Updated Results of a First-in-Human Dose-Finding Study of the ALK/EGFR Inhibitor AP26113 in Patients with Advanced Malignancies

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Disclosures

Camidge- ARIAD:

- Advisory Role: Ad hoc advisory boards/consultations
- Honoraria: Seminar/talks to industry
- Research funding

Langer- ARIAD: Research funding

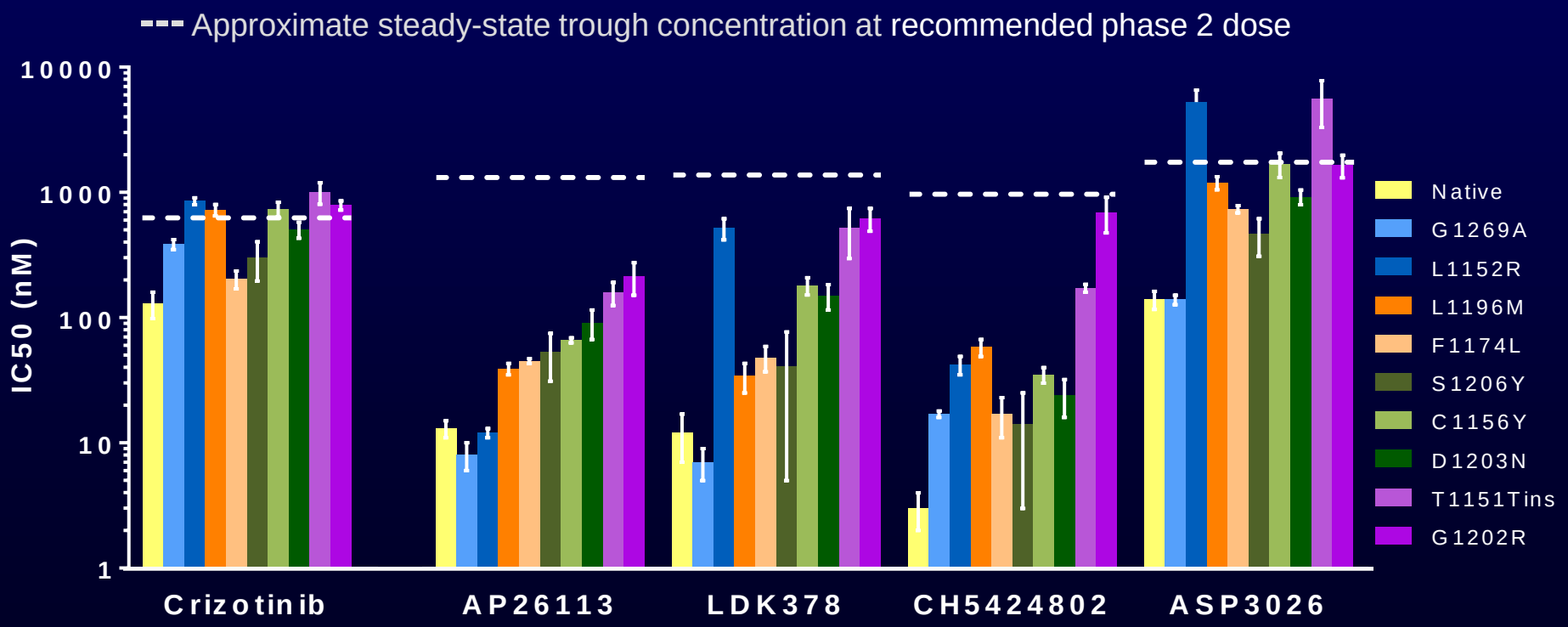
Shaw- ARIAD: Consultant/advisory role

Narasimhan, Dorer, and Zhang- ARIAD: Employment and stock ownership

Bazhenova, Salgia, Weiss and Gettinger- Nothing to disclose

AP26113 is a Potent ALK Inhibitor

- Crizotinib is active in patients with ALK+ NSCLC, but most patients eventually progress
  - ~46% of patients first progress in brain, suggesting inadequate CNS exposure[1]
  - Systemic progression usually occurs later, through diverse mechanisms, including multiple ALK mutations[1,2,3]
- In vitro, AP26113 has low nM activity against ALK (13 nM) and broadest range of activity against known resistance mutations in class

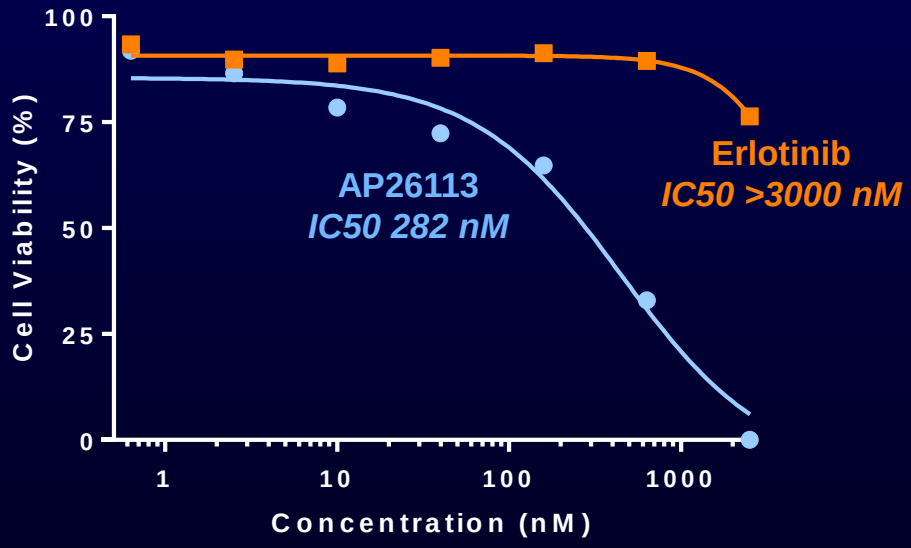


[1]Weickhardt et al, J Thorac Oncol, 2012;7:1807–1814; [2]Doebele et al, Clin Cancer Res, 2012;18(5):1472–82; [3]Katayama et al, Sci Transl Med, 2012;4(120)
Data on file, ARIAD Pharmaceuticals, Inc.

AP26113 Also Inhibits ROS1 and Mutant EGFR (Activated and Gatekeeper)

- Potently inhibits ROS1 fusions at concentrations similar to ALK (IC50 18 nM)
- Inhibits activated EGFRm variants, including the T790M gatekeeper mutation (IC50s ~10-40x higher than ALK)
- Does not inhibit native EGFR

Potency of AP26113 vs. Erlotinib in Ba/F3 EGFR-DEL+T790M



AP26113 Activity in Cellular Models

EGFR Ba/F3 Cell Line	IC50 (nM)
DEL	112
DEL + T790M	282
L858R	456
L858R + T790M	694
Native EGFR	>3000
(Parental Ba/F3)	>3000

DEL = Exon 19 deletion; Zhang et al, presented at AACR 2010, Abstract LB-298 ; Rivera et al, presented at AACR 2012, Abstract 1794; Data on file, ARIAD Pharmaceuticals, Inc.

AP26113 Phase 1/2 Study
Study Design

Phase 1

Dose Escalation,
3+3 Design: N=30 to 60
Advanced malignancies (all histologies except leukemia) until MTD and RP2D established

Phase 2

Cohort 1, NSCLC: N=20
ALK+ and ALK inhibitor naïve

Cohort 2, NSCLC: N=20
ALK+ and crizotinib-resistant

Cohort 3, NSCLC: N=20
Documented T790M and resistant to 1 prior EGFR TKI

Cohort 4: N=20
Other cancers with AP26113 targets
(eg, ALK, ROS1, EGFR ineligible for Cohort 3, and others)

Added May 2013

Cohort 5, NSCLC: N=25
ALK+ and naïve or resistant to crizotinib with active brain mets

Summary of Phase 1 Dose Escalation

- Dose escalation, with expansion, up to 300 mg QD. Maximum tolerated dose not formally determined
- Early dyspnea, hypoxia noted in some patients
- Re-evaluated 90-180 mg/d with narrowed inclusion criteria (no O_2; no interstitial disease; ECOG 0,1); no pulmonary events observed
- RP2D of 180 mg QD in Ph 2 expansion; 240 mg/d in select T790M patients

Patients Treated (All Cohorts)

Dose (mg/d)[a]	Total Treated N=91	Evaluable for Response[b] N=72
30	3	3
60	3	3
90	8	8
120	18	18
180	45[c]	28[c]
240	12	10
300	2	2

[a] Assigned dose
[b] Patients were evaluable for response if they had a post-baseline tumor assessment or discontinued from the study
[c] 26 treated and 9 evaluable for response in Phase 2
54 patients remain on study

Data as of 6 Sept 2013

Patient Characteristics

	All Patients N=91	History of ALK+ N=44	History of EGFRm N=37
Median age, yrs (range)	57 (31-83)	52 (31-73)	60 (39-83)
Sex, male, n (%)	36 (40)	20 (45)	12 (32)
Race, n (%)			
White	71 (78)	36 (82)	26 (70)
Asian	12 (13)	6 (14)	5 (14)
Other	8 (9)	2 (5)	6 (16)
Diagnosis, n (%)			
NSCLC[a]	83 (91)	40 (91)	36 (97)
Other	8 (9)	4 (9)	1 (3)
Prior targeted therapy, n (%)			
Crizotinib	42 (46)	37 (84)	2 (5)
EGFR-targeted TKI	47 (52)	8 (18)	34 (92)
Neither crizotinib nor EGFR-targeted TKI	12 (13)	7 (16)	2 (5)
Prior systemic therapy, n (%)			
1-2 regimens	38 (42)	18 (41)	17 (46)
≥3 regimens	50 (55)	23 (52)	20 (54)

[a] 75 adenocarcinoma, 3 adenosquamous, 1 large cell, 1 signet cell, and 3 squamous cell carcinoma

Data as of 6 Sept 2013

Adverse Events (≥10% overall, all grades) Treatment Emergent

Preferred term	30,60 mg N=6	90 mg N=8	120 mg N=18	180 mg* N=45	240 mg N=12	300 mg N=2	Total N=91
Nausea	3 (50)	2 (25)	6 (33)	18 (40)	6 (50)	0	35 (38)
Fatigue	2 (33)	3 (38)	6 (33)	10 (22)	9 (75)	1 (50)	31 (34)
Diarrhea	1 (17)	4 (50)	7 (39)	10 (22)	7 (58)	0	29 (32)
Headache	0	4 (50)	2 (11)	8 (18)	4 (33)	0	18 (20)
Vomiting	1 (17)	1 (13)	4 (22)	6 (13)	3 (25)	0	15 (16)
Dyspnea	0	1 (13)	5 (28)	5 (11)	3 (25)	1 (50)	15 (16)
Muscle spasms	1 (17)	1 (13)	1 (6)	5 (11)	2 (17)	0	10 (11)
Cough	1 (17)	3 (38)	4 (22)	5 (11)	5 (42)	1 (50)	19 (21)
Amylase increased	0	2 (25)	3 (17)	4 (9)	2 (17)	0	11 (12)
Decreased appetite	0	3 (38)	1 (6)	3 (7)	3 (25)	1 (50)	11 (12)

*Preferred terms ranked by incidence at 180 mg

Data as of 6 Sept 2013

Adverse Events
Treatment Emergent, Grades ≥3

Preferred term (≥2 patients)	30,60 mg N=6	90 mg N=8	120 mg N=18	180 mg* N=45	240 mg N=12	300 mg N=2	Total N=91
Dyspnea	0	0	1 (6)	1 (2)	1 (8)	1 (50)	4 (4)
Fatigue	1 (17)	0	0	1 (2)	2 (17)	0	4 (4)
Pneumonia	0	0	3 (17)	1 (2)	0	0	4 (4)
Hypoxia	0	0	0	1 (2)	1 (8)	1 (50)	3 (3)
Lung infection	0	0	1 (6)	1 (2)	0	0	2 (2)
Pneumonitis	0	0	1 (6)	1 (2)	0	0	2 (2)
Lipase increased	0	0	1 (6)	0	2 (17)	0	3 (3)
Diarrhea	0	0	0	0	2 (17)	0	2 (2)
Hyponatraemia	0	1 (13)	0	0	1 (8)	0	2 (2)

*Preferred terms ranked by incidence at 180 mg

- **Treatment-related Grade ≥3 AEs in ≥2 patients: dyspnea (4%), fatigue (3%), diarrhea (2%), hypoxia (2%), and pneumonitis (2%)**

Data as of 6 Sept 2013

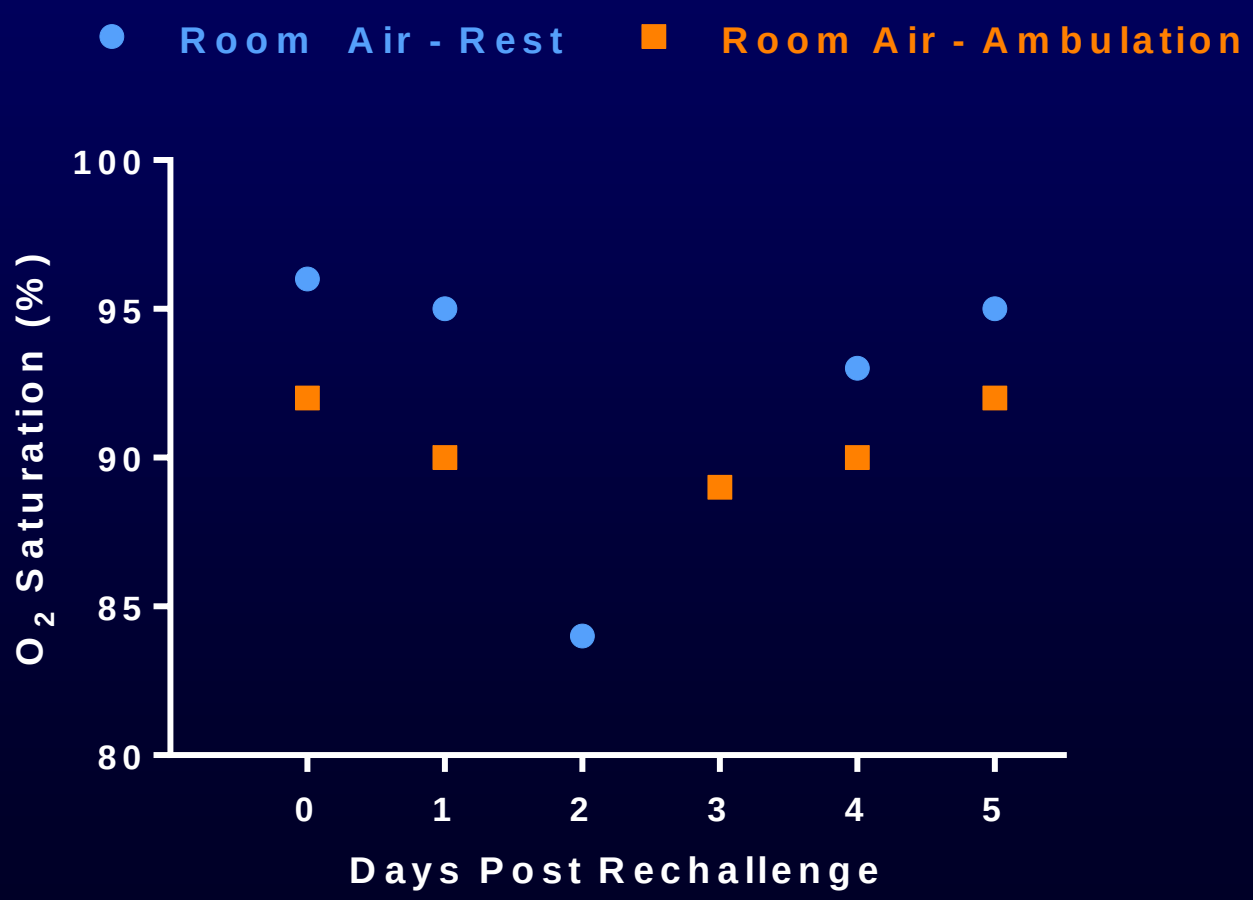
Clinical Presentation of Early Onset Pulmonary Symptoms

- Observed in 3/26 patients (12%) at 180 mg QD in Ph 2 expansion (4/45 (9%)) overall), 1/3 T790M at 240 mg/d
- Occurred at lower doses, but less common; not observed at these doses with narrowed eligibility criteria
- Early onset (typically day 1 or 2) of shortness of breath, O_2 desaturation, chest tightness, fever in some, and patchy GGO
- Reversible, responsive to drug interruption and steroid support; documented recurrence with rechallenge but some cases resolved with continued dosing w/o additional intervention; 1 case associated with fatality concurrent with progressive malignancy (Ph 1)

GGO- ground glass opacities

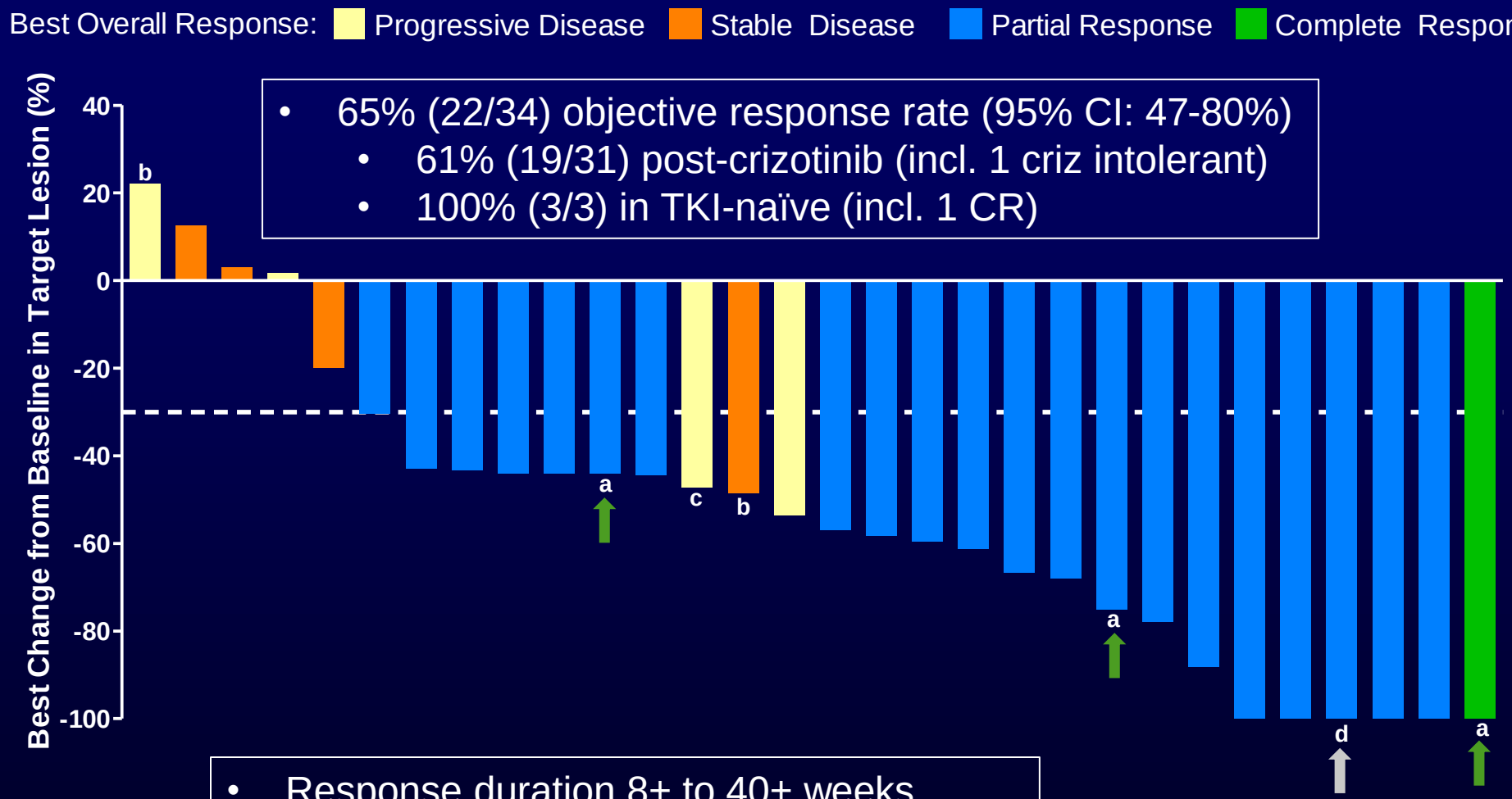
Reversibility of Early Onset Pulmonary Symptoms with Continued Dosing

60 mg prednisone QD premedication
180 mg AP26113 rechallenge
O_2 as needed



Data from single patient

ALK+ NSCLC Anti-Tumor Activity Target Lesions (N=34)



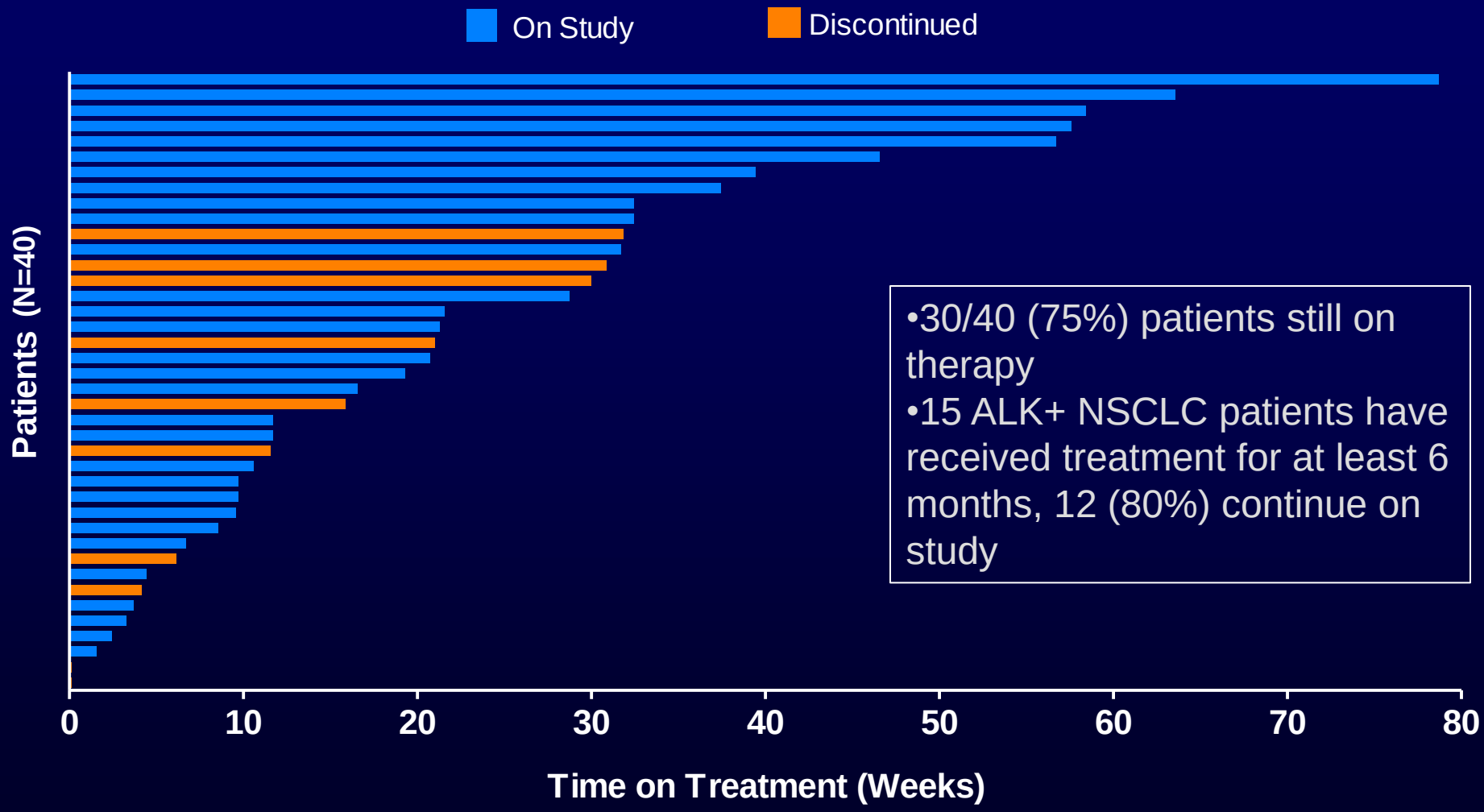
- 65% (22/34) objective response rate (95% CI: 47-80%)
  - 61% (19/31) post-crizotinib (incl. 1 criz intolerant)
  - 100% (3/3) in TKI-naïve (incl. 1 CR)

- Response duration 8+ to 40+ weeks
  - 14 confirmed, 4 awaiting confirmation

All patients received prior crizotinib unless otherwise indicated; Doses ranged from 60-240 mg/d (23 pts ≥180mg/d); [a]TKI-naïve; [b]Received prior crizotinib and LDK378; [c]PD by RECIST 1.1 due to 2nd primary tumor of melanoma; [d]Crizotinib-intolerant

Data as of 6 Sept 2013

ALK+ NSCLC Time on Treatment



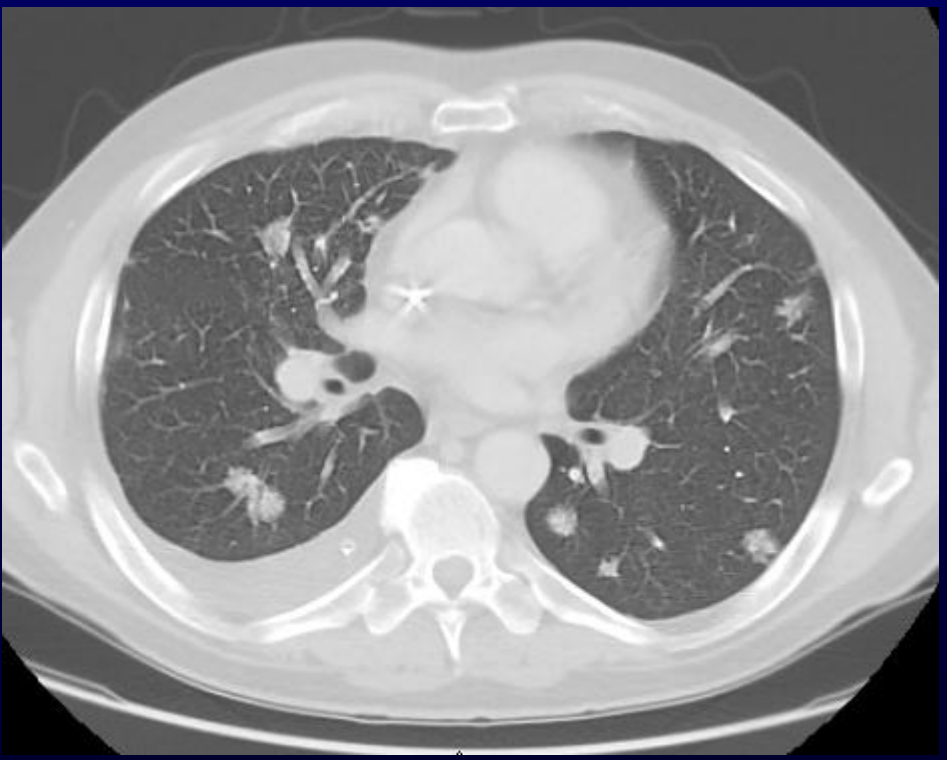
- 30/40 (75%) patients still on therapy
- 15 ALK+ NSCLC patients have received treatment for at least 6 months, 12 (80%) continue on study

First dose to last dose if discontinued, first dose to date of data cut if on study

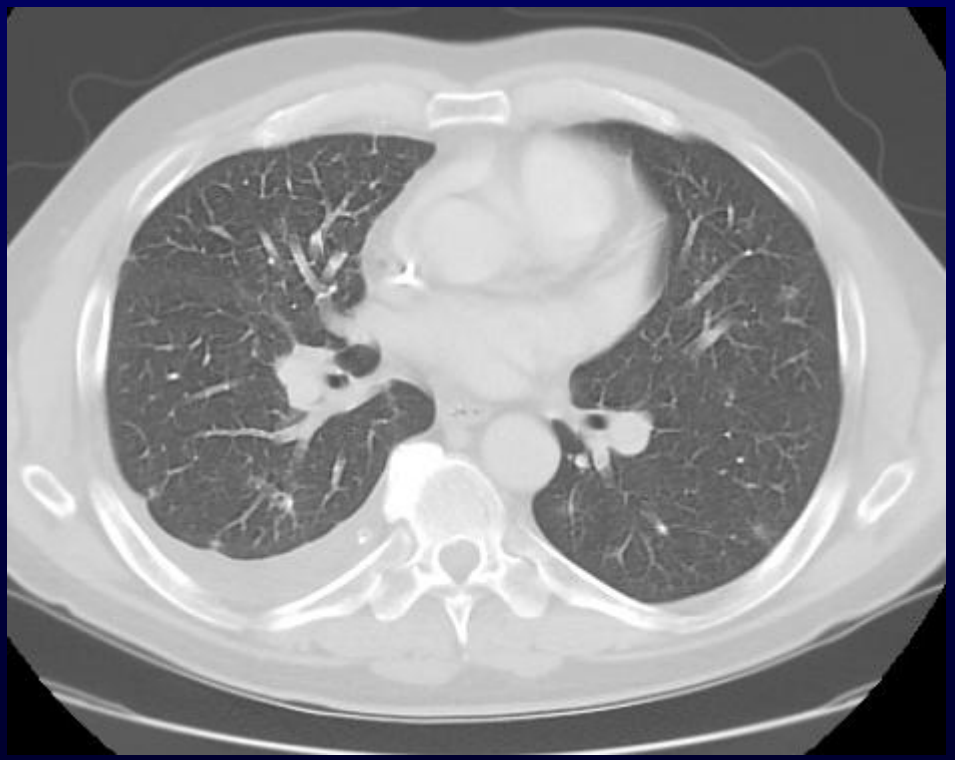
Data as of 6 Sept 2013

Response at 60 mg BID in Crizotinib-resistant ALK+ NSCLC

Baseline



After 12 Weeks of AP26113



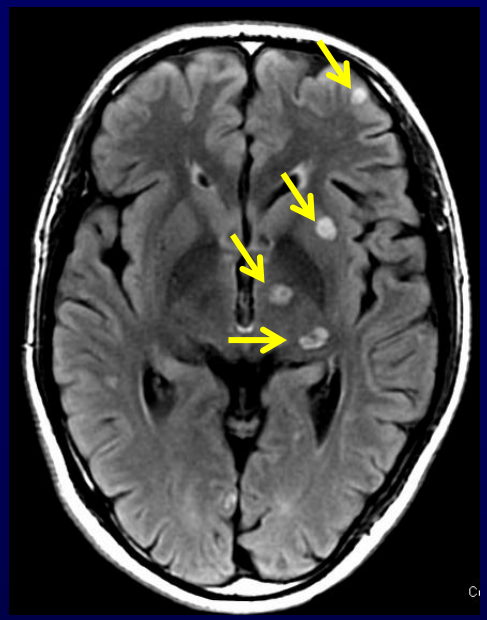
PR is ongoing, 16+ weeks; Images courtesy of Dr. S. Gettinger

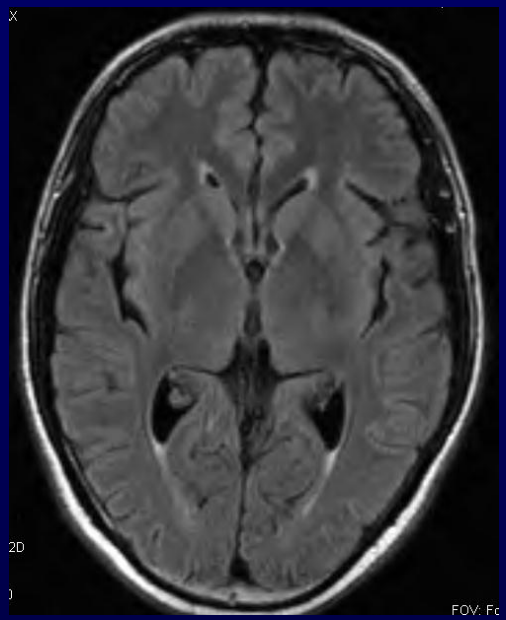
Data as of 6 Sept 2013

Brain Metastases Activity

Baseline

After 8 Weeks of 180 mg AP26113

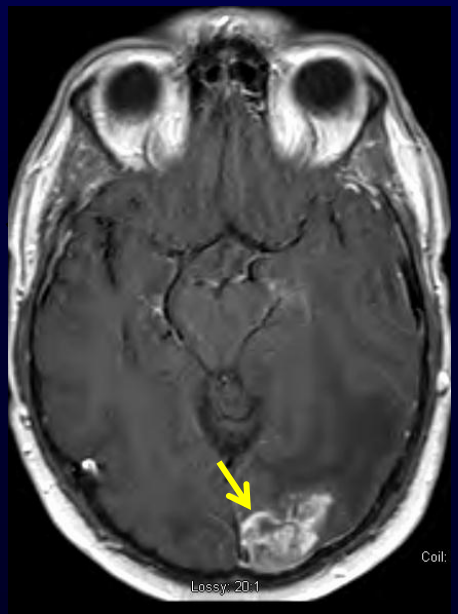


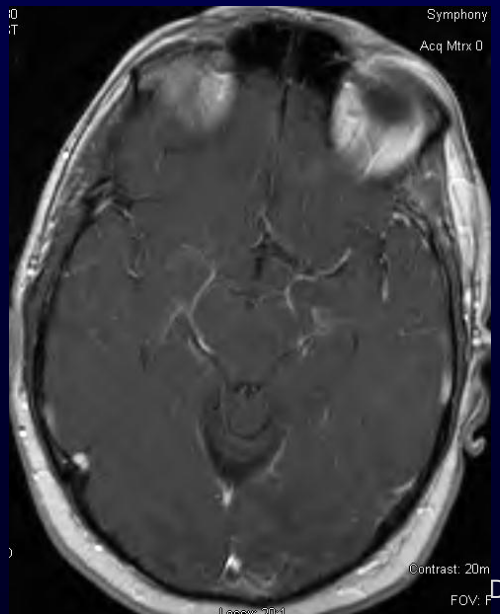


Patient 1

Both patients have crizotinib-resistant ALK+ NSCLC

Images courtesy of Dr. D.R. Camidge

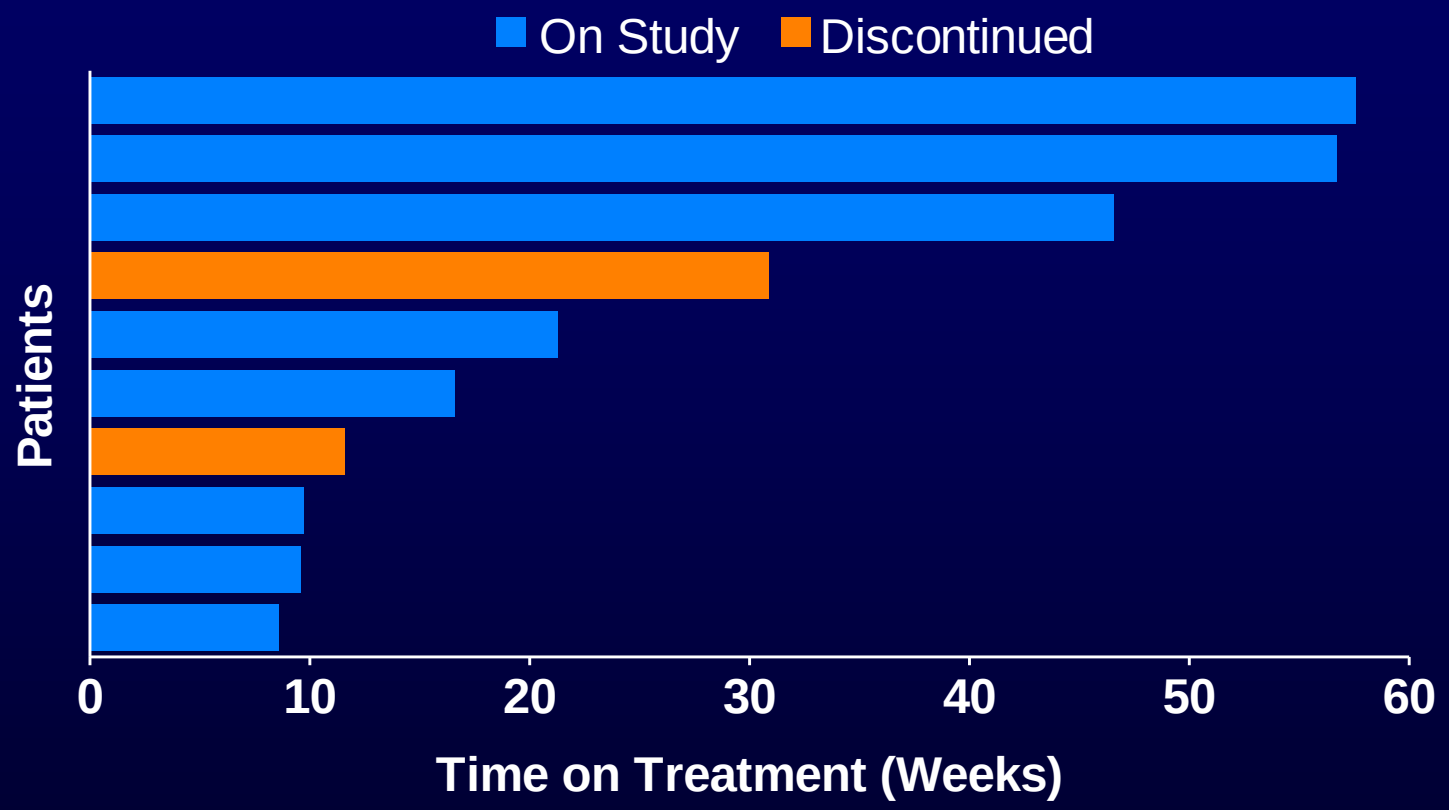




Patient 2

Data as of 6 Sept 2013

Brain Metastases Activity



- 8 of 10 ALK+ NSCLC patients with active brain lesions at baseline had evidence of radiographic improvement in brain
- Duration of CNS benefit[a] ranging from 8+ to 40+ weeks

[a]First dose to last scan with evidence of radiographic improvement

Data as of 6 Sept 2013

T790M Patients

- Total treated: N=18 (15 T790M by history, 3 confirmed)

	60 mg QD	120 mg QD	180 mg QD	120 mg BID	240 mg QD	300 mg QD
N	1	3	8[a]	2	3	1

- Total treated with narrowed T790M criteria[b]: N=3 at 240 mg/d (1 evaluable)
- Total evaluable for response: N=12 (N=8 ≥180 mg/d)
  - 5 SD (incl. 1 patient with narrowed criteria)
  - 4 PD
  - 3 discontinued before assessment

[a]Ph 1: n=3; Ph 2, Cohort 4: n=5

[b]1 prior TKI; documented T790M following progression on most recent TKI; AP26113 within 30 days of stopping prior TKI

Data as of 6 Sept 2012

AP26113 Phase 2 Dosing Strategy

- Substantial activity in crizotinib refractory patients, including in patients with brain metastases after crizotinib
- Dosing objective is to optimize drug exposure systemically and in the brain
- Early onset pulmonary symptoms
  - Observed in 9-12% of patients treated at 180 mg QD; not observed at 90 mg QD
  - Observed in some patients post single dose, but not later in course of treatment, despite continued dosing and higher blood concentrations
  - Suggests “step up” regimen of initial lower dose followed by escalation to RP2D
- RP2D 180 mg QD, preceded by 90 mg QD for 1 week under way

Summary

- AP26113 exhibited robust anti-tumor activity in patients with ALK+ NSCLC
  - 61% objective response rate post-crizotinib (n=31)
  - 100% objective response rate in TKI-naïve patients (n=3)
- AP26113 is active in ALK+ brain metastases, demonstrating frequent responses of clinically meaningful duration
- No responses seen in T790M patients to date (n=12 evaluable)
- Early onset pulmonary symptoms observed in some patients. RP2D 180 mg QD, preceded by 90 mg QD for 1 week
- Phase 2 registration trial in crizotinib-resistant ALK+ NSCLC to begin shortly

Data as of 6 Sept 2012

Acknowledgements

We thank the following for their contributions to this trial:

- Patients, along with their families and caregivers, for participation in the trial
- Clinical sites, including study investigators and their team members
- AP26113 Study Team (ARIAD Pharmaceuticals, Inc.)