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TSR-011, A Potent ALK Inhibitor with Clinical Activity in Phase I/IIa Development

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Background

Anaplastic lymphoma kinase (ALK) is a tyrosine kinase that is an oncogene in a number of cancers, including non-small cell lung cancer (NSCLC), anaplastic large cell lymphoma (ALCL), neuroblastoma and inflammatory myofibroblastic tumors (IMT). Genetic aberrations at the ALK locus, including point mutations, amplifications, translocations and inversions, are observed in tumors. Inversions are seen in ~3-8% of NSCLC patients, and generate oncogenic fusion proteins, most commonly EML4-ALK. Despite availability of crizotinib, a dual cMet/ALK inhibitor, significant unmet medical needs remain. In order to address limitations of crizotinib, such as resistance mutations in ALK, TSR-011, a potent, dual ALK and TRK inhibitor is undergoing clinical evaluation.

TSR-011 has very high affinity for the wild type recombinant ALK kinase activity with an IC50 value of 0.7 nM and exhibits sustained potent inhibition of ALK-dependent tumor growth in mouse models. ALK amplification and mutations that are important drivers of NSCLC cell growth and crizotinib resistance are inhibited by TSR-011 at low nM (IC50 values of 0.1 to 2.2 nM) concentrations. In addition, TSR-011 inhibits TRK kinase activity and is capable of inhibiting cancer cell line proliferation driven by either rearranged or NGF stimulated TRKA (aka NTRK1). Approximately 3% of marker-negative NSCLC was reported to have rearrangement of TRK-A in a recent study[1]. We are conducting a Phase I/IIa dose escalation and cohort expansion study to evaluate safety, tolerability, PK, and efficacy of TSR-011; and are reporting the preliminary results from the Phase I study.

Objectives

- To evaluate the safety and tolerability of orally administered TSR-011
- To determine DLT and MTD of TSR-011
- To determine the pharmacokinetics of TSR-011
- To determine the objective response rate and PFS following treatment with TSR-011 (Phase IIa only)

Methods/Study Design

This is a sequential, open-label, non-randomized study with dose escalation in Phase I followed by expansion into selected cohorts in Phase IIa.

Key Eligibility Criteria:
Eligible patients must have metastatic or locally advanced solid tumors that have failed to respond to standard therapy, have progressed despite standard therapy or for whom standard therapy does not exist.. All patients will be ≥18 years of age, except where age of majority is 16 years in a particular country (eg, UK), with an ECOG performance status ≤ 2. Patients must also have a predicted life expectancy of ≥ 3 months. All patients enrolled in this study must have tumor tissue available. Patients were excluded for leukemia, pregnancy or breastfeeding, and uncontrolled medical conditions.

TSR-011 is a Dual ALK/TRK inhibitor[2]

Binding and inhibition of ALK, TRKA, B and C

Kinase	Recombinant Protein		Cellular[a] IC50 (nM)
	Kd (nM)	IC50 (nM)	
ALK	0.36	0.7	< 1.0
TRKA	4.7	0.5	1.8
TRKB	1.2	1.5	14.2
TRKC	7.1	2.4	26.9

[a.] Direct comparison of cellular activity was evaluated in engineered BaF3 cell line dependent on the specific kinase for proliferation

Inhibition of Proliferation (IC50: nM)			
H3122 cells *EML4-ALK*	NB-1 cells *ALK amplification*	KM12 cells *TPM3-TRKA*	TF-1 cells *NGF stimulated*
1	10	25	42

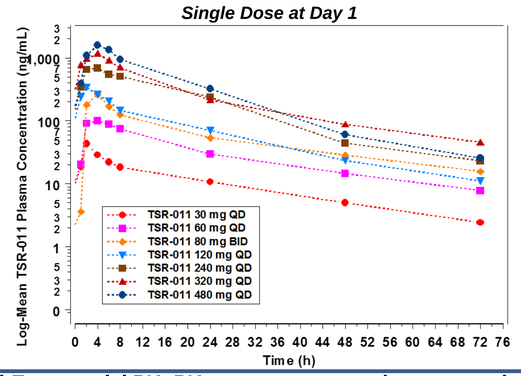
- ❖ TSR-011 displays potent inhibition of tumor growth in ALK⁺ tumor xenograft models
- ❖ TSR-011 causes regression in ALK⁺ tumor graft derived from a patient progressing on crizotinib
- ❖ TSTSR-011 is a potent inhibitor of TRKA, B and C and inhibits proliferation of naturally-occurring TRKA-rearranged colorectal cancer cell line KM12

Patient Demographics

Patient Demographics: All Treated Patients (n= 19)	
Characteristics	**No.**
Sex	
Male	6
Female	13
Age, years	
Median	68.5
Range	52-88
ECOG PS at screening	
0	3
1	15
2	1
Cancer type	
Lung (NSCLC)	8
Pancreatic	3
Papillary Thyroid	1
Ovarian	3
Carcinoid of cecum	1
Colon	1
Bladder	1
Cholangiocarcinoma	1
ALK⁺ NCLC	4
- crizotinib treated	3

Pharmacokinetic (PK) Profile

Single Dose at Day 1



- ❖ Bi-Exponential PK; PK parameters were dose proportional
- ❖ The terminal elimination $t_{1/2}$ was estimated at 12- 24 hours
- ❖ Approximately two fold accumulation was observed with once a day repeat dosing

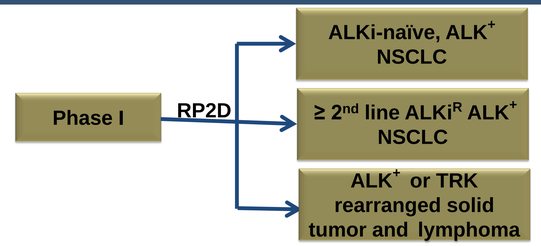
Safety/Tolerability

Summary of Dose Limiting Toxicities (DLT*) And Grade ≥2 Related Adverse Events								
	Dose (in mg; schedule is once daily unless otherwise indicated)							
Adverse Event	30 (n=1)	60 (n=1)	80 (n=3)	120 (n=1)	60 q12hr (n=3)	240 (n=4)	320 (n=3)	480 (n=4)
Anorexia	-	-	-	-	-	n=1	-	-
Peripheral Neuropathy	-	-	-	-	-	n=1	-	-
Dysaesthesia	-	-	-	-	-	n=1 (DLT)	-	-
Fatigue/Asthenia	-	-	-	n=1	-	n=1	-	-
QTc prolongation	-	-	-	-	-	n=1	n=1 (DLT)	n=2 (DLT)

**DLT is defined (per protocol) as occurring in Cycle 1, drug-related and Grade ≥3*

- ❖ TSR-011 is tolerated at doses that provide plasma concentrations above the EC50 in animal xenograft studies
- ❖ No drug related Grade 4 or Grade 5 adverse events observed

Phase 2a Plan



Anti-tumor Activity

Tumor Type	Dose (mg)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9
Papillary Thyroid	120	→	→	→	→	→	→	→	→	→
ALK+ NSCLC	480 > 240	→	→	→	→	→	→	Non-RECIST PR		
Pancreatic	480 > 240	→	→	→	→	→				
Colon	320	→	→	→						
ALK+ NSCLC	240	→	→	→						
ALK+ NSCLC	120 (60 mg, q12)	→	PR							
ALK wt NSCLC	120 (60 mg, q12)	→								
Ovarian	120 (60 mg, q12)	→								
Cholangioca	80	→								

- ❖ All three evaluable ALK⁺ NSCLC patients remain on study (as of 20 Sept 2013):
  - RECIST Partial Response (PR)
  - Non-RECIST PR**
  - Stable Disease (SD)
- ❖ Long term SD observed in papillary thyroid, colorectal and pancreatic cancers

***Investigator assessed thinning of pleural disease; Duration on therapy over 5 months after progressed on crizotinib (3.5 months)*

Conclusions

- ❖ TSR-011 is a potent dual inhibitor of ALK and TRK kinases. Phase IIa will explore the activities of TSR-011 in both ALK- or TRK-positive tumors including lung cancer.
- ❖ TSR-011 was rapidly absorbed following oral administration and displayed dose proportional PKs with an elimination $t_{½}$ of 12-24 hours
- ❖ The reversible DLTs include dysaesthesia and monitorable ECG changes including QTc prolongation
- ❖ Safe and well tolerated doses are currently being explored for selection of a RP2D
- ❖ TSR-011 exhibits anti-tumor activity in at least 2 of 3 patients with ALK mutations who have progressed previously following treatment with crizotinib:
  - ALK+ NSCLC patients have achieved a RECIST PR at 4 weeks
  - A non-RECIST PR on TSR-011 therapy 80% longer than on prior crizotinib
- ❖ Clinical benefit was observed in a papillary thyroid and pancreatic cancer patients without ALK expression
- ❖ These preliminary data demonstrate a disease control (SD + PR) at 8 weeks of 65% in the 17 evaluable patients

Reference

1. *Doebele R , Vaishnani A, Capeletti M et al, NTRK1 Gene Fusions as a Novel Oncogene Target in Lung Cancer, ASCO #8023, June 2013.*
2. *Keith Wilcoxen KM, Brake RL, Saffran D et al, Characterization of a novel series of potent, selective inhibitors of wild type and mutant/ fusion anaplastic lymphoma kinase, AACR, April, 2012; Publication in preparation*