Phase I/II trial of ensartinib+ (X-396), a novel anaplastic lymphoma kinase (ALK) inhibitor, in patients with ALK+ non-small cell lung cancer (NSCLC)

Ticiana Leal[1], Heather Wakelee[2], Karen Reckamp[3], Saiama N. Waqar[4], George R. Blumenschein[5], Corey A. Carter[6], Jeffrey R. Infante[7], Jon P. Gockerman[8], Christine Lovly[9], Gary Dukart[10], Kimberly Harrow[10], Chris Liang[10], James J. Gibbons[10], Leora Horn[9]

[1]University of Wisconsin, Madison, WI; [2]Stanford University School of Medicine, Stanford, CA; [3]City of Hope Comprehensive Cancer Center, Duarte, CA; [4]Washington University, St. Louis, MO; [5]University of Texas M.D. Anderson Cancer Center, Houston, TX; [6]Walter Reed Medical Center, Bethesda, MD; [7]Tennessee Oncology, PLLC/SCRI, Nashville, TN; [8]Novella Clinical, Morrisville, NC; [9]Vanderbilt Ingram Cancer Center, Nashville, TN; [10]Xcovery Holding Company, Palm Beach Gardens, FL

BACKGROUND

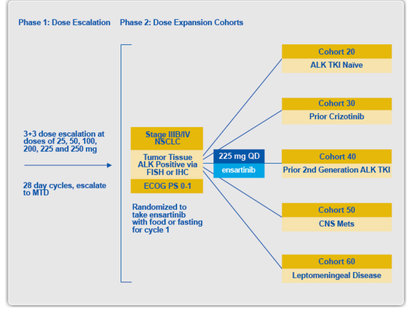
- The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is genomically altered in a variety of malignancies
- Ensartinib is a novel, potent ALK small molecule tyrosine kinase inhibitor (TKI)
- Ensartinib has additional activity against MET, ABL, Axl, EPHA2, LTK, ROS1 and SLK
- It has demonstrated significant pre-clinical anti-tumor activity in both ALK TKI-naïve and crizotinib-resistant models of ALK rearranged NSCLC[1]

METHODS

Expansion Cohort Major Inclusion Criteria:

- Advanced or recurrent NSCLC with a documented activating ALK rearrangement
- May have received prior crizotinib and/or second generation ALK TKIs or have been ALK TKI naïve
- ECOG performance status of 0 or 1
- Asymptomatic treated and untreated brain metastases permitted

Dose Schema:



RESULTS

Note: Information in the database as of 13July2016

Demographics- All Patients Dosed (n=83)	
Median Age (Range)	54 (21-80)
Gender:	
Female	42 (51%)
Male	41 (49%)
Ethnicity:	
Caucasian	65 (78%)
Asian	9 (11%)
African American	5 (6%)
Unknown/Other	4 (5%)
ECOG:	
0	(36%)
1	(64%)
Lines of Prior Treatment:	
0	13 (16%)
1	15 (18%)
2	19 (23%)
3	9 (11%)
≥4	27 (32%)

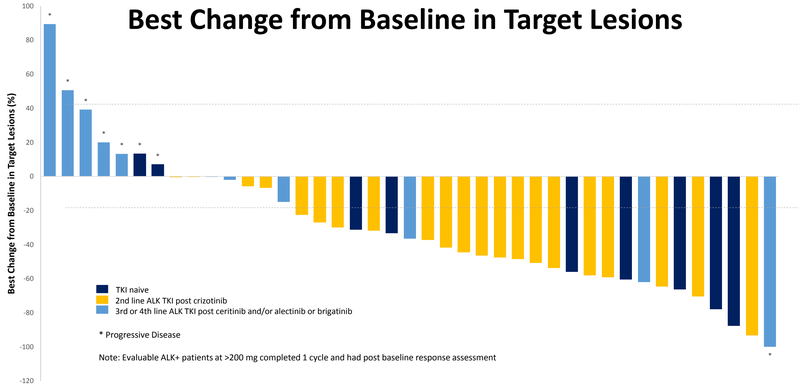
Demographics – ALK+ Evaluable* Patients at ≥ 200 mg (n= 42)	
Median Age (Range)	53 (21-80)
Gender:	
Female	23 (55%)
Male	19 (45%)
Ethnicity:	
Caucasian	33 (79%)
Asian	6 (14%)
Black/African American	1 (2%)
Unknown	2 (5%)
ECOG:	
0	17 (40%)
1	25 (60%)
Smoking Status:	
Never	27 (64%)
Former	13 (31%)
Current	2 (5%)
Lines of Prior Treatment:	
0	8 (19%)
1	8 (19%)
2	8 (19%)
3	6 (14%)
≥4	12 (29%)
Prior ALK TKI Treatment:	
ALK TKI Naive:	9 (21%)
Prior Crizotinib only	22 (52%)
Prior Crizotinib and Ceritinib	7 (17%)
Prior Crizotinib, Ceritinib, and Alectinib	3 (7%)
Prior Crizotinib, Ceritinib, and Brigatinib	1 (2%)

*Evaluable = Patient completed 1 cycle and had post baseline response assessment

Treatment-Related Toxicities

Most Common Drug- Related Adverse Events* (n=83)					
AE	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)
At Least 1 AE	26 (31%)	26 (31%)	15 (18%)	2 (2%)*	69 (83%)
Rash (all)	25 (30%)	10 (12%)	9 (11%)	-	44 (53%)
Nausea	22 (27%)	4 (5%)	1 (1%)	-	27 (33%)
Vomiting	17 (20%)	4 (5%)	1 (1%)	-	22 (27%)
Pruritus	12 (14%)	5 (6%)	3 (4%)	-	20 (24%)
Fatigue	11 (13%)	5 (6%)	2 (2%)	-	18 (22%)
Decreased Appetite	13 (16%)	-	1 (1%)	-	14 (17%)
Edema (all)	7 (8%)	6 (7%)	1 (1%)	-	14 (17%)
Dry Skin	8 (10%)	1 (1%)	-	-	9 (11%)

*Thrombotic microangiopathy considered possibly related by the investigator; however, thought to be unlikely related by the sponsor



- Most common drug-related adverse events (AEs), mostly Grade 1-2, include rash, nausea, vomiting, pruritus and fatigue
- In patients taking X-396 with food, few patients had nausea or vomiting
- Few drug-related AEs of diarrhea (7%, Grade 1), constipation (2%,Grade 1), abdominal pain (4%, Grade 1-2), myalgia/ musculoskeletal pain (5%, Grade 1), transaminase elevations (9%, Grade 1), or QT prolongation (2%, Grade 2)
- Rash is most prominent AE: for Grade 1-2, treated topically, for Grade 3, hold dose until improvement, then resume at lower dose, use steroids if necessary

Anti-Tumor Activity

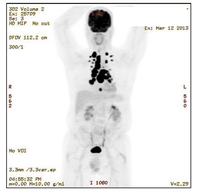
Overall Efficacy			
Prior Therapy	**PR**	**SD**	**PD**
ALK TKI Naïve	7 / 9 (78%)	-	2 / 9 (22%)
Prior Crizotinib	15 / 22 (68%)	6 / 22 (27%)	1 / 22 (5%)
Prior Second Generation ALK TKI	2 / 11 (18%)	3 / 11 (27%)	6 / 11 (55%)

For the 42 evaluable ALK+ patients at 200 mg or above

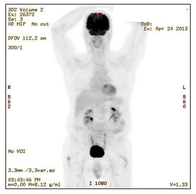
- 24 patients had a PR (57%) and 9 had SD (21%) as best response
- Duration of treatment has been from 1 to 34+ months

Activity in ALK TKI Naïve Patient

- 72 year old gentleman with metastatic ALK+ lung cancer
- No previous chemotherapy or targeted therapy
- Treated with ensartinib 100 mg daily, remained on therapy for 25 months



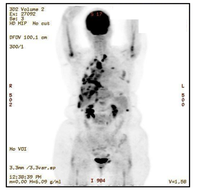
Baseline



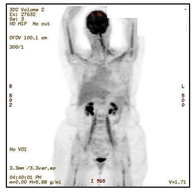
~ 6 weeks post ensartinib

Activity in Patient with Prior Crizotinib

- 56 year old female with metastatic ALK+ lung cancer
- PR to crizotinib, progression after 2 years of therapy
- Treated with ensartinib 100 mg daily, remained on therapy for 29 months



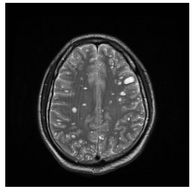
Baseline



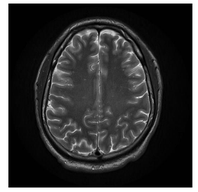
~ 6 weeks post ensartinib

Activity in Patient with CNS

- 21 yr old male with metastatic ALK+ NSCLC progressed on crizotinib and then treated with ensartinib 225 mg QD with food
- Achieved a PR after 2 cycles
- 86% reduction in the CNS target lesions with the disappearance of CNS non-target lesions



Baseline



6 months post ensartinib

CONCLUSIONS

- Ensartinib has shown promising activity in both crizotinib-naïve and crizotinib-resistant ALK+ NSCLC patients
- Responses are seen in patients with CNS disease and patients with prior 2nd generation ALK TKI
- Ensartinib is generally well tolerated with most common toxicities being rash and nausea/vomiting, the latter often resolved with food
- A phase III trial is ongoing comparing ensartinib to crizotinib in TKI naïve ALK-positive NSCLC patients. (NCT02767804)

REFERENCES

1. Lovly et al., Cancer Research 2011 71:4920

ACKNOWLEDGEMENTS

- The patients and families for participation in the study
- Participating sites
- Our colleagues at Xcovery Holding Company

+ensartinib = proposed International Non-proprietary Name (INN), formerly referred to as X-396