mice strain, *Id1* status in tumor cells and treatment were quatified. Mice's survival was calculated in those groups.Tumors PD-L1 expression and CD8+ and CD3+ TILs and CD68+ cells were quatified by specific immunostainings. **Results:** Id1 inhibition in the tumor environment and the injected tumor cells, combined with anti-PD-1 treatment, induced a significant tumor growth impairment ($p < 0.0001$) and increased survival ($p = 0.0051$). CD3+ and CD8+ TILs and tumor CD68 + cells were significantly higher in tumors from mice with the combined *Id1*-PD-1 blockade treated with the anti-PD-1 inhibitor compared to control animals suggesting that tumor increased immune-related cells infiltration exerts the effector phase of the antitumor immune response. Additionally, PD-L1 expression seemed to be higher when Id1 expression was absent in the immune microenvironment ($p = 0.04$). **Conclusions:** *Id1* and PD-1 combined blockade in our syngeneic murine lung cancer model significantly impaired tumor growth and increased survival. Increased tumor PD-L1 expression and CD3+ and CD8+ TILs and CD68+ cells may explain these findings.

12086 Poster Session (Board #199), Mon, 1:15 PM-4:45 PM

Novel ex vivo patient-derived 3D model as a powerful tool to apply precision medicine. *First Author: Kayla Simeone, Centre de recherche du CHUM, Montreal, QC, Canada*

Background: Among the several therapeutic options available to treat Castrate-Resistant Prostate Cancer (CRPC), choosing the most suitable option for an individual patient remains a clinical challenge. For this, our group has developed a novel ex-vivo model based on patient-derived micro-dissected tissues (MDT) cultivated in microfluidic devices to determine patient sensitivity profile in the presence of therapeutic agents. **Methods:** MDTs (~400 μm in diameter) derived from PC cell line xenografts (DU145 and LnCaP) were exposed to docetaxel (10 nM for 12 hours) or enzalutamide (10 μM for 24 hours) and analyzed after a 12-hour recovery period or immediately after exposure time. Cell fate was measured using flow cytometry techniques (Annexin V for apoptotic cells and DRAQ7 for dead cells) and by a technique based on formalin fixed paraffin embedding of MDTs within a microfluidic device creating a high-density MDT-Array (MDTA). Using MDTA we can monitor MDT viability (cleaved caspase-3), proliferation (Ki-67) and epithelial composition (CK 8/18) by immunohistochemistry (IHC) and immunofluorescence (IF). MDTs were also separately treated with TNF-α at a concentration of 10 ng/mL for 30 minutes and analyzed by MDTA. **Results:** We show that the microfluidic device does not affect the viability (> 85% by flow cytometry) or proliferative capacity (60% by IHC) of the MDTs during a culture period of 15 days in PC cell line xenograft models (N = 3 for LNCaP, N = 2 for DU145). Pharmacological responses to docetaxel showed 50% increase in caspase-3 activity by IF and 20% increase in cell death by flow cytometry compared to control MDTs. Enzalutamide response was dependent on the cells 2D hormone sensitivity profile. The nuclear translocation of p65 was also monitored in 80% of MDTs treated with TNF-α. **Conclusions:** Within less than 5 days, we can obtain treatment response analysis using our ex vivo drug response model, appropriate for clinical decision-making, The precise techniques developed within our lab, allows the characterization of molecular responses of cancerous cells in the presence of various therapeutic agents while conserving the natural tumor microenvironment.

12087 Poster Session (Board #200), Mon, 1:15 PM-4:45 PM

Genetic and chemical screens in 2-D vs. 3-D generate distinct leads for target and drug discovery. *First Author: Piyush Gupta, Whitehead Institute/MIT, Cambridge, MA*

Background: Oncology drug discovery programs commonly utilize genetic or chemical screens with cancer cell lines propagated on two-dimensional (2D) plastic surfaces. While convenient for high-throughput screens, such cultures do not incorporate the extracellular matrix (ECM) present in patient tumors, which plays a critical role in determining cancer cell signaling. This has led to significant concerns about the biological relevance of targets discovered using standard 2D cultures, but the extent to which performing assays in 3D ECM would alter the leads generated by screening is not known. **Methods:** We have recently developed 3D hydrogel scaffolds that replicate the physical and signaling characteristics of human tissues. We performed both high-throughput CRISPR and chemical screens, doing so in parallel either in standard 2D cultures or in 3D ECM. The CRISPR screen included 10 sgRNAs targeting each of 507 kinases in the human genome. The chemical screen was performed with 780 drugs approved by the FDA for oncology and other indications. **Results:** The CRISPR screen identified major differences in the kinase pathways utilized by cancer cells in 3D vs. 2D. We discovered 29 kinases that were essential for promoting growth in 3D tissues but had no phenotype when inhibited in 2D. In addition, 3 kinases were essential in 2D culture but were not essential in 3D ECM. The drug screen identified agents that inhibited cancer cell viability or invasion. Drugs that inhibited viability were strongly enriched for FDA-approved oncology drugs. By contrast, most of the 26 drugs that were potent inhibitors of cancer cell invasion in 3D were approved for non-oncology indications (22/26), identifying opportunities to 'repurpose' drugs to target cancer invasion. **Conclusions:** Our findings establish the importance of conducting target and drug discovery efforts in biomimetic 3D conditions that replicate the matrix content of human tissues. Continued use of standard 2D cultures poses a risk of generating both false-positives and false-negatives – identifying spurious leads that will not validate in follow up studies, or failing to identify novel leads that are promising candidates for follow-up validation.

12088 Poster Session (Board #201), Mon, 1:15 PM-4:45 PM

Early assessment of treatment effect in advanced lung adenocarcinoma via longitudinal ctDNA analysis. *First Author: Xiaoju Max Ma, Roche Molecular Syst, Pleasanton, CA*

Background: Despite routine use of chemotherapy in advanced non-small-cell lung cancer (NSCLC) patients, the knowledge of optimal prognostic methods is still limited to imaging-based methods. We hypothesized that an early response assessed by mutant molecules count in plasma could predict the treatment effect. **Methods:** We employed AVENIO ctDNA Surveillance Kit, a 197-gene NGS assay, which allowed us to perform longitudinal ctDNA analysis and measure the mutant molecules per milliliter-of-plasma (MMPM), which quantifies ctDNA at the variant level. The association between changes in ctDNA levels and survival was evaluated in advanced lung adenocarcinoma subjects. Post-treatment MMPM values were compared with the MMPM value at baseline and/or the previous treatment timepoint. **Results:** At baseline (b0), we identified variants in all (93/93) subjects to enable ctDNA monitoring. From the training cohort (50 subjects), we were able to set the cutoff of 40 for the mean MMPM at post-first treatment cycle (p1). Applying the MMPM cutoff of p1 to the validation cohort (43 subjects with stage IV lung adenocarcinoma, from a prospective, observational study) low levels of ctDNA toward the end of first treatment cycle was associated with better progression-free survival (PFS) (P = 0.0088 HR 0.4; 95% CI 0.20 - 0.83) and overall survival (OS) (P = 0.0026 HR 0.32; 95% CI 0.15 - 0.71). The prognostic value is increased by applying the Continuous Responder algorithm, defined by a continuous drop in ctDNA levels represented by mean MMPM reduction over time ($p2 < p1 < b0$), to a mean MMPM below 8 at p2. As a result, continuous responders 13/43 (30%) were associated with a better therapy response indicated by PFS (P = 0.028 HR 0.45; 95% CI 0.23 - 0.90) and OS (P = 0.0074 HR 0.3; 95% CI 0.12 - 0.77). The continuous responders demonstrated a median overall survival benefit of 11.25 months over the poor responders. **Conclusions:** A decrease in post-treatment ctDNA level measured by NGS was associated with better prognosis in advanced lung adenocarcinoma. An early assessment of treatment effect can be measured by mutant molecule counts in the plasma within 1 or 2 treatment cycles.

12089 Poster Session (Board #202), Mon, 1:15 PM-4:45 PM

Quantitative measurement of total erbB2 (H2T), p110 t-erbB2, and erbB2: erbB3 (H23D) heterodimer expression and p110 t-erbB2 in malignant progression from ductal carcinoma in situ (DCIS) to invasive ductal carcinoma (IDC). *First Author: Yu Zong, Stanford Cancer Institute, School of Medicine, Stanford University, Stanford, CA*

Background: We previously reported that human mammary epithelial cell lines stably expressing p110 t-erbB2, but not p95 nor erbB2 intracellular C-terminal fragment, significantly increased cell migration, invasion and xenograft formation – more than full length p185 erbB2 [Ward, *et al.*, Oncogene. 2013;32(19):2463-74]. Moreover, published frequency of erbB2 overexpression is higher in DCIS (41%) than IDC(~20%), suggesting erbB2 may play a role in tumor initiation, rather than progression to invasion. We hypothesized that p185 erbB2 in DCIS is insufficient to cause an invasive phenotype, and that enrichment of p110 t-erbB2 facilitates malignant progression to IDC. **Methods:** H2T, p110 t-erbB2, and H23D were quantified using the proximity-based HERmark and VeraTag assay technology (CLIA/CAP-certified conditions) in 67 DCIS and 70 IDC erbB2-amplified/overexpressed FFPE samples. Macrodissection ensured pure IDC or DCIS samples. Measurements were normalized to cell line standards of known H2T, p110 t-erbB2 and H23D levels, with cutoffs established as previously described [Huang W, *et al.*, Am J Clin Pathol. 2010;134:303-311; Sperinde J, *et al.*, Clin Cancer Res. 2010;16(16):4226-35]. **Results:** p110 t-erbB2 was higher in IDC than DCIS cases (p = 0.036). Level of H2T overexpression was strongly associated with high p110 t-erbB2 levels in IDC patients (R^2= 0.51, $p < 0.001$), but not in DCIS. p110 t-erbB2 difference between IDC vs. DCIS was more pronounced in the H2T overexpressed subset ($p < 0.001$). H2T and p110 t-erbB2 expression were in agreement with erbB2 IHC staining (H2T p = 0.002; p110 t-erbB2 p = 0.04, respectively); and inversely correlated with estrogen receptor levels (H2T p = 0.009; p110 t-erbB2 p = 0.004, respectively). In IDC, high expression of H23D levels were not significantly different between DCIS and IDC cases (p = 0.13). **Conclusions:** Our study is the first quantitative assessment of H2T, p110 t-erbB2 as well as H23D expression in both DCIS and IDC. These data suggest a potential pathophysiologic role of p110 t-erbB2 in driving progression of erbB2 positive DCIS to IDC.

12090 Poster Session (Board #203), Mon, 1:15 PM-4:45 PM

Towards a molecular algorithm predicting glioma treatment response and resistance: A biomarker analysis and path to real time profiling in N^2M^2. *First Author: Tobias Kessler, Neurology Clinic, DKFZ, DKTK, Heidelberg, Germany*

Background: Gliomas regularly evade current therapies through primary and acquired resistance and the effect of temozolomide is mainly restricted to the subgroup of *methylguanin-O6-methyltransferase promoter* (*MGMT)* hypermethylated tumors. Further resistance markers and pathways against chemotherapy, radiotherapy and targeted agents are unknown, but will be important in targeted warehouse studies like NCT Neuro Master Match (N^2M^2). **Methods:** The diagnostic pipeline involves clinical and molecular analysis of WHO grade III (n = 116) and WHO grade IV (n = 400) glioma patient samples focusing on methylation profiles as well as a prospective feasibility study of real time multilayer molecular profiling on various levels in 43 WHO grade IV patients with an unmethylated *MGMT* promoter. **Results:** *Isocitrate dehydrogenase* (*IDH)* wildtype glioblastomas mainly show three different methylation clusters (RTKI, RTKII and mesenchymal). Samples of Cluster 1 (RTKII) had higher prevalence of *MGMT* methylation, *TERT* methylation and *TERT* promoter mutation. *MGMT* methylation is only prognostic in this cluster, likely to be linked to *TERT* status. *TERT* promoter mutation is further associated with changes in the global methylation profile. DNA damage response (DDR) gene methylation patterns show association with survival in grade IIII and IV glioma, including *POLE4* linked to radiation response. The prospective N^2M^2 pilot study demonstrates feasibility of complex molecular profiling within four weeks and identified high confidence markers for targeted therapy in 35% of the patients. Furthermore, a therapeutic algorithm is proposed to allocate patients with high grade gliomas to the best possible treatment based on molecular biomarkers. This algorithm is ready to be adjusted by continues input from targeted clinical and preclinical studies and *in vivo* CRISPR screens. **Conclusions:** Multilayer molecular biomarker analysis for high grade glioma is feasible and can be implemented in a therapeutic algorithm estimating the most promising therapy according to current knowledge. Specifically, the TERT-DDR axis may be involved in resistance to chemo- and radiotherapy in high-grade glioma.

12091 Poster Session (Board #204), Mon, 1:15 PM-4:45 PM

***PBRM1* mutation and immunotherapy efficacy: A comprehensive genomic profiling (CGP) assessment.** *First Author: Gennady Bratslavsky, SUNY Upstate Medical University, Syracuse, NY*

Background: *PBRM1*, a member of the SWI/SNF family, is involved in chromatin remodeling. Recent evidence indicates that *PBRM1* inactivating mutations are associated with clinical benefit from immune checkpoint inhibitor treatments in clear cell renal cell carcinoma (ccRCC). **Methods:** CGP was performed on 140,411 specimens from solid tumors and hematologic malignancies using a hybrid capture-based NGS assay. Profiles were assessed for neoantigen load, tumor mutational burden (TMB), determined on 1.1 Mbp of sequenced DNA, and microsatellite instability (MSI) determined by principal components analysis of optimal homopolymer loci. Genomic alterations (GA) in *PBRM1* considered here were known loss-of-function GA or homozygous GA in the tumor. **Results:** *PBRM1* GA were identified in 3,674 (2.6%) cases. Compared to other tumor types, the *PBRM1* GA frequency was significantly higher in ccRCC at 45% ($P < 0.0001$); other tumor types with frequent *PBRM1* GA were renal cell carcinoma NOS (27%), site-specific mesothelioma (MESO) (7-20%), cholangiocarcinoma (CCA) (12%), and chordoma (11%). *PBRM1* GA were found in < 3% of highly prevalent tumors, including melanomas, carcinomas of lung, breast, colon and prostate, and all hematolymphoid malignancies. For ccRCC the most common co-altered genes with *PBRM1* were *VHL* (80%), *SETD2* (31%), *KDM5C* (15%), *PTEN* and *TP53* (13%), *TSC1* and *CDKN2A* (7%), *TERT*, *PIK3CA*, *BAP1* and *CDKN2B* (6%) and *MTOR* (5%). Top co-mutated genes in other tumors were *BAP1* (84%) and *NF2* (27%) in MESO; *ARID1A* (33%) and *IDH1* (30%) in CCA; and *PTEN* (11%) and *CDKN2A* (8%) in chordoma. Median TMB for *PBRM1*-mutated ccRCC was 2.5 mutations (mut)/Mb, with only one highly mutated sample (MSI-High and TMB ≥20 mut/Mb). These results were similar for *PBRM1* WT ccRCC (median 2.6 mut/Mb; no MSI-High or TMB ≥20 mut/Mb). Neoantigen load in ccRCC is significantly associated with *PBRM1* GA positivity ($p < 0.02$), but not TMB ($p < 0.50$). **Conclusions:** This study confirms *PBRM1* GA are significantly enriched in ccRCC, an immunotherapy responsive tumor type lacking high MSI or TMB. Further study of *PBRM1* GA in both renal and non-renal malignancies appears warranted, including evaluation of co-occuring GA that may predict ICPI efficacy.

12092 Poster Session (Board #205), Mon, 1:15 PM-4:45 PM

***PD-L1* genomic alterations (GA) in solid tumors and hematologic malignancies: A comprehensive genomic profiling (CGP) study.** *First Author: Laurie M. Gay, Foundation Medicine, Inc., Cambridge, MA*

Background: Amplification (AMP) of *PD-L1* (*CD274/B7H1*) has recently been linked to enhanced benefit from immune checkpoint inhibitor (ICPI) treatment. We used CGP to evaluate the *PD-L1* GA landscape in cancer. **Methods:** Specimens from 140,411 cancers representing > 450 individual disease ontologies were sequenced using a hybrid capture-based, next-generation sequencing assay. PD-L1 protein expression was measured by immunohistochemistry (IHC) in a subset of cases using the Dako 22C3 anti-PD-L1 antibody. **Results:** 1383 (0.9%) tumors had *PD-L1* GA (1414 GA): 879 (62%) AMP, 471 (33%) short variants (SV) and 60 (0.4%) truncating rearrangements (RE). *PD-L2* (*PDCD1LG2*) and *JAK2* were co-amplified in 94% and 82% of *PD-L1* AMP samples; other genes commonly altered with *PD-L1* AMP included *TP53* (77%), *CDKN2A/B* (28%/20%), *MYC* (21%), and *TERT* (13%). For samples with RE or SV, *PIK3CA* (19%; 21%) GA were common and *TERT* GA were in 7% or 14% of samples. Most SV GA were missense (88%), compared with truncating (10%) or splice site (2%) GA. Recurrent somatic variants of unknown significance (VUS) were observed, including frameshift and missense GA that may regulate PD-L1 stability. Of 10 common tumors, breast (213) and lung (210) carcinomas (CA) represented the most *PD-L1* AMP cases. Select cancers with notable *PD-L1* AMP frequencies were anaplastic thyroid CA (4%), head and neck squamous CA (HNSCC) (2.5%), cervical SCC (2.6%), and breast (1.4%), lung (0.7%) and bladder (0.6%) CA. Of common tumor types, such as colorectal, pancreatic, ovarian, or prostatic CA, melanoma and glioblastoma, ≤0.3% had *PD-L1* AMP. There was strong correlation between *PD-L1* AMP and PD-L1 expression by IHC in NSCLC, with 89% AMP positive samples showing > 50% IHC staining and 11% with positive but < 50% staining. Major clinical responses to ICPI therapies for tumors with *PD-L1* AMP will be presented. **Conclusions:** *PD-L1* AMP or other GA occur rarely across many cancer types. Many somatic PD-L1 GA are uncharacterized VUS. PD-*L1* AMP correlates with high membrane expression of PD-L1 measured by IHC and is linked to durable response to ICPI therapies. Further evaluation of *PD-L1* AMP as a potential biomarker for immunotherapy selection appears warranted.

12093 Poster Session (Board #206), Mon, 1:15 PM-4:45 PM

Dual MAPK inhibition (dMAPKi) as an effective therapeutic strategy for class II BRAF mutant (mt) metastatic melanoma (MM). *First Author: Matthew Dankner, McGill University, Montréal, QC, Canada*

Background: dMAPKi with BRAFi and MEKi improves survival in BRAF V600E/K mt MM, but the effects of these inhibitors on nonV600 BRAF mt MM is poorly understood. We sought to characterize nonV600/class II (enhanced kinase activity, dimerization dependent) BRAF mt MM and to investigate their responsiveness to MAPKi. **Methods:** We analyzed 3 MM datasets (PMH next generation sequencing (NGS) cohort, TCGA, GENIE) for clinicopathologic correlations and outcomes of nonV600 BRAF mt MM pts. Tumors from patients with BRAF WT, V600E (class I), and L597S (class II) MM were used to generate patient-derived xenografts (PDX); both were subjected to NGS analysis with the CANCERPLEX assay. We generated and obtained 8 MM cell lines with class IIa (activation segment) or IIb (p-loop) mt and compared these to BRAF WT and V600E/K MM cells. Cell lines and PDXs were treated with BRAFi (vemurafenib, dabrafenib, encorafenib) and MEKi (cobimetinib, trametinib, binimetinib), or the combination. They were investigated with immunoblots, *in vitro,* and *in vivo* growth assays. We identified two patients with BRAF L597S MM who were treated with dMAPKi. **Results:** NonV600 BRAF mutants comprise 10-35% of all BRAF mts in MM. NonV600 BRAF mts are frequently co-expressed with NRAS mts and associated with poor survival compared to BRAF V600E/K MM (HR 1.49, 95% CI 1.09-2.06). BRAFi impaired Erk phosphorylation and cell growth in class I and IIa BRAF mt cells. dMAPKi was more effective than either single MAPKi at inhibiting cell growth in all class IIa and IIb cell lines tested. PDXs retained high genomic fidelity to the primary tumors from which they were derived. In two independent BRAF L597S (class IIa) PDX models, single MAPKi only slowed the progression of tumor growth whereas dMAPKi resulted in significant tumor shrinkage. Two patients with BRAF L597S mt melanoma obtained objective clinical responses to dual MAPKi. **Conclusions:** NonV600 BRAF mt MM are associated with poor prognosis. Class II BRAF mt MM are growth inhibited by dMAPKi. Responses to dMAPKi have been observed in two patients with class II BRAF mt MM. Our data provide rationale for clinical investigation of dual MAPKi in patients with class II BRAF mt MM.

12094 Poster Session (Board #207), Mon, 1:15 PM-4:45 PM

Large-scale analyses of tumor mutation burdens (TMBs) across various advanced gastrointestinal (GI) malignancies in the nationwide cancer genome screening project, SCRUM-Japan GI-SCREEN. *First Author: Yoshiaki Nakamura, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Tumor mutation burdens (TMBs) in advanced gastrointestinal (GI) malignancies have not been well-characterized. We analyzed TMB in tissue samples from advanced GI malignancies using the Oncomine Cancer Research Panel (OCP), a targeted next-generation sequencing panel, as part of the Nationwide Cancer Genome Screening Project (SCRUM-Japan GI-SCREEN). **Methods:** The performance of the OCP panel for TMB analysis was assessed using whole-exome sequencing (WES) data from 10,183 samples in the Cancer Genome Atlas (TCGA). Then, TMBs were calculated based on somatic non-synonymous mutations in the following 1,759 GI tumors: colorectal cancer (CRC, n = 751), gastric cancer (GC, n = 509), esophageal cancer (EC, n = 143), pancreatic cancer (PC, n = 136), biliary tract cancer (BTC, n = 92), small intestinal cancer (SIC, n = 30), gastrointestinal stromal tumor (GIST, n = 29), hepatocellular carcinoma (HCC, n = 27), neuroendocrine tumor/cancer (NET/NEC, n = 27), appendiceal cancer (AC, n = 12), and anal canal cancer (ACC, n = 3). High TMB was defined as more than 20 mutations per megabase (mt/Mb). CRC microsatellite instability (MSI) status was assessed using a PCR-based method. **Results:** TMBs estimated from the OCP-targeted region based on TCGA data were strongly correlated with those from TCGA whole-exome sequencing data (R^2 = 0.720). TMBs in the GI-SCREEN ranged from 0 to 103.6 mt/Mb across various tumor subtypes. In CRC, 75% of MSI-high (MSI-H) and 17% of non-MSI-H tumors had high TMB. In non-CRC, high TMB was identified in 13% of GC, 17% of EC, 28% of PC, 26% of BTC, 30% of SIC, 7% of GIST, 7% of HCC, 15% of NET/NEC, 25% of AC, and 33% of ACC tissues. TMB was not associated with sex, age, histology (adenocarcinoma vs. squamous cell carcinoma), prior chemotherapy, or radiotherapy. Tumors with mutations in DNA damage response (DDR) genes (*ATM*, *BRCA1*, *BRCA2*, *MLH1,* and *MSH2*) had higher TMB than those with wild-type DDR genes ($p < 0.001$). **Conclusions:** TMB varied widely across various advanced GI malignancies. TMB analysis may be used as an agnostic histologic indicator to identify patients with GI malignancies who can benefit from immunotherapy. Clinical trial information: UMIN000016343.

12095 Poster Session (Board #208), Mon, 1:15 PM-4:45 PM

Preselection of lung cancer cases using FGFR1 mRNA and gene copy number for treatment with ponatinib. *First Author: Terry L. Ng, University of Colorado Cancer Center, Aurora, CO*

Background: NSCLC and SCLC cell line data suggested high FGFR1 mRNA levels and FGFR1 amplification (FGFR1-AMP) could predict sensitivity to FGFR TKIs. Overlap with KRAS mutations did not preclude TKI sensitivity. Ponatinib is a multi-kinase inhibitor of ABL, RET and FGFR1-4. **Methods:** Metastatic EGFR- and ALK-negative lung cancers were pre-screened for FGFR1-mRNA by in-situ hybridization (ISH) and FGFR1-AMP by silver in-situ hybridization (SISH). Initial positivity cutpoints were based on cell line sensitivity at predicted ponatinib exposure. ISH and SISH positive cases were offered treatment with ponatinib at 45 mg QD. Differences in overall survival (OS) between cohorts were assessed using log-rank test. Association of FGFR1 positivity with clinicopathologic features were assessed using Fisher's exact test and Kruskal-Wallis rank sum test. **Results:** From 2013-2017, 171 cases were prescreened (123 SISH and 126 ISH samples reported): 9/123 (7.3%) were SISH+; 53/126 (42.1%) were ISH+; 6 were concordantly positive for SISH and ISH. At the initial cutpoint, no specific correlations with age, sex, smoking status, or response to platinum therapy were identified. However, SISH+ cases had fewer coincident KRAS mutations (p = 0.03) than SISH- cases, and ISH+ cases had worse OS (p = 0.020) than ISH- cases. Exploring data for natural higher cutpoints did not alter SISH positivity but did suggest a higher cutpoint for FGFR1 ISH (≥ 20% dot cluster [23% [29/126] cases]), associated with SCLC histology (p = 0.022), soft tissue metastases (p = 0.050) and shorter OS (p = 0.031). Four patients received ponatinib: All were FGFR1 ISH+ by the initial cutpoint (≥ 1% dot cluster), 2/4 were ISH ≥ 20% dot cluster, and 1/4 was SISH+. Tolerability was poor. The best response for the two ISH ≥ 20% cases was SD and for the two ISH ≥ 1% cases, it was PD (ORR 0%, DCR 50%). **Conclusions:** High FGFR1-mRNA is more common than FGFR1-AMP and was associated with worse OS. Higher levels of FGFR1 mRNA may be associated with a specific phenotype and is worthy of further exploration. Ponatinib's poor tolerance suggests further FGFR exploration in ISH+ cases should utilize more selective FGFR1 inhibitors. Clinical trial information: NCT01935336.

12096 Poster Session (Board #209), Mon, 1:15 PM-4:45 PM

***RAS* alterations: Next-generation sequencing of 1,526 patients with diverse malignancies reveals prognostic and therapeutic correlates.** *First Author: Shumei Kato, University of California, San Diego, La Jolla, CA*

Background: To date, there is no successful strategy to target *RAS* alterations. To better understand the clinical impact of different *RAS* abnormalities, we interrogated the genomics of diverse metastatic/recurrent solid cancers. **Methods:** We evaluated the molecular profiles of 1,526 patients with diverse malignancies for *RAS* aberrations as well as co-altered genes using clinical grade next-generation sequencing (NGS) (Foundation Medicine) (182 - 406 gene panels). Therapy and clinical outcomes were assessed (NCT02478931). **Results:** Overall, 23.5% (358/1,526) harbored *RAS* alterations (*KRAS*: 19.3%, *NRAS*: 3.2%, *HRAS*: 1.1% [N = 1 with both *K*- and *NRAS* alterations]). Patients with *RAS* alterations had shorter overall survival (OS) than *RAS* wild-type patients: OS (hazard ratio [HR]: 1.24, 95% confidence interval [CI]: 1.03-1.48, P = 0.02) (multivariate analysis). Amongst *RAS* mutations, *KRAS G12V, KRAS G13D*, and *KRAS* amplification had the shortest OS (multivariate analysis, P = 0.004, 0.004, and 0.02). Co-alterations were seen in 96.4% (345/358) of *RAS*-mutated patients; patients with PI3K signaling pathway or cell cycle-associated co-altered genes had significantly worse OS when compared to patients without such alterations (HR: 1.52, 95% CI: 1.15-2.01, P = 0.004 and HR: 1.99, 95% CI: 1.49-2.67, P < 0.0001 respectively) (multivariate analysis). 293/358 *RAS*-mutated recurrent/metastatic solid tumors were evaluable for progression-free survival (PFS). Patients treated with matched therapy targeting non-MAPK co-altered signals (N = 124) had a trend towards longer PFS (HR: 0.79, 95% CI: 0.61-1.03, P = 0.07) but OS was not impacted (HR: 0.98; P = 0.92) when compared to patients who received unmatched therapies (N = 143). **Conclusions:** Across cancers, *RAS* alterations were independently associated with poor OS, with *KRAS G12V, KRAS G13D*, and *KRAS* amplification having the shortest survival. Most *RAS*-mutated tumors harbored co-altered genes. Therapy that included drugs matched to co-altered genes did not impact survival, suggesting that MAPK is an important resistance pathway even in the presence of other tractable genomic alterations. Clinical trial information: NCT02478931.

12097 Poster Session (Board #210), Mon, 1:15 PM-4:45 PM

Landscape of *BRCA1* and *BRCA2* germline, somatic, and reversion alterations detectable by cell-free DNA testing among patients with metastatic breast, ovarian, pancreatic, or prostate cancer. *First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: PARP inhibitors (PARPi) have shown efficacy in breast (BC), ovarian (OC), pancreatic (PaC), and prostate (PrC) cancers harboring deleterious germline or somatic alterations (alts) in *BRCA1* or *BRCA2 (gBRCA, sBRCA).* Additional acquired reversion alts (*rBRCA)* which restore the open reading frame (ORF) have been reported in the setting of resistance to PARPi or platinum-based chemotherapy. Next-generation sequencing (NGS) of cell-free DNA (cfDNA) provides a platform to evaluate the relative frequency of all three of these types of *BRCA* alts in pts with advanced cancers. **Methods:** *BRCA* alts were identified among 1,122 samples from 828 pts with metastatic BC, OC, PaC, or PrC with tumor DNA detected on a clinical 73-gene cfDNA NGS assay (tests run between 11/2016-10/2017, Guardant360). This assay evaluates single nucleotide variants and indels in *BRCA1/2* and tracks individual DNA molecules allowing for phasing. *BRCA* alts were classified as *gBRCA, sBRCA,* or *rBRCA* based the variant allele fraction (VAF), AFs of neighboring germline SNPs, and relative positions of all alts in a sample. Treatment history was obtained from test request forms. **Results:** At least one deleterious *BRCA* alt was detected in 67 pts (8.1%), including 35/472 pts with BC, 6/47 OC, 5/85 PaC, and 21/223 PrC. 36 of these patients had putative *gBRCA* alts, 8 of whom had additional alts consistent with *rBRCA* (5 had BC, 3 had PrC). The remaining 31 *BRCA+* pts had only *sBRCA,* 1 of whom had BC and multiple somatic alts consistent with *rBRCA.* Treatment history was available for 29/67 *BRCA+* pts. Among the 7 who were indicated as having exposure to a PARPi, 2 had a *rBRCA.* **Conclusions:** Rates of cfDNA-detected g*BRCA* and *sBRCA* alts in pts with advanced BC, OC, or PaC are comparable to that reported by TCGA, and higher among men with PrC. Approximately half of the *BRCA+* pts had *gBRCA* and half only had *sBRCA*, highlighting the value of cfDNA NGS testing to identify both types of targetable *BRCA* alts. Moreover, *rBRCA* were identified in a significant percentage (13%) of *BRCA*+ pts without foreknowledge of germline- or tissue-based testing, and may identify pts unlikely to respond to PARPi.

12098 Poster Session (Board #211), Mon, 1:15 PM-4:45 PM

Genetic variants within the glucocorticoids related genes to predict outcome in patients with metastatic colorectal cancer (mCRC). *First Author: Alberto Puccini, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Glucocorticoids (GC) have important anti-inflammatory and pro-apoptotic activities. CRC cells produce immunoregulatory GC, a process regulated by nuclear receptor liver receptor homolog-1 (LRH-1). Additionally, LRH-1 plays a critical role in the control of cell cycle and tumorigenesis. Therefore, CRC cells have a strong steroidogenic potential and tumor-derived GC may contribute to tumor immune evasion. Thus, we aim to evaluate whether variations in *LRH1* and GC receptor (*NR3C1*) genes may predict outcome in mCRC patients treated with first-line FOLFIRI and bevacizumab (bev). **Methods:** Genomic DNA from whole blood samples was obtained from 378 mCRC patients who were treated with FOLFIRI/bev in the TRIBE (discovery cohort; N = 215, female/male 83/132; median age 60; median follow-up 48.9 months) and MAVERICC (validation cohort; N = 163, female/male 60/103; median age 62; median follow-up 23.3 months) trials, and subsequently genotyped through the OncoArray, a custom array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of six selected SNPs in *LRH1* and *NR3C1* genes were analyzed. **Results:** In the discovery cohort, patients carrying *NR3C1 rs10041520* any C showed a longer OS compared to T/T variant in the univariate analysis (28.9 months vs 20.5 months, HR = 0.69, 95%CI = 0.50-0.97, P = 0.029). *LRH1 rs2737656* any T variant showed longer PFS compared to C/C genotype in multivariate analysis (10.3 months vs 9.4 months, HR = 0.62, 95%CI = 0.41-0.93, P = 0.020). Patients carrying any G in *LRH1 rs2690034* showed shorter OS compared to those carrying C/C variant in multivariate analysis (25.0 months vs 29.8 months, HR = 1.46, 95%CI = 1.02-2.10, P = 0.040). The *NR3C1 rs10041520* findings were validated in the MAVERICC FOLFIRI/bev arm. Here, patients carrying any C variants had a longer OS compared to T/T genotype in multivariate analysis (27.9 months vs 26.5 months, HR = 0.42, 95% CI = 0.19-0.92, P = 0.030). **Conclusions:** Our results provide the first evidence that the genetic variants within *NR3C1* and *LRH*-1 genes might serve as a prognostic/predictive markers in patients with mCRC treated with first-line FOLFIRI and bevacizumab.

12099 Poster Session (Board #212), Mon, 1:15 PM-4:45 PM

Phosphorylation of AKT kinase substrates to predict response to the AKT inhibitor MK2206 in the I-SPY 2 trial in both HER2- and HER2+ patients. *First Author: Julia Dianne Wulfkuhle, George Mason Univ, Columbia, MD*

Background: In the I-SPY 2 TRIAL, the allosteric AKT inhibitor MK2206 was available to all HR/HER2 subtypes and graduated in the HR-/HER2+ signature. Qualifying biomarker analysis was performed on 26 proteins/phosphoproteins in the HER-AKT-mTOR pathway to identify candidate proteins correlated with pCR in the HER2+ and HER2- populations treated with MK2206. We postulated that response to MK2206 could be predicted by the relative level of phosphorylation of AKT kinase substrates. **Methods:** Of 151 patients in the MK2206 and control arms, 138 patients (MK2206: 87, controls: 51) had RPPA and pCR data. Data for 26 (phospho-) proteins involved in HER-AKT-mTOR signaling were assessed for association between biomarker and response in the MK2206 and control arms alone (likelihood ratio test), and relative performance between arms (biomarker x treatment interaction) using a logistic model. Analysis was also performed adjusting for HR/HER2 status. Markers were analyzed individually; p-values are descriptive and were not corrected for multiple comparisons. **Results:** In the HER2+ cohort, phosphorylation of the AKT kinase substrates mTOR S2448 (p = 0.004), GSK3 S21/9 (p = 0.009), FOXO1 S256 (p = 0.007), FOXO1 T24/FOXO3a T32 (p = 0.026), S6RP S240/S244 (p = 0.036), Tuberin/TSC1 Y1571 (p = 0.043) and eIF4G S1108 (p = 0.047) were associated with response. FOXO1 S256 also had a significant interaction with treatment in logistic model testing. In the HER2- population, AKT S473 (p = 0.012), AKT T308 (p = 0.011), Estrogen Receptor alpha (p = 0.013), mTOR (p = 0.04), NFkB S536 (p = 0.017) and Tuberin/TSC2 Y1571 (p = 0.03) were negatively associated with MK2206 response. FOXO S253 (p = 0.031) and ERBB2 Y877 (p = 0.02) were both positively associated with response and had a significant interaction with treatment in this cohort. **Conclusions:** While our sample size is too small to draw definitive conclusions, our results suggest that the measurement of AKT kinase substrate phosphoproteins could be predictive of MK2206 clinical activity in both HER2+ and HER2- tumors regardless of HR status. These results will need to be validated in independent study sets in order to judge the significance of these initial findings. Clinical trial information: NCT01042379.

12100 Poster Session (Board #213), Mon, 1:15 PM-4:45 PM

Non-V600 BRAF mutations in advanced malignancies: Prevalence and survival impact. *First Author: Ed Kheder, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *BRAF* mutations that occur outside of codon 600, non-V600 BRAF ($^{non\text{-}V600}$*BRAF*), have been detected in various types of tumors. Prevalence, and prognostic impact remain underestimated **Methods:** We conducted a retrospective study to characterize prevalence, and potential survival impact of $^{non\text{-}V600}$*BRAF* in advanced malignancies. We pooled patients who had *BRAF* mutant malignancies at MD Anderson Cancer Center. We used Kaplan-Meier to estimate survival outcomes and log rank test to compare OS between groups. We used chi-squared tests to compare mutation prevalence between cancer types. We computed survival from *BRAF* positive biopsy date. **Results:** Between September/2006 and July/2017, 3337 patients were found with *BRAF* mutant tumors. $^{non\text{-}V600}$*BRAF* mutations were detected in 596 (18%) patients. [238 (40%) female, 358 (60%) male; median age: 63 years, range (4, 90), 345 (58%) > 60 years; median OS, 25.0 months]. Most common cancers (%): melanoma 179 (30%); non-small cell lung (NSCLC) 83 (14%); colorectal 76 (13%), leukemia 52 (9%); myeloma 19 (3%); prostate 15 (3%); sarcoma 14 (2%); bladder, brain 11 (2%) each. Most common mutations (%): [G469A 64 (11%); D594G 58 (10%); K601E 46 (8%); D594N 37 (6%); G466E 23 (4%); G466V 22 (4%); G469V 19 (3%); E26D, G469E, G469R 18 (3%) each; S467L 15(3%); L597R, N581I, N581S 11 (2%) each]. Common mutations against common cancers are summarized in table-1. Three-year survival rate significantly changed with tumor type (P: < 0.0001): Melanoma 65%; Leukemia 62%; NSCLC 40%; other 30%; Colorectal 24%, but not with sex, age (P = 0.22); or $^{non\text{-}V600}$*BRAF* subtypes (P = 0.4). **Conclusions:** Non-V600 BRAF mutations occur in 18% of advanced malignancies. Their survival impact and prevalence significantly vary among tumor types. Future studies are warranted with MAPK or ERK kinase inhibitors.

Cross-tabulation of common mutations against common cancers.

Tumor	Number	D594G (%)	D594N (%)	G469A (%)	K601E (%)
Colorectal	76	22 (29%)	4 (5%)	8 (11%)	4 (5%)
Leukemia	52	3 (6%)	2 (4%)	5 (10%)	9 (17%)
Lung	83	7 (8%)	4 (5%)	16 (19%)	4 (5%)
Melanoma	179	8 (4%)	13 (7%)	11 (6%)	17 (9%)
Other	206	24 (12%)	35 (17%)	6 (3%)	3 (1%)
P-value		*< 0.0001*	*0.85*	*0.033*	*0.038*

12101 Poster Session (Board #214), Mon, 1:15 PM-4:45 PM

Exploring the association between somatic molecular features and tumor mutation burden in 513 non–small-cell lung cancer. *First Author: Chenchen Zhu, Geneplus-Beijing Institute, Changping District, Beijing, China*

Background: Tumor mutation burden (TMB) is new clinical marker that predicts responses to immunotherapy, but the molecular basis of TMB is unknown. Understand the association between genomic landscape and TMB may help to a better guidance of immunotherapy. **Methods:** We performed a retrospective review of 513 non–small-cell lung cancers (NSCLC) patients. Tumor tissues were acquired from initial diagnosis before any drug treatment and sequenced by Next Generation Sequencing (NGS) of 1021 genes. TMB (mutations/Mb) was analyzed as the number of somatic non-synonymous base substitution and indel per Mb in coding region. The top quartile was classified as TMB high. **Results:** A total of 513 patients had an average TMB of 7.5 mut/Mb. The median TMB was 5.8 mut/Mb (range, 1 to 67.68 mut/Mb). 128 patients were assessed as TMB high (TMB-H) and 385 patients were TMB low (TMB-L). The median TMB was 14 and 4.32 mut/Mb for patients with TMB-H and TMB-L respectively. *EGFR* mutations were detected in 28 patients with TMB-H (21.9%) compared with 228 with TMB-L (59.2%; $P < 0.01$). And other known drivers were significantly more common in patients with TMB-L than with TMB-H, which included *ALK* fusion, *ROS1* fusion, *MET* splice and *BRAF* V600E ($P < 0.01$). *KRAS* and *TP53* mutations were more common in patients with TMB-H than with TMB-L, but no significant difference of *KRAS* mutations were found between TMB-H and TMB-L (12.5% *vs* 7.8%; $P = 0.15$). Significant differences of *TP53* mutations were found between TMB-H and TMB-L (81.3% *vs* 54.8%; $P < 0.01$). In addition, alterations of homologous recombination repair and mismatch repair gene were more likely to be the high TMB, e.g. alterations in *BRCA1, BRCA2, ATM, ATR, PMS2* and *MSH2* were significantly enriched in patients with TMB-H. **Conclusions:** TMB-H is associated with lack of current druggable oncogenic drivers, such as *EGFR* mutations/ ALK or *ROS1* fusion. TMB detection provides a clinically useful predictor of response to immunotherapy. *TP53* and *KRAS* mutations specifically enriched in patients with TMB-H, may be served as potential predictive factors in guiding immunotherapy. Lastly, DNA damage repair mutations strongly correlated with high TMB, and may be a primary molecular mechanism for TMB.

12102 Poster Session (Board #215), Mon, 1:15 PM-4:45 PM

Impact of tumor-infiltrating lymphocytes on response to neoadjuvant chemotherapy in triple-negative early breast cancer: Translational subproject of the WSG-ADAPT TN trial. *First Author: Cornelia Liedtke, Charité - Universitätsmedizin Berlin, Berlin, Germany*

Background: In triple-negative breast cancer (TNBC), pathological complete response (pCR, ypT0/is/ypN0) is associated with improved prognosis. The randomized prospective WSG-ADAPT TN phase II trial showed higher pCR with Nab-paclitaxel / Carboplatin (NP/C) compared to paclitaxel / gemcitabine (NP/G) as 12-week neoadjuvant therapy. Presence of tumor-infiltrating lymphocytes (TILs) is associated with increased pCR rates after neoadjuvant chemotherapy, but the role of TIL dynamics during (specific) chemotherapy regimens is still unknown. **Methods:** This pre-planned translational analysis focuses on semi-quantitative TIL measurements in ADAPT-TN among tumor samples at baseline (TIL-0) and after 3 weeks of chemotherapy (TIL-3). Associations of continuous TIL-0 and TIL-3 levels with pCR, with chemotherapy arm and with other clinical / pathological measurements were analyzed using logistic regression, rank correlations, t and chi-square statistics. **Results:** 336 patients were enrolled. TIL-0 and TIL-3 were available among 311 (92.6%) and 223 (66.4%) patients, respectively. "Low cellularity" in 3-week biopsies (tumor necrosis, lack of invasive tumor cells) was recorded in 82 patients. TIL-0 and TIL-3 were strongly correlated (0.64, $p < .001$); average relative increase was about 30%. TIL-0 was significantly associated with baseline tumor grade, clinical tumor size, and nodal status. TIL-3 was significantly associated with nodal status and grade in both biopsies. In all patients, higher levels of both TIL-0 ($p < .001$) and TIL-3 ($p = .002$) were associated with pCR. Higher TIL-0 was also significantly associated with pCR in both arms separately. "Low cellularity" was also associated with pCR in all patients (OR = 3.9, 95%-CI: 2.3-6.8) and in both arms separately (NP/G: OR = 3.6, 95%-CI: 1.7 to 7.9; NP/C: OR = 4.2, 95%-CI: 1.9-9.3). **Conclusions:** In TNBC patients, higher levels of tumor-infiltrating lymphocytes were associated with pCR, both at baseline and after 3 weeks of neoadjuvant chemotherapy. "Low-cellularity" at week 3, which indicates extensive response to chemotherapy, was itself strongly associated with response to therapy.

12103 Poster Session (Board #216), Mon, 1:15 PM-4:45 PM

Association of activation levels of TIE2 with response to the angiogenesis inhibitor trebananib in HER2+ patients in the I-SPY 2 trial. *First Author: Rosa Isela Gallagher, George Mason University, Manassas, VA*

Background: Trebananib (T), an angiopoietin 1/2 neutralizing peptibody that inhibits interaction with TIE2 receptors, was available to all HR/HER2 subtypes in the I-SPY2 TRIAL. The agent did not achieve the prescribed graduation threshold for any eligible signatures prior to accrual of maximum sample size. We postulated that response to a drug that blocks TIE2 receptor-ligand interaction could be predicted by the measurement of basal TIE2 phosphorylation and downstream signaling in the pre-treatment biopsies. **Methods:** Of 267 patients in the T and control arms, 203 patients (T: 128, controls: 73) had reverse phase protein microarray (RPPA) and pCR data available. RPPA data for 33 (phospho- and total) proteins involved in TIE2 signaling were evaluated for association between biomarker and response in the T and control arms alone (likelihood ratio test), and relative performance between arms (biomarker x treatment interaction) using a logistic model (LM). Analysis was also performed adjusting for HR/HER2 status. Markers were analyzed individually; p-values are descriptive and were not corrected for multiple comparisons. **Results:** In the TN subpopulation, TIE2 receptor levels ($p = 0.037$), ERBB3 ($p = 0.048$), total ERα ($p = 0.05$) and ERα S118 ($p = 0.016$) were negatively associated with response to T. In HER2+ patients, phospho-TIE2 Y1119 ($p = 0.001$) and Y992 ($p = 0.0007$) were positively associated with T response, as were downstream AKT-mTOR signaling activation proteins such as eIF4G S1108 ($p = 0.005$), p70S6K T389 ($p = 0.011$) and T412 ($p = 0.038$) and FOXO3a S253 ($p = 0.041$). ERBB2 Y877 ($p = 0.028$) was negatively associated with response in these patients. TIE2 Y1119, TIE2 Y992, eIF4G S1108, ERBB2 Y877, and FOXO3a S253 all demonstrated a significant treatment interaction by LM. **Conclusions:** While small sample sizes preclude drawing definitive conclusions, our results suggest that activation levels of the TIE2 receptor may be predictive of T efficacy in HER2+ patients and signaling activation downstream of TIE2 such as AKT-mTOR signaling may correlate with response in the HER2+ and TN populations. These results need to be independently validated to determine the significance of these findings. Clinical trial information: NCT01042379.

12104 Poster Session (Board #217), Mon, 1:15 PM-4:45 PM

Single-cell profiling of NSCLC tumor treated with Durvalumab and in combination with Tremelimumab. *First Author: Yashaswi Shrestha, MedImmune, Gaithersburg, MD*

Background: Combination of anti-PD1/L1 and anti-CTLA4 is under investigation for treatment of multiple tumors. However, how this combination modifies the immune micro-environment of tumors is not well understood. Using single cell RNA sequencing (scRNAseq), we are systematically characterizing the ex vivo cellular and molecular effects of Durvalumab (D) and Tremelimumab (T) treatment on NSCLC tumors. **Methods:** Commercially available dissociated NSCLC tumor was treated with low dose interleukin-2 (IL-2) plus D, D+T or isotype control (IsoCtrl) at 20ug/ml each. For scRNAseq, T cells were isolated using αCD4 and αCD8 beads. Over 20,000 immune cells were profiled on D7 after treatment using 10X genomics. Exhausted T cells were defined based on the signature by Singer et al. (2016). Cell clustering and differential expression analyses were conducted using R package Seurat. Functional enrichment analyses, including KEGG and GO were performed by ClusterProfiler. **Results:** At D7 of D or D+T treatment, intracellular IFNG expression increased 60 and 80%, respectively. scRNAseq results were consistent with this functional data, showing 6% and 12% more IFNG expression in CD4+/CD8+ T cells following D and D+T, respectively. Checkpoint inhibitor expression (*PDCD1, CTLA4, TIGIT, LAG3, HAVCR2*) increased 4-9% and 7-15% upon D or D+T treatment, respectively. D and D+T treatment increased fraction of total CD4+ cells from 21% to 27% and 28%, respectively; however, there was a reduction in the specific CD4 subfraction of T regs (*CD4+FOXP3+*) in both treatments compared to IsoCtrl. D+T treatment shifted the molecular phenotype of exhausted T cells toward a more activated state by inducing a significant upregulation of *PTPRCAP, ITGB1*, and *KLF2*, genes important for T cell activation and/or reduced T reg function. **Conclusions:** Single-cell profiling of NSCLC tumor suggest that D+T treatment alters the molecular profile of exhausted T cells and T regs to generate a more active phenotype, which may contribute to clinical benefit for patients treated with this combination.

12105 Poster Session (Board #218), Mon, 1:15 PM-4:45 PM

A gene expression signature of *FOXM1-AURKB-CDKN1A* to recapitulate molecular characteristics of standardized uptake value of ^{18}F-FDG-PET in breast cancer. *First Author: Sung Gwe Ahn, Gangnam Severance Hospital, Seoul, Korea, Republic of (South)*

Background: We previously showed that standardized uptake value (SUV), an indicator of the degree of glucose uptake in ^{18}F-FDG-PET, could be used as a prognostic marker in breast cancer and has a correlation with 21-gene recurrence score. We explored genomic features associated with SUV and identified a molecular signature reflecting SUV in breast cancer. **Methods:** Transcriptomic profiling was carried out using gene expression data from 60 breast cancer patients who underwent preoperative FDG-PET to identify a molecular signature associated with SUV. The prognostic value of the signature was verified in other three cohorts (namely YSU, UNC, and TCGA cohorts, n = 301, 500, and 815, respectively). The association between the SUV signature and prognosis of breast cancer patients was assessed. To compare mutation profiles between two patient subgroups divided by SUV signature in the TCGA cohort, we obtained two predefined gene sets involved in oncogenic or metabolic pathways and estimated a difference of their mutation frequencies. **Results:** The determination of gene expression patterns by transcriptome data analysis identified 1,528 genes associated with SUV ($|r| > 0.35$, $p < 0.01$ by Pearson correlation test). The patient subgroups classified by those genes (i.e., SUV-high-cluster and SUV-low-cluster) were significantly similar with patient classification by SUV ($p < 0.001$). When estimating prognostic value of the molecular signature associated with SUV in three cohorts, the signature showed a strong prediction ability in breast cancer prognosis (each $p < 0.05$ by log-rank test). Gene network analyses revealed that a signaling defined by *FOXM1-AURKB-CDKN1A* could be an important pathway reflecting SUV characteristics. Lastly, a mutation profiling in the TCGA cohort showed that *POLD1*, *UGT2A1*, and *UGT1A3* involved in tumor metabolism would be important mediators. **Conclusions:** Our results unveil genomic characteristics of increasing glucose uptake of breast cancer captured by FDG-PET, supporting a poor prognosis in patients with high SUV. Our works shed light on understanding a molecular basis of glucose metabolism in patients with breast cancer.

12106 Poster Session (Board #219), Mon, 1:15 PM-4:45 PM

Circadian clock gene *PER1* mutations in colorectal cancer (CRC). *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: *PER1* encodes for one of the main negative regulator of the clock genes pathway, which modulates the circadian expression of key target genes at the cellular level. Downregulation of *PER1* has been observed in CRC and lower expression levels have been associated with poor survival and increased incidence of liver metastases. Few data are available on *PER1* gene mutations (*PER1*mut) in CRC. Therefore, we aimed to explore the clinical and molecular differences between *PER1* mutated versus wild-type (WT) CRCs. **Methods:** 4079 CRCs tested with tumor profiling (Caris Life Sciences, Phoenix, AZ) were included in this analysis. NextGen sequencing (NGS) was performed on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq platform (Illumina, Inc., San Diego, CA) on 592 genes. Microsatellite instability high (MSI-H) status was tested by NGS in 3996 tumors. Pathogenicity of PER1mut was estimated using Poly-Phen and SIFT. **Results:** Main characteristics in the global population were as follow: M/F 52.4/47.6%, median age 61 (16-90 yr), primary tumor right-sided 27.4%/left-sided 43.5%/NOS 29.1%, mutational status all WT 38.7%/*RAS*mut 53.4%/*BRAF*mut 7.9%, MSI-H 6.6% (n = 262). Overall, 185 unique *PER1*mut/variants were identified in 304 samples (7.45%); 45 were classified as pathological/possibly pathological (PATHmut) according to predictive scores. *PER1*mut were significantly associated with right-sided tumor location ($p < 0.001$) and MSI-H ($p < 0.001$). Overall incidence of *PER1*mut and PATHmut in the MSI-H group were 24% and 3.4%, respectively. In the multivariate analyses PATHmut were independently associated with mutations in *ARAF*, *BAP1*, *CHEK2*, *NF1*, *PIK3CA* and *POLE*. **Conclusions:** Our results provide the first exploratory data on *PER1*mut association with clinical and molecular features in CRC, in a large population of patients with extensive genetic testing. A deeper understanding of *PER1*mut pathogenicity and functional role is necessary to guide future analyses. Nevertheless, our results suggest a significant association with MSI-H, possibly reflecting an interplay between mismatch repair status and the clock genes pathway in CRC, consistent with previous data and warranting further investigation.

12107 Poster Session (Board #220), Mon, 1:15 PM-4:45 PM

Genetic variations in the β2M/HLA-E immunomodulatory complex to predict outcomes in metastatic colorectal cancer (mCRC) patients (pts) treated with first line FOLFIRI/Cetuximab: Data from the phase III FIRE-3 trial. *First Author: Madiha Naseem, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Cetuximab(cet) is an anti-EGFR mAb which enhances the antibody-dependent cellular cytotoxicity (ADCC) by Natural Killer (NK) cells in EGFR+ CRCs. Overexpression of MHC class I antigen E (HLAE), and its membrane stabilizer, βeta-2 microglobulin (β2M) inhibit cet-induced ADCC. We hypothesize that single nucleotide polymorphisms (SNPs) in HLAE/β2M will influence cet-dependent NK cell lysis and clinical outcomes. **Methods:** Genome wide association studies were conducted on whole blood from 236 mCRC pts in the randomized phase III FIRE-3 trial treated with FOLFIRI/cet(n = 129) and FOLFIRI/bevacizumab(bev)(n = 107). The OncoArray database provided by Illumina containing 530K SNP markers from these pts was used to extract data on 4 functional SNPs from β2M and HLAE. Log-rank test and Cox proportional hazard regression models evaluated SNP associations with PFS/OS in uni- and multivariable analyses. **Results:** FOLFIRI/cet and FOLFIRI/bev cohort characteristics: median FU (29.1/26.7mo); PFS (12.8/11.5mo); OS (49.8/31.4mo); RAS WT(64%/62%) and RAS mut (15%/16%). Multivariable analysis showed worse PFS in RAS WT pts treated with FOLFIRI/cet with HLAErs1059510 T/T alleles (12.2 vs 13.3 mo; HR = 2.59; 95%CI = 1.05-6.39; p = 0.039) and HLAErs1264457 G/G alleles (12.3 vs 12.9 mo; HR = 2.36; 95%CI = 1.14-4.88; p = 0.021). These effects were not observed in RAS mut pts. β2Mrs1901531 mutant C allele carriers showed improved OS (67.4 vs 40.9 mo) independent of RAS status in FOLFIRI/cet arm in both univariate (HR = 0.27; 95%CI = 0.12-0.59; $p < 0.001$) and multivariable analysis (HR = 0.19; 95%CI = 0.07-0.48; $p < 0.001$). No significance was observed in FOLFIRI/bev overall or FOLFIRI/bev RAS WT pts. **Conclusions:** For the first time, we show that clinical outcomes in mCRC pts treated with FOLFIRI/cet are predicted by genetic variations in HLAE/β2M, which are not observed in FOLFIRI/bev. The predictive utility of HLAE is dependent on RAS status, whereas that of β2M is independent of RAS. The HLAE/β2M complex could be a promising therapeutic target for overcoming cet resistance. Validation in larger cohorts is required.

12108 Poster Session (Board #221), Mon, 1:15 PM-4:45 PM

Landscape of osimertinib resistant mutations between the two common subtypes of EGFR 19del or L858R in NSCLC. *First Author: Yan Zhang, Geneplus-Beijing Institute, Changping District, Beijing, China*

Background: Acquired *EGFR* mutations (C797, L792, G796) co-occurring with T790M were reported to lead the resistance to osimertinib. It was reported that for advanced NSCLC patients, exon 19 deletion (19del) might be associated with longer PFS compared to L858R mutation accepted EGFR-TKIs therapy. In this study, we try to analyze the difference of the resistant mutation spectrum in patients accepted osimertinib treatment carrying these two types of mutations. **Methods:** Using targeted gene capture and next-generation sequencing technologies, we analyzed the somatic mutations in 110 NSCLC patients (pts) that were clinically resistant to osimertinib. **Results:** All of the 110 patients had an *EGFR* activating mutation (19del in 64 pts and L858R in 46 pts) and 104 were *EGFR* T790M positive. *EGFR* mutations which may lead to the acquired resistance of osimertinib were identified in 52.7% (58/110) patients, including C797S (43 pts), C797G (6 pts), L792H (6 pts), L792V (2 pts), G796S (3 pts), G796C (1 pts), L718V (4 pts), L718Q (7 pts), and 18 patients had multi-clonal resistant mutations. In all analyzable patients, at least one resistant mutation was identified *in cis* with T790M, and two of them also carrying an *in trans* mutation who were also co-existent with L858R. No patient had only *in trans* mutation in our study. The resistant mutation were more frequently detected in 19del group than in L858R (62.5% *vs* 39.1%, $p = 0.015$), with 21.9% *vs* 10.9% patients had mult-clones and 15.6% *vs* 8.7% *EGFR* amplification. These may due to the larger drug selection pressure from longer treatment of 19del group. Bypass or downstream co-occurring activating mutations detected were *EML4-ALK* rearrangement (1 pts), *MET* amplification (1 pts), *RET-CCDC6* rearrangement (1 pts), *KRAS* mutations (1 pts), *BRAF* mutations (7 pts), *PIK3CA* mutations (5 pts), and *PTEN* deficiency (3 pts). **Conclusions:** In our study, acquired *EGFR* mutations leading to osimertinib resistance were more likely to be identified with *EGFR* 19del than L858R mutation NSCLC patients. Understanding these resistance mechanisms may be useful to develop more effective therapies for patients resistant to osimertinib.

12109 Poster Session (Board #222), Mon, 1:15 PM-4:45 PM

Comparison of annotation services for the VA Precision Oncology Program. *First Author: Evangelia (Eva) Katsoulakis, SUNY Downstate Medical Center, Bayside, NY*

Background: Multigene NGS testing has become widespread, including through the VA healthcare system through the VA Precision Oncology Program (POP). Algorithms to interpret the pathogenicity of NGS-detected sequence variants and clinical actionability have been implemented as clinical services, but little is known about their relative performance in clinical practice. **Methods:** NGS testing results from patients who had NGS results from VA POP were included. NGS results were generated at Personal Genome Diagnostics and Personalis and annotated by a commercial annotation service (N-of-One) as well as through Watson for Genomics (WfG) and OncoKB. Comparison of annotation results consisted of two parts: determination of pathogenicity and treatment actionability recommendations. Cohen's kappa statistic was calculated for agreement between annotation services. **Results:** Among 1228 NGS results, 1388 unique variants were observed in 117 genes (TP53 270, STK11 92, CDKN2A 81, ATM 67, PTEN 52). Cancer type was lung adenocarcinoma in 440 samples, colon adeno 113, lung squamous 111, unknown primary 88, prostate 62, melanoma 57, H&N 41, NSCLC 40. For pathogenic and likely pathogenic variants, there was 87% agreement between WfG and N-of-One (kappa 0.729), 76% agreement between WfG and OncoKB (kappa 0.227) and 42% agreement between N-of-One and OncoKB (kappa -0.078). For level 1 drug actionability recommendations (not available from N-of-One) there was 91% agreement between WfG and OncoKB (kappa 0.19) with 54 variants identified only by WfG as level 1 and 74 variants identified only by OncoKB as level 1. **Conclusions:** There is substantial variability in assessment of pathogenicity of NGS variants in solid tumors by clinically available annotation services. In addition, there was only slight agreement in level 1 therapeutic actionability recommendations. Improvement of the precision of oncology NGS annotation is needed.

12110 Poster Session (Board #223), Mon, 1:15 PM-4:45 PM

Identification of actionable genomic alterations utilizing cfDNA. *First Author: Nora Sylvia Sanchez, Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy/ University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cell-free DNA (cfDNA) next-generation sequencing has become a more accessible, non-invasive approach for genomic testing. We report alteration identification frequency and clinical actionability in patients with advanced/metastatic cancer. **Methods:** Enrollment criteria for prospectively consented patients: Active metastatic/local inoperable advanced cancer, considering trial enrollment within next 2 lines of therapy, and either exhausted tissue block, archival tissue $>$ 1 year, available tissue block but progressed on compelling intervening therapy. Patients had cfDNA testing on a CLIA-certified panel (Guardant360) for point mutations, indels, amplifications, fusions. Alterations were assessed and ranked for functional impact, therapeutic implications and patient's overall actionability profile was determined. **Results:** 295 patients with $\geq$ 6 months follow-up were evaluated. Major diseases represented ($\geq$ 10 patients): hepatocellular (59), pancreatic (51), bile duct/cholangio(37), appendiceal(24), breast(20), sarcoma(18), lung(15), and colorectal(12). Majority of patients were male(167), Caucasian(222), median age 54.5 years. ECOG performance status (PS) upon enrollment: 0 (72), (185), 2(26), 3(2). 77.9% of patients (230/295) had $\geq$1 alteration detected; 56%(128/230) had an alteration in gene associated with FDA approved drug for specific biomarker/tumor type. Evaluation of variant functional significance in context of patient's disease identified 30.5 % (39/128) of patients as high potential for clinical action. Of these, 18%(7/39) were matched to targeted therapy: clinical trial enrollment(4), off label drug use(1), standard of care (SOC)(2). Amongst unmatched patients, 37.5% (12/32) did not return to institution/lost to follow up, 31.4%(11) had poor PS after return of results, while the rest enrolled on another trial(2), continued existing therapy (2) or other(6). **Conclusions:** cfDNA testing represents a readily accessible method for genomic testing and allows for detection of genomic alterations in most patients with advanced disease. Utility may be higher in patients with interest in genomically selected therapy, adequate PS, and enhanced by earlier testing in treatment course.

12111 Poster Session (Board #224), Mon, 1:15 PM-4:45 PM

Pan-cancer mesenchymal assay to predict response to MEK inhibitors. *First Author: Nuala McCabe, Almac Diagnostics, Craigavon, United Kingdom*

Background: Unsupervised hierarchical clustering of gene expression data from 265 high grade serous ovarian cancer (HGSOC) patients identified 3 major molecular subgroups. One subgroup is driven by activation of the MAPK-pathway and is associated with a mesenchymal phenotype, poor prognosis and resistance to platinum.The MAPK pathway is currently being targeted by novel therapeutics and hence an assay to detect activation of the pathway across cancers would be highly valuable as a clinical trial enrichment tool. **Methods:** Using TCGA data we show the existence of the mesenchymal subgroup across a range of solid tumours including stomach, bladder colon, lung, melanoma and prostate cancer. Further to this, a common gene list was generated to include only transcripts with high variability and expression across diseases, and used as a starting list for the development of a 15 transcript assay which can be used to prospectively identify the mesenchymal subgroup from archived tissue. The 15 gene expression assay was tested in preclinical model systems to assess its utility at predicting response to MEK inhibitors. **Results:** The 15 gene expression mesenchymal assay was a poor prognostic marker in 13 different solid tumours: overall HR = 1.78 [95% CI:1.65-1.92]) $p < 0.0001$. Additionally the assay was associated with a mesenchymal phenotype (migration, invasion) and activated MAPK (phospho-MAPK) signalling in preclinical cell line models. The assay also predicted phospho-MEK expression in clinical samples ($p < 0.05$). The assay score was reduced by MEK inhibition ($p < 0.05$) and elevated by KRAS, NRAS and MEK1 overexpression ($p < 0.05$). The assay predicted response to the MEK inhibitors Trametinib and Selumetinib across cell line models from multiple diseases ($p < 0.001$) and to Trametinib in mouse xenograft studies of lung cancer cell lines. **Conclusions:** A 15 gene expression assay has been developed from FFPE samples across multiple diseases to detect a mesenchymal molecular subgroup associated with MAPK signalling. The assay predicted sensitivity to MEK inhibitors in pre-clinical cell line and mouse model systems. Further work aims to validate the assay as a predictive biomarker in clinical samples from patients treated with MEK targeted therapies.

12112 Poster Session (Board #225), Mon, 1:15 PM-4:45 PM

Association of mucosal Fusobacterium with clinical stage and immune gene signatures of rectal adenocarcinoma. *First Author: Michael Sangmin Lee, UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Alterations in gut microbial composition are associated with development and progression of colorectal cancer (CRC), and may contribute to interpatient biologic and clinical heterogeneity. Fusobacterium is enriched in CRC and is associated with a proinflammatory microenvironment. We hypothesized that Fusobacterium was associated with distinct clinicopathologic characteristics and inflammatory gene signatures among patients with locally advanced rectal cancer. **Methods:** Patients with T3-4 or N+ rectal adenocarcinoma planned to receive neoadjuvant chemoradiation were prospectively consented to undergo pretreatment endoscopic tumor biopsy. The V1-V2 region of the 16S bacterial ribosomal RNA gene was sequenced to identify tumor mucosal microbiota taxonomy. Tumor mRNA sequencing (RNASeq) was also completed and gene set enrichment analysis (GSEA) with curated immunologic signatures in MSigDB was performed. Multivariate analyses were conducted using PRIMER VII and SPSS v24 software. P-values were determined using Mann-Whitney tests, and Benjamini-Hochberg procedure was used and only results with false discovery rate $<$ 0.25 are presented. **Results:** Of 43 total samples, 37 had adequate bacterial 16S rRNA gene sequencing, and 31 also had adequate RNA quality for RNASeq analysis. Among the 37 patients, mean age at diagnosis was 54 (range 30-77) and pre-treatment clinical stage was II (30%) vs. III-IV (70%). Higher clinical stage (stage III-IV vs II) was associated with enrichment of Fusobacterium (16.2% vs 5.6%, p = 0.019) and Parvimonas (4.6% vs 1.4%, p = 0.033) genera. In the 9 subjects with $>$ 20% relative abundance of Fusobacterium, 179/4872 Immunologic gene sets, were enriched with p-value $<$ 0.01 and FDR $<$ 0.20. Significant gene sets included increased myeloid cell signatures, like monocytes/macrophages and neutrophils, and decreased effective cytotoxic T cell signatures. **Conclusions:** Fusobacterium was more abundant in the mucosal microbiome of rectal cancer with higher clinical stage and was associated with different immune gene signatures. Further investigation into the impact of Fusobacterium on immune cell infiltration and function in colorectal cancers is warranted.

12113 Poster Session (Board #226), Mon, 1:15 PM-4:45 PM

Co-expression patterns of immune checkpoint molecules in relation to *PD-L1* expression. *First Author: Sumanta K. Pal, City of Hope, Duarte, CA*

Background: Targeting immune checkpoints has led to clinical benefit across a variety of tumor types, and employing combinations has enhanced response rates even further. We hypothesize that profiling the tumor and associated microenvironment can help tailor rational combinations of immunotherapeutic strategies. **Methods:** Whole transcriptomic sequencing (RNA-Seq; ~$200x10^6$ reads per tumor) of 1,880 unselected clinical cases was performed (NantHealth; Culver City, CA). Cases reflected 38 distinct histologies including but not limited to breast (17.8%), colon (9.5%), lung (7.9%), pancreatic (6.5%), ovarian (5.4%), brain (4.9%) and prostate cancer (2.7%). Cases were categorized as *PD-L1*-low, *PD-L1*-normal and *PD-L1*-high by cutoffs defined in TCGA expression profiles. Expression and co-expression of 6 checkpoint markers (*PD-L1*, *PD-L2*, *CTLA4*, *IDO1*, *LAG3* and *TIM3*) were analyzed for tissue-specific enrichment and within *PD-L1*-defined categories. Immune-cell infiltration was estimated using RNA deconvolution based on known immune cell marker genes (Bindea *et al* 2013). **Results:** Checkpoint expression did not cluster in a tissue-dependent manner. *PD-L1* shows no significant co-expression pattern with any of the analyzed checkpoint markers aside from its ortholog *PD-L2* ($R = 0.77$; $P = 1.9x10^{-285}$). Within the *PD-L1*-low category, *IDO1* and *TIM3* had relatively high expression and were highly correlated with each other ($R = 0.81$; $P = 4.6x10^{-17}$). The *PD-L1*-low category was especially deprived of memory T cells and eosinophils. Within the *PD-L1*-high category, overall expression of all checkpoint markers was higher. Amongst *PD-L1* high patients, *CTLA4* expression was highly variable (mean 2.5 ± 1.1; $\log_2$[TPM+1]) and lacked correlation with *PD-L1* ($R = -0.09$). In contrast, while *LAG3* also had variable expression in the *PD-L1*-high setting, it was strongly correlated with *CTLA4* ($R = 0.79$, $P = 7.4x10^{-14}$). The *PD-L1*-high category was especially enriched for Th1, NK $CD56_{dim}$, and CD8 T-cells. **Conclusions:** High and low *PD-L1* expression in the tumor and adjacent microenvironment are associated with variations in key checkpoint molecules. Low expression of *PD-L1* may be an ideal setting for use of IDO- or TIM3-directed therapies.

12114 Poster Session (Board #227), Mon, 1:15 PM-4:45 PM

Genomic landscape of diverse rare tumors: Next-generation sequencing of paired DNA and RNA analysis. *First Author: Ryosuke Okamura, Moores UCSD Cancer Center, La Jolla, CA*

Background: Patients (pts) with rare tumors (defined as incidence of < 15/100,000 per year) and ultra-rare tumors (prevalence < 2,000 in the U.S.) may lack standard or investigational therapeutic options. We have recently shown that matched targeted therapy approach based on the molecular profiling may result in responses in these cancers. Herein, we interrogated paired DNA/RNA among rare tumors using next-generation sequencing (NGS). **Methods:** A total of 286 pts with a rare tumor diagnoses were available for this analysis from NantHealth database. Somatic-specific variants were identified using paired tumor/normal comprehensive NGS. Analysis was focused on the 200 most frequently mutated genes in this cohort. Deep whole transcriptomic sequencing (RNA-Seq) (~200x106 reads per tumor) was used to determine expression of observed somatic variants. **Results:** Median age was 57.8 (range 0.60 – 87.7 yo), 48.6% (139/286) were women. The most common diagnoses were bone and soft tissue sarcomas (39.5%, N = 113) followed by oral and throat cancers (9.4%, N = 27) and cholangiocarcinoma (7.3%, N = 21). Ultra-rare tumors such as carcinoma of thymus (N = 10), adrenal (N = 5) and ampulla of Vater (N = 1) were included. All 286 pts had at least one alteration (including characterized alterations and variant of unknown significance). 79.0% (226/286) had ≥ 1 characterized alteration, with median number of alteration = 1 (range: 0-42). Among pts with characterized alterations, 74.3% (168/226) had ≥ 1 potentially actionable target (median: 1, range: 0-12) (with FDA-approved [on- or off-label] or investigational drug). Paired DNA/RNA sequencing revealed 44.1% (126/286) of pts had ≥1 DNA alteration that was not seen at the RNA level. **Conclusions:** Most pts with rare and ultra-rare cancers had theoretically tractable alteration. Interestingly, not all the DNA alterations were seen in RNA level, indicating potential silencing at the RNA level.

12115 Poster Session (Board #228), Mon, 1:15 PM-4:45 PM

Computer-extracted features relating to spatial arrangement of tumor infiltrating lymphocytes to predict response to nivolumab in non-small cell lung cancer (NSCLC). *First Author: Cristian Barrera, Case Western Reserve University, Cleveland, OH*

Background: Immune checkpoint inhibitors are now approved for use as therapy in advanced stage NSCLC. These drugs can decrease risk of progression by up to 60% when compared to standard chemotherapeutic regimens, but only about 20% of treated patients show significant benefit. The current gold standard for predicting response is increased tissue expression of PD-L1, but recent studies have shown this measure to be inadequate. TILs are correlated with PD-L1 levels and with antigen-induced anti-tumor immune pressure, with increased TILs associated with treatment response and longer survival. Recent work suggests that the spatial arrangement of TILs may be prognostic of outcome in several different cancer types. Here we evaluate whether computer-extracted features relating to spatial arrangement of TILs on digitized H&E images could predict response to Nivolumab in NSCLC. **Methods:** The study included fifty-six NSCLC patients with diagnostic tumor biopsies who were treated with Nivolumab. Responders and non-responders were classified according to clinical improvement and radiologic assessment by RECIST criteria on the first post-treatment CT scan. Two expert pathologists manually delineated tumor regions on digitized H&E images of the biopsies. Computerized algorithms automatically identified TILs within these regions, defined TIL clusters based on TIL proximity, and utilized network graph concepts to capture measurements relating to arrangement of these TIL clusters. **Results:** The top five features determined by a statistical feature selection method reflected the area and density of TIL clusters and the spatial proximity of the TILs to each other and to tumor cells. A machine learning classifier trained on these top 5 features had an AUC of 0.76 on the training set (n = 32) and an AUC of 0.64 on an independent validation set from another institution (n = 24). **Conclusions:** Computer extracted features relating to spatial arrangement of TIL clusters on digitized H&E images distinguished between patients who did and did not respond to Nivolumab. These findings need to be validated on in larger, multi-site validation sets.

12116 Poster Session (Board #229), Mon, 1:15 PM-4:45 PM

Detection of germline homologous recombination deficiency (HRD) in patients with metastatic esophagogastric (EG) cancer using clinical next generation sequencing (NGS). *First Author: Yelena Yuriy Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Although EG cancer is included in Lynch syndrome (LS) and hereditary diffuse gastric cancer (HDGC), the prevalence of HRD-associated germline mutations in patients with EG cancer remains to be elucidated. To determine the potential therapeutic implications, we assessed the prevalence of clinically actionable germline mutations detected by matched tumor-normal sequencing. **Methods:** The matched tumor-normal DNA were evaluated for somatic (up to 468 genes) and germline (76 genes) alterations under MSK IRB approved protocols. Prevalence of likely pathogenic and pathogenic germline alterations were reported in genes and correlated with clinical and somatic findings. **Results:** Of 400 consecutive pts with metastatic EG adenocarcinoma: 53% had esophagus/GEJ and 47% gastric cancer. 48 (12%) of patients had clinically actionable mutations conferring cancer susceptibility, including 38 moderate- to high- penetrance mutations. 30 of 400 pts (7.5%) pts had deleterious somatic (n = 17) or pathogenic germline (n = 19) mutations in the most commonly observed HRD genes (*ATM, BRCA1, BRCA2*). The prevalence of clinically actionable germline mutations among gastric versus esophagus/GEJ tumors was 15.5% and 8.9%, respectively (p = 0.043). Interestingly, one individual harbored both a *BRCA1* and an *ATM* mutation. Germline DNA mismatch repair mutations, diagnostic of LS, were present in only two pts, both with gastric cancer, *MSH2* mutations, with both tumors exhibiting a mismatch repair deficient signature. Other germline mutations of interest include: 6 *CDH1*, 1 *TP53*, 1 *BRIP1*, 1 *STK11* pts as well as 1 biallelic *MUTYH* carrier diagnostic of *MUTYH*-associated polyposis. When available, correlative tumor data, including somatic mutations and loss of heterozygosity in the gene(s) corresponding to the germline mutation will be presented. **Conclusions:** Clinical NGS in paired germline-tumor DNA samples increases detection of individuals with potential clinically significant germline/somatic mutations. Analysis of therapeutic implications of these HRD mutations is ongoing and updated data will be presented.

12117 Poster Session (Board #230), Mon, 1:15 PM-4:45 PM

Three-fold overestimation of tumor mutation burden using 248 gene panel versus whole exome. *First Author: Andrew Nguyen, NantOmics, LLC, Santa Cruz, CA*

Background: Next generation sequencing (NGS) Gene panel testing is used to imputed tumor mutational burden (iTMB) and has shown rough correlation with TMB derived from whole exome sequencing (WES). TMB is used to estimate immune checkpoint inhibitor (ICT) response based on potential neoantigen load. We hypothesized that actual TMB (aTMB), consisting of mutations across the exome, and expressed TMB (eTMB), consisting of expressed genes, would differ substantially from iTMB. **Methods:** Retrospective analysis of a database from a commercial DNA tumor:normal and RNAseq platform was carried out. We analyzed 890 clinical samples composing of both primary and metastatic disease by whole genome sequencing (WGS) or WES and RNA sequencing (RNA-Seq), and compared true tumor mutational burden to a predicted tumor mutational burden from a list of 248 genes thought to drive cancer. (COSMICv76) **Results:** Estimated tumor mutational burden based only on the list of 248 genes had an average of 15.79 mutations per megabase (14.16–17.43, 95% CI) whereas WGS/WES derived TMB had an average of 5.09 mutations per megabase of coding DNA (4.22–5.96). The relationship between gene panel size, aTMB and eTMB will be presented. **Conclusions:** In this retrospective analysis using a 248 gene list as a panel to impute TMB, we observed a roughly 3-fold over-estimate of TMB. This may impact ICT prescription and expectation of clinical benefit.

12118 Poster Session (Board #231), Mon, 1:15 PM-4:45 PM

Seventeen percent of NGS 50 gene panel variants are not expressed in RNAseq. *First Author: Razelle Kurzrock, Moores Cancer Center, La Jolla, CA*

Background: Next Generation Sequencing (NGS) has gained widespread clinical adoption for the determination of molecular targets for therapy in oncology. Standard NGS panels evaluate DNA only. RNAseq has shown that molecular targets identified by NGS panels are not universally expressed. We hypothesized that heterogeneous epigenomic factors may lead to low or absent RNA expression. We sought to determine the frequency of non-expressed variants that would be tested by a standard NGS panel. **Methods:** Retrospective analysis of a database from a commercial DNA tumor:normal and RNAseq platform was carried out. 992 samples were identified with paired DNA(WGS or WES)/RNAseq NGS. An analysis of expressed variant status for SNVs of the following type: synonymous, silent, missense, nonsense. Expressed variants are based on whether at least 2 alternate reads in the RNA are present at that variant site. A 50 gene panel (AmpliSeq HotSpot V2) was used as the reference comparison: ABL1, EGFR, GNAS, KRAS, PTPN11, AKT1, ERBB2, GNAQ, MET, RB1, ALK, ERBB4, HNF1A, MLH1, RET, APC, EZH2, HRAS, MPL, SMAD4, ATM, FBXW7, IDH1, NOTCH1, SMARCB1, BRAF, FGFR1, JAK2, NPM1, SMO, CDH1, FGFR2, JAK3, NRAS, SRC, CDKN2A, FGFR3, IDH2, PDGFRA, STK11, CSF1R, FLT3, KDR, PIK3CA, TP53, CTNNB1, GNA11, KIT, PTEN, VHL **Results:** A total of 225,727 SNVs were detected in the 992 samples. 669 samples had at least 1 SNV in the 50 gene panel set for a total of 1661 SNVs, of which 1375 SNVs were expressed in the RNAseq (82.8%). Across 37 tumor types the range of expression was 57% (melanoma)-100% (uterine). **Conclusions:** In this retrospective analysis using a 50 gene commonly used hotspot panel as a hypothetical reference comparison, 17% of detected variants were not expressed in the RNAseq. The lack of RNA expression may contribute to less than expected clinical benefit with molecularly targeted therapies. Since the distribution is non-uniform, identification of these genes can yield improved testing algorithms and treatment strategies.

12119 Poster Session (Board #232), Mon, 1:15 PM-4:45 PM

FDG-uptake and expression levels of TILs and PD-L1 in primary breast cancer. *First Author: Tomoko Hirakata, Department of General Surgical Science, Gunma University, Maebashi, Gunma, Japan*

Background: ^{18}F-Fluorodeoxyglucose-positron emission tomography (FDG-PET) is used to evaluate the glucose metabolic rates of cancers. Several studies have reported that high FDG uptake is predictive of poor prognosis and aggressive features in patients with breast cancer (BC). However, FDG-uptake is influenced by many factors, including inflammation. In this study, we investigated the relationship between FDG uptake and immunological factors, including degrees of Tumor-infiltrating lymphocytes (TILs), CD8 and programmed cell death ligand 1 (PD-L1), which has been suggested as prognostic factor in BC. **Methods:** Invasive carcinoma tissues of 97 BC patients who underwent surgery without preoperative therapy were examined. Grade of stromal-TILs was immunohistochemically (IHC) evaluated using the criteria of the International Working Group for TILs in BC: low (10-20%), intermediate (20-40%) and high (50-90%). CD8 positive and PD-L1 positive were evaluated by IHC. The evaluation of PET was determined using standardized uptake value max (SUVmax): low (< 5) and high ($\geqq 5$). The relationships between SUVmax and expressions of TILs, CD8 and PD-L1 were investigated. **Results:** Among the 97 patients, 22 (22.7%) had high SUVmax in the primary tumor. We divided the cases into two groups based on the value of SUVmax, low and high. The analysis revealed that large tumor size ($p = 0.004$), high nuclear grade ($p = 0.019$), high degree of TILs ($p = 0.004$) and positive expression of PD-L1 ($p = 0.003$) were significantly associated with high SUVmax in the primary tumor. There were associations between SUVmax and degree of TILs, and between SUVmax and the positive expression of PD-L1 ($r = 0.428$, $p < 0.001$ and $r = 0.413$, $p < 0.001$, respectively). All cases with high degree of TILs showed high expression of CD8. **Conclusions:** The present study demonstrated that the finding of preoperative FDG uptake in BC may be reflective of the grades of TILs and expression of PD-L1 in the tumor. High TILs is to be better prognostic factor, however, high expression of PD-L1 is to be a poor prognostic factor. In light of our results, FDG uptake may be predictive of immunological features in addition to aggressive features among patients with BC.

12120 Poster Session (Board #233), Mon, 1:15 PM-4:45 PM

Survival outcome of breast cancer (BC) patients presenting with recurrent and de novo isolated contralateral lymph node metastases (CLNM). *First Author: Aydah Al-Awadhi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In the current staging system, BC patients with isolated CLNM are considered to have distant or stage IV disease. The prognosis of these patients has not been described in contemporary series. In this study we compared the outcomes of patients with CLNM and those with stage IV disease with metastases other than CLNM. **Methods:** We identified metastatic BC patients treated at MD Anderson Cancer Center between 2000-2015. 235 patients had isolated recurrent CLNM (supraclavicular, infraclavicular and/or axillary) and 7617 patients had metastases other than CLNM. Among patients diagnosed with stage IV de novo, 37 had isolated CLNM and 1544 had distant metastases other than CLNM. Overall survival (OS) and breast cancer-specific survival (BCSS) were calculated from date of distant metastases for the recurrent cohort and from date of diagnosis for the de novo cohort. Descriptive statistics, Kaplan-Meier method with log-rank test and Cox proportional hazards model were used. **Results:** In the recurrent cohort (median follow-up 20 months) the 3-year OS rate was 43% for CLNM patients and 41% for those with non-CLNM ($p = 0.04$). After multivariable adjustment, patients with recurrent CLNM had decreased risk of death (HR = 0.66; 95%CI 0.56-0.78) compared to patients with metastases other than CLNM. Patients with CLNM had comparable OS to the subgroup of patients with bone-only metastases (HR = 0.97; 95%CI 0.82-1.16). Among stage IV de novo patients (median follow-up 31 months) the 3-year OS was 62% for patients with CLNM and 57% for patients with metastases other than CLNM ($p < 0.001$). In multivariable analyses, CLNM patients had decreased risks of death (HR = 0.63; 95%CI 0.39-1.00) compared to patients with metastases other than CLNM. BCSS analysis was similar. **Conclusions:** Metastatic BC patients with isolated CLNM have better outcomes compared to patients with non-CLNM metastases. The prognosis of patients with isolated CLNM was similar to the prognosis of patients with bone-only metastases. Our data can be helpful in identifying patients with limited regional disease that may potentially benefit from multidisciplinary treatment given improved outcomes.

12121 Poster Session (Board #234), Mon, 1:15 PM-4:45 PM

Early mortality with immune checkpoint inhibitors (IOs) in solid tumors: An inconvenient truth? *First Author: Eric Winquist, Western University and London Health Sciences Centre, London, ON, Canada*

Background: Overall survival (OS) benefit with IOs has been demonstrated in several solid tumor types leading to their rapid adoption and use in practice. We noticed IO randomized controlled trials (RCTs) with early crossover of OS Kaplan-Meier (KM) curves favoring control therapy but with overall benefit favoring IO therapy. This suggests a subpopulation of patients at a higher risk of death on IO therapy compared to control therapy early in treatment. We performed a systematic review to examine the frequency and characteristics of IO RCTs showing this negative discordant crossover (NDC). **Methods:** RCTs studying IOs and non-IOs in solid tumors with published OS KM curves were identified by electronic database search and FDA approvals 2015-17. Early OS divergence was identified by blinded reviewers. NDC of OS KM curves was defined as early divergence discordant with an overall beneficial survival trend. RCT characteristics were compared using Fisher's exact test. **Results:** 29 IO RCTs providing 33 comparisons and 24 non-IO RCTs providing 25 comparisons were identified. Nine IO RCTs (27%) and 1 non-IO RCT (4%) demonstrated NDC ($p = 0.03$). NDC occurred in NSCLC (3/9), urothelial cancer (2/2), melanoma (2/9), SCLC (1/2) and CRPC (1/2) RCTs. RCTs with NDC trended to less often study melanoma (22% v 46%) and squamous cancer (0% v 13%), and less often report OS benefit (22% v 71%). They trended to more often study urothelial cancer (22% v 0%) and 2nd-line treatment (56% v 38%), and more often have active treatment control arms (89% v 75%). **Conclusions:** Early NDC of overall survival curves occurs commonly in IO RCTs. This suggests a subpopulation of patients at higher risk of early death with IO therapy. Causes of this mortality are unclear but could include toxicity of IO therapy, superior antitumor effects of control therapy, and/or tumor growth promoting effects of IO therapy. We are quantitating this risk. Such crossover complicates proportional hazards modeling. Further research to identify the causes of and patients at risk for early mortality with IO therapy should be a priority and patients should be informed of this potential risk.

12122 Poster Session (Board #235), Mon, 1:15 PM-4:45 PM

Acquired *BRAF* fusions as a mechanism of resistance to *EGFR* therapy. *First Author: Morana Vojnic, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While multiple genetic mechanisms have been identified in *EGFR* mutant lung cancers as mediators of acquired resistance (AR) to EGFR tyrosine kinase inhibitors (TKI), either first generation (EGFR T790M), or third generation (EGFR C797S), or both (gains of MET or ERBB2), many cases lack a known mechanism of AR. **Methods:** To identify novel mechanisms of EGFR TKI, we performed targeted large panel sequencing (MSK-IMPACT assay; PMID: 28336552) on 374 consecutive patients with metastatic *EGFR* mutant lung cancer, including 200 tested prior to EGFR TKI, 136 tested after progression on EGFR TKI, and 38 patients with both types of samples. Genetic alterations hypothesized to confer AR were introduced into drug-sensitive EGFR-mutant lung cancer cell lines (H1975, HCC827, PC9) using CRISPR-Cas9 genome editing. We also generated a cell line from a biopsy of a patient with AR (MSK-LX138cl). A kinase-focused inhibitor library was used to screen for agents that would overcome AR. **Results:** We identified 4 patients with a *BRAF* fusion (3 *AGK/BRAF*, 1 *PJA2/BRAF*) in a sample obtained at AR to EGFR TKI (2 post-erlotinib; 2 post-erlotinib and post-osimertinib). A pre-TKI sample was available in one of these 4 patients and was negative for BRAF fusion. In the 200 patients only studied pre-EGFR TKI, no BRAF fusions were identified, further supporting the acquired nature of the BRAF fusion. Induction of *AGK/BRAF* formation in H1975 (L858R+T790M), PC9 (ex19del) and HCC827 (ex19del) cells by genome editing increased phosphorylation of BRAF, MEK1/2, ERK1/2 and STAT3, and conferred resistance to growth inhibition by osimertinib. A patient-derived cell line, MSK-LX138cl, with ex19del and the *PJA2/BRAF* fusion, was confirmed to be resistant to EGFR TKIs and then used to screen a library of 61 drugs targeting the MAPK pathway in the absence or presence of osimertinib to derive a potential therapeutic strategy. This identified trametinib as an agent that reduced growth of MSK-LX138cl and H1975-AGK/BRAF cells in a synergistic manner with osimertinib. **Conclusions:** Our findings identify acquired BRAF fusion as a recurrent mechanism of AR to EGFR TKIs including osimertinib and suggest combined MEK and EGFR inhibition as a possible therapeutic strategy.

12123 Poster Session (Board #236), Mon, 1:15 PM-4:45 PM

A comprehensive genomic analysis of squamous cell carcinomas of the lung, esophagus, and head and neck. *First Author: Lara Ann Kujtan, University of Missouri at Kansas City, KC, MO*

Background: Squamous cell carcinomas (SCC) of the lung, esophagus and head and neck (H&N) are indistinguishable by histology. Data from large-scale genomic studies have identified significant similarities in the mutational profiles of these tumors. Combined genomic analysis will lead to the discovery of unique molecular similarities and dissimilarities of these tumors. **Methods:** We analyzed whole exome, RNA, miRNA and methylation data of 1221 patients with lung (39.6%), esophagus (26.3%), and HPV-negative H&N SCC (34.1%) from the Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC). WTSI Mutational Signature Framework was used to develop mutational signatures (MS). **Results:** Nine novel significantly mutated genes were identified in the combined analysis, including *PYHIN1,* a key mediator in the inflammasome pathway. Mutations in the inflammasome pathway (*PYHIN1*, *MNDA*, *CIITA*, *AIM2*, *IFIT*, *IFNG*), which is key for tumor antigen processing and presentation to T cells, were identified in 136 SCC samples (11.1%). All mutations were mutually exclusive of one another. We also discovered a novel tumor suppressor gene mutation in Asian patients with esophageal SCC, *NEFH* (7%), which was mutually exclusive of the *TP53* mutation. Seven novel gene amplifications and two deletions were detected in the combined population. Two novel MS with high stability (0.83 and 0.85) were recognized in H&N (7% and 13% of all mutations) with maximum cosine similarities of 0.37 and 0.34 respectively. All TCGA samples displayed COSMIC MS 1(age-related), 2 (APOBEC), and 4 (tobacco-related), while the esophageal ICGC sample showed COSMIC MS 13(APOBEC) and 17 (unknown). **Conclusions:** Our analysis identified a novel tumor suppressor mutation in Asians with esophageal SCC. We report possible dysregulation of the tumor antigen-processing pathway in a small but significant proportion of patients. Two novel MS in H&N SCC were identified, and the remaining MS were similar across all three tumor types in the TCGA. Esophageal ICGC tumors had different mutational profiles suggesting a unique mutational process in Asians.

12124 Poster Session (Board #237), Mon, 1:15 PM-4:45 PM

Molecular comparison of interval and screen-detected breast cancers. *First Author: Dane Anthony Cheasley, Peter MacCallum Cancer Centre, North Melbourne, Australia*

Background: Breast cancer diagnosed after a negative mammogram but prior to the next screening episode are termed an "interval breast cancer" (IBC) and account for ~20% of breast cancer diagnoses in women attending population-based screening programs. IBCs are a major issue limiting the effectiveness of mammographic screening particularly as IBCs are generally diagnosed at later stages and have a worse prognosis in compared to screen detected breast cancer (SDC). To understand if IBC are biologically distinct from SDC we assessed the frequency of germline and acquired somatic genomic aberrations in a prospective cohort is 1060 screen detected and interval breast cancers. **Methods:** Using the Lifepool cohort, an Australian prospective population-based cohort of over 54,000 women, 1001 cases of breast carcinoma (811 invasive and 180 in situ) with known screening status at time of diagnosis were identified. Clinicopathological information, mammographic density data, and family history data was recorded. Germline and tumour DNA was also collected where available and sequenced for breast cancer predisposition and driver genes. **Results:** IBCs were significantly associated with more aggressive tumour characteristics including higher grade, more advanced stage and higher proportion hormone receptor negative cancers. Women diagnosed with an IBC also had a higher frequency of actionable germline mutations in HBOC genes (4.4% versus 2.3%). Analysis of the breast cancers did not identify any significant differences in the somatic mutation spectrum or frequency, overall copy number profiles or homologous recombination deficiency scores. **Conclusions:** In the emerging era of clinical sequencing, it is timely to investigate the genomic alterations of IBCs, as they impose a major limitation on effective mammography screening and are associated with a high mortality burden. Within this study, Clinicopathological and molecular differences observed rather form the continuum from less aggressive (SDC) to more aggressive (IBC) cancers. Whilst analysis of an actionable germline mutations revealed subtle risk increases in IBCs (in particular BRCA2), additional cohorts will be required to define

12125 Poster Session (Board #238), Mon, 1:15 PM-4:45 PM

Are racial differences in obesity and insulin resistance related to aggressive breast cancer? *First Author: Emily Gallagher, Division of Endocrinology, Diabetes and Bone Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Black women are more likely to die of breast cancer and develop more aggressive subtypes than white women. Black women are also more likely to be obese and have insulin resistance than white women. Insulin resistance has been associated with faster tumor growth but has not been studied as a potential mediator of racial disparities in women with breast cancer. We hypothesized that black women would present with more aggressive breast cancer and this would be associated with obesity and insulin resistance. **Methods:** We recruited 810 (83% white, 17% black) women with new primary breast cancer, measured fasting blood glucose and insulin, body mass index (BMI), triple negative breast cancer (TNBC) & Nottingham prognostic index (NPI). We classified aggressive breast cancer as NPI $>$ 4.4. We calculated insulin resistance scores (HOMA) and classified insulin resistance as HOMA $>$ 2.8. Patients self-identified race. Immunohistochemistry (IHC) of insulin receptors (IR) was performed on a subset of tumor specimens (N = 181). **Results:** Of 810 women, average age was 58 years (sd = 12.2). 293 (37%) were stage 2+ at time of diagnosis; 18% had an NPI $>$ 4.4. Black women presented with higher stage of cancer than white women (stage 2+: 48% vs 35%; p = 0.004), were more insulin resistant (18% vs 11%, p = 0.03), had higher BMI (31.1kg/m^2 vs 26.7 kg/m^2; p $<$ .0001), and NPI scores (4.0 vs 3.6; p $<$ .05). Black women had more TNBC than white women (17% vs 6%, p = 0.0001). HOMA score was not associated with NPI score (r = 0.06; p = 0.12). IR expression was intermediate or highly expressed in 79% of cancers in black women & 51% in white women (p = 0.004) but was not significantly related to NPI $>$ 4.4 (66% vs 54%; p = 0.2). **Conclusions:** In women with newly diagnosed breast cancer, black women are more likely to be obese, have higher HOMA & NPI scores than white women. While these data are consistent with the hypothesized relationship of hyperinsulinemia promoting more aggressive breast cancer, to date, insulin resistance does not appear to mediate the effect of race and poor prognostic breast cancer.

TPS12126 Poster Session (Board #239a), Mon, 1:15 PM-4:45 PM

A phase 1/2 dose-escalation and expansion study of a conditionally active anti-AXL humanized monoclonal antibody (BA3011) in patients with advanced solid tumors. *First Author: Jordi Rodon Ahnert, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The AXL receptor tyrosine kinase is often highly expressed in certain cancers. AXL appears to sustain resistance to anticancer therapies including chemotherapy, targeted therapy and immune checkpoint inhibitors (1, 2). BA3011 is an anti-AXL humanized monoclonal antibody conjugated to monomethyl auristatin E using a cleavable linker (CAB-AXL-ADC) and specifically binds to AXL under conditions found within the tumor microenvironment. The pharmacokinetic (PK) and toxicity profile of BA3011 has been established in cynomolgus monkeys; anti-tumor activity has been shown in non-small-cell lung cancer (NSCLC), pancreatic, castration-resistant prostate cancer (CRPC) and other tumor models. **Methods:** A multi-center, open-label, Phase 1/2 study will evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of BA3011 in patients with advanced solid tumors. The study consists of a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2). The primary objective of Phase 1 is to define the safety profile (including dose-limiting toxicity [DLT]), maximum tolerated dose, and recommended Phase 2 dose (RP2D). BA3011 will be administered every 3 weeks (q3w) via intravenous infusion, with a starting dose of 0.3 mg/kg, escalating to 2.4 mg/kg using a modified Fibonacci method, until DLT occurs. In Phase 2, patients will receive the RP2D. Treatment will continue q3w until disease progression or unacceptable toxicity; safety and efficacy will be evaluated in specific tumor types (NSCLC, CRPC, and pancreatic ductal adenocarcinoma). Approximately 120 patients will be enrolled (11-30 in Phase 1 and approximately 90 in Phase 2). Patients must have histologically or cytologically confirmed locally advanced, unresectable or metastatic solid tumors and have failed available standard-of-care therapy and for whom no curative therapy is available. Follow-up information will be collected approximately every 3 months after the last dose until disease progression for patients with stable disease or better at the end of treatment. Clinical trial information: NCT 03425279.

TPS12127 Poster Session (Board #239b), Mon, 1:15 PM-4:45 PM

Canadian profiling and targeted agent utilization trial (CAPTUR/PM.1): A phase II basket precision medicine trial. *First Author: Tanya Skamene, McGill University, Montreal, QC, Canada*

Background: Genomic profiling of cancers is increasingly used to refine prognostication and aid in treatment decisions by allowing matching of targeted agents to specific genetic variants. Clinical reports to date suggest that 30-80% of advanced solid tumours harbor potentially actionable genomic variants but difficulties in obtaining matched targeted agents in clinical practice limits the application of precision medicine. CAPTUR is a pan-Canadian trial leveraging existing clinical genomic profiling platforms and the research capabilities of the Canadian Cancer Trials Group (CCTG) to evaluate targeted drug-genetic variant matches in patients with advanced cancers. CAPTUR was developed in collaboration, and plans to share data, with ASCO's TAPUR and the Netherland's DRUP trials. **Methods:** CAPTUR/PM.1 (NCT03297606) is a multi-centre, open-label, phase II basket trial, matching Canadian patients who have undergone genomic profiling with genetic variants to appropriate targeted agents. Drug matches are drawn from a list of 17 commercially available anticancer agents. Patients must have incurable metastatic solid tumours, multiple myeloma, or B cell non-Hodgkin lymphoma, must have no standard treatment options known to prolong life and must have an actionable genomic variant known to be a target of, or predict sensitivity to, the commercially available targeted anticancer drug. Patients who possess an actionable tumour genetic variant and meet non-drug specific study requirements are entered into the study. A drug-variant match is assigned based on protocol specified matching criteria or input of the Molecular Tumour Board. Determination of the best treatment is then made by physician and patient based on drug-specific eligibility requirements. Cohorts are defined by tumour type, genomic alteration and matched drug treatment. The primary endpoint is response rate, as determined by disease-appropriate objective criteria. Maximum sample size per cohort is 24 patients based on a Simon 2-stage admissible design. Maximum planned number of cohorts is 30 (maximum sample size for the trial of 720 patients). CAPTUR was activated November 2017 and is open to enrolment. Clinical trial information: NCT03297606.

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