eXalt3: A phase 3 study of ensartinib (X-396) in anaplastic lymphoma kinase (ALK) - positive non-small cell lung cancer (NSCLC)

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BACKGROUND

- Variants of anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase, have been found in a variety of malignancies[1] including approximately 2-7% of patients with non-small cell lung cancer (NSCLC)[2]
- Crizotinib, an ALK tyrosine kinase inhibitor (TKI), was US FDA approved for ALK+ NSCLC in 2011
- The median duration of response with crizotinib is 7.7 months for patients that had previously received chemotherapy, and 10.9 months for patients without prior chemotherapy[3]
- Ensartinib, a novel, potent ALK inhibitor, exhibited favorable effectiveness in in vitro and in vivo studies, including some that are resistant or become resistant to crizotinib[4]
- The safety profile of ensartinib appears to be different than other ALK TKIs
- Ensartinib has additional activity against ROS, TRKA, TRKC, EPHA2, MET, Axl, MER, and CSF1R/FMS

Table 1: Kinase Activity

Kinases Most Potently Inhibited by ensartinib (IC_{50} in nM)*			
Kinase	**IC_{50} (nM)**	**Kinase**	**IC_{50} (nM)**
ALK	0.16	AXL	12.3
ALK (C1156Y)	0.28	c-MER	18.8
ALK (F1174L)	0.16	c-MET	9.59
ALK (F1174L)-EML4	0.53	EPHA1	6.22
ALK (F1174L)-NPM1	0.47	EPHA2	1.14
ALK (F1174S)	0.17	EPHB1	8.59
ALK (G1202R)	3.83	FMS	13.44
ALK (G1269A)	1.14	LTK	11.00
ALK (G1269S)	1.39	NEK1	6.08
ALK (L1152R)	0.58	ROS/ROS1	1.41
ALK (L1196M)	0.32	ROS1-GOPC	0.98
ALK (R1275Q)	1.06	SLK	11.00
ALK (S1206R)	0.17	TRKA	8.00
ALK (T1151-L1152insT)	0.26	TRKA-TFG (TRK-T3)	0.46
ALK (T1151M)	0.13	TRKA-TPM3	0.62
ALK-NPM1	0.68	TRKA-TPR	1.22
ALK-TFG	0.73	TRKB	3.39
ALK-TPM3	0.21	TRKC	0.46

*Isotope labeled biochemical assay

Phase 2 Trial of Ensartinib in ALK+ NSCLC:

Note: Information in the database as of 24 April 2017

- An open-label Phase1/2 trial of ensartinib in patients with advanced ALK+ NSCLC
- Recommended dose of 225mg QD was chosen to move forward

Table 2: Preliminary Phase 2 Results

Overall Efficacy*			
Prior Therapy	**PR**	**SD**	**PD**
ALK TKI Naïve	13 / 15 (87%)	0 / 15 (0%)	2 / 15 (13%)
Prior Crizotinib Only	22 / 31 (71%)	8 / 31 (26%)	1 / 31 (3%)

*Evaluable ALK+ Patients at ≥ 200 mg who completed 1 cycle and had post baseline response assessment

- Two ALK TKI naïve patients that did not respond to ensartinib were ALK+ locally but ALK- via next generation sequencing
- In patients with central nervous system (CNS) target lesions, ensartinib had a 69% response rate, including 2 complete responses and a 94% disease control rate

Table 3: Phase 2 Treatment Related AEs

Note: Information in the database as of 25January2017

Most Common Drug- Related Adverse Events (n=94)					
AE	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)
At Least 1 AE	29 (31%)	31 (33%)	18 (19%)	1 (1%)**	79 (84%)
Rash (all)	31 (33%)	12 (13%)	10 (11%)	-	53 (56%)
Nausea*	26 (28%)	7 (7%)	1 (1%)	-	34 (36%)
Pruritus	17 (18%)	5 (5%)	4 (4%)	-	26 (28%)
Vomiting*	19 (20%)	5 (5%)	1 (1%)	-	25 (27%)
Fatigue	12 (13%)	6 (6%)	2 (2%)	-	20 (21%)
Decreased Appetite	15 (16%)	1 (1%)	1 (1%)	-	17 (18%)
Edema (all)	8 (9%)	6 (6%)	1 (1%)	-	15 (16%)
Dry Skin	11(12%)	1 (1%)	-	-	12 (13%)
AST Increased	10 (11%)	-	1 (1%)	-	11 (12%)
Diarrhea	10 (11%)	-	-	-	10 (11%)

*20 (80%) of patients with vomiting and 23 (68%) of the patients with nausea took ensartinib fasting

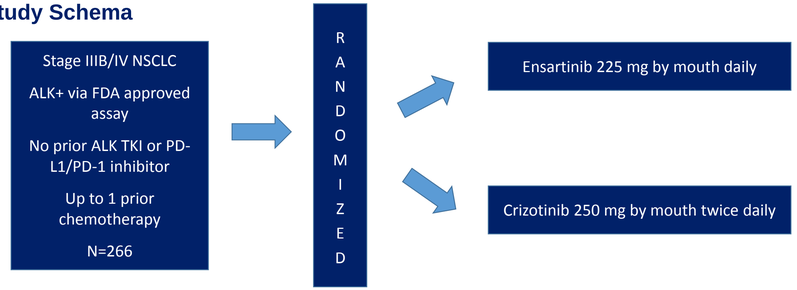
**One patient with thrombotic microangiopathy was considered possibly related by the investigator; however, thought to be unlikely related by the sponsor

Rationale for Phase 3 Study

- Ensartinib has shown promising activity in NSCLC patients that were both ALK TKI naïve and patients that received prior crizotinib, including patients with CNS disease
- Ensartinib has activity in patients with ALK resistant kinase domain mutations
- Ensartinib is generally well tolerated, with the most common AEs being rash, nausea, pruritus, vomiting and fatigue (mostly grade 1)

PHASE 3 STUDY DESIGN

Figure 1: Study Schema



- Open-label, randomized study of ensartinib and crizotinib given as single agents to adult patients with ALK+ NSCLC
- Patients will be randomized 1:1
- Up to 266 patients are expected to be enrolled
- Study drugs will be given orally daily on a 28-day schedule

STUDY OBJECTIVES

Primary:

- To evaluate the efficacy and safety of ensartinib vs crizotinib in patients with ALK+ NCSLC that have received up to 1 prior chemotherapy regimen and no prior ALK TKI

Secondary:

- To obtain additional pharmacokinetic (PK) data on ensartinib

Exploratory:

- To compare quality of life in patients receiving ensartinib vs crizotinib
- To evaluate the status of exploratory biomarkers and correlate with clinical outcome
- To obtain germline DNA samples for possible pharmacogenetics analysis in the event that outliers with response to efficacy, tolerability/safety, or exposure are identified

KEY ELIGIBILITY CRITERIA

Key Inclusion Criteria:

- Histologically confirmed diagnosis of Stage IIIB/IV NSCLC that is ALK+
- Eastern Cooperative Oncology Group Performance Status of 0-2
- Life expectancy of at least 12 weeks
- Adequate organ function
- Brain metastases allowed if asymptomatic at study baseline
- Patients must be ≥ 18 years of age
- Patients must have measurable disease per RECIST v 1.1

Key Exclusion Criteria:

- Patients that have previously received an ALK TKI or PD-1/PD-L1 therapy and patients currently receiving cancer therapy
- Use of an investigational agent within 21 days prior to first dose
- Any chemotherapy within 4 weeks
- Patients with primary CNS tumors and leptomeningeal disease
- Patients receiving strong CYP3A inhibitors or inducers or CYP3A substrates with narrow therapeutic window
- Clinically significant cardiovascular disease
- Patients who are immunosuppressed

STUDY ENDPOINTS

Key Efficacy Endpoints:

- Primary endpoint is progression-free survival (PFS) as assessed by independent radiology review based on RECIST 1.1
- Secondary efficacy endpoints include:
  - Overall survival
  - Objective response rate
  - PFS based on investigator assessment
  - Time to response
  - Duration of response
  - CNS response rate
  - Time to CNS progression

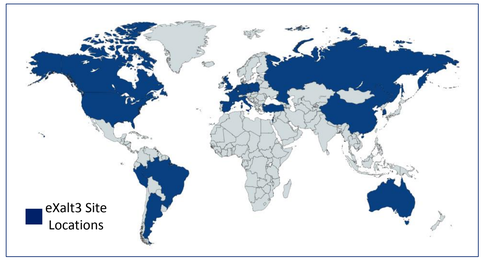
STATISTICAL DESIGN

- Open-label, randomized, phase 3 trial
- Stratification will be based on prior chemotherapy, performance status, CNS metastases at baseline and geographic region
- Primary efficacy analysis will be in the intend-to-treat population (n=266)
- A total of 190 PFS events will be required to detect 60% increase in median PFS in patient who receive ensartinib compared with crizotinib
- Sample size of 266 will allow detection of hazard ratio of 0.625 with 90% power and 2-sided alpha of 0.05
- Safety endpoints will be analyzed in all randomized patients who receive at least one dose of study medication and will be based on the actual treatment received

ENROLLMENT

- The trial was initiated in June 2016
- 42 sites have been activated as of 20APR2017
- Clinicaltrials.gov identifier: NCT02767804

Figure 2: Locations of eXalt3 Sites



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ACKNOWLEDGEMENTS

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

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POSTER PRESENTED AT European Lung Cancer Conference, May 5-8, 2017, Geneva, Switzerland