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 including approximately 2-7% of patients with non-small cell lung cancer

• 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

• Ensartinib, a novel, potent ALK inhibitor, exhibited favorable effectiveness in vitro and in vivo studies, including some that are resistant or become resistant to crizotinib

• The safety profile of ensartinib appears to be different than ALK TKIs

• Ensartinib has additional activity against RDRD, TRKA, TRKC, EphA3, ETG, MET, Axl, MER, and CSF1R/ITIMs

Table 1: Kinase Activity

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Most Potentially Inhibited by ensartinib (Km=μM)</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>0.16 AL 12.3</td>
<td></td>
</tr>
<tr>
<td>ALK+</td>
<td>0.29 AL 10.8</td>
<td></td>
</tr>
<tr>
<td>ALK/(ALK+)</td>
<td>0.16 AL 9.9</td>
<td></td>
</tr>
<tr>
<td>ALK/(EPHA1)</td>
<td>0.03 EPHA 42.2</td>
<td></td>
</tr>
<tr>
<td>ALK/(EPHA2)</td>
<td>0.07 EPHA 11.4</td>
<td></td>
</tr>
<tr>
<td>ALK/(EPHA3)</td>
<td>0.17 EPHA 8.9</td>
<td></td>
</tr>
<tr>
<td>ALK/(EPHA4)</td>
<td>3.83 EPHA 14.4</td>
<td></td>
</tr>
<tr>
<td>ALK/(EPHA5)</td>
<td>1.14 EPHA 10.6</td>
<td></td>
</tr>
<tr>
<td>ALK/0230</td>
<td>0.39 NCKX 6.9</td>
<td></td>
</tr>
<tr>
<td>ALK/0246</td>
<td>0.58 ROS/Ros 1.6</td>
<td></td>
</tr>
<tr>
<td>ALK/1950</td>
<td>0.32 ROS/Ros 0.4</td>
<td></td>
</tr>
<tr>
<td>ALK/2012</td>
<td>1.96 SLK 15.5</td>
<td></td>
</tr>
<tr>
<td>ALK/2030</td>
<td>0.17 SLK 6.0</td>
<td></td>
</tr>
<tr>
<td>ALK/1950/15220a</td>
<td>0.20 TKK-TPD (16:9:13)</td>
<td></td>
</tr>
<tr>
<td>ALK/1950/2030</td>
<td>0.06 TKK-TPD (9:5:6)</td>
<td></td>
</tr>
<tr>
<td>ALK/0417</td>
<td>0.68 TKK-TRP 3.9</td>
<td></td>
</tr>
<tr>
<td>ALK/PSG</td>
<td>0.73 TKK-TRP 3.9</td>
<td></td>
</tr>
<tr>
<td>ALK/PSG</td>
<td>0.46 TKK-TRP 3.9</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Information in the database as of 24 April 2017

Table 2: Preliminary Phase 2 Results

<table>
<thead>
<tr>
<th>Overall Efficacy*</th>
<th>Prior Therapy</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK TKI Naive</td>
<td>13 / 15 (87%)</td>
<td>6 / 15 (40%)</td>
<td>2 / 15 (13%)</td>
<td></td>
</tr>
<tr>
<td>Prior Crizotinib Only</td>
<td>22 / 33 (71%)</td>
<td>8 / 31 (26%)</td>
<td>1 / 31 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluable ALK+ Patients that did not respond to ensartinib were ALK+ locally via ALK next-generation sequencing.

**In patients with central nervous system (CNS) target lesions, ensartinib had a 63% response rate, including 2 complete responses and a 94% disease control rate.

Table 3: Phase 2 Treatment Related AEs

<table>
<thead>
<tr>
<th>Most Common Drug Related Adverse Event (n=94)</th>
<th>Grade 1 (%)</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>33 (35%)</td>
<td>18 (19%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>53 (56%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32 (34%)</td>
<td>14 (15%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>50 (53%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>26 (28%)</td>
<td>10 (11%)</td>
<td>6 (6%)</td>
<td>0</td>
<td>42 (45%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (18%)</td>
<td>9 (10%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>30 (32%)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>16 (17%)</td>
<td>7 (8%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>24 (26%)</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>15 (16%)</td>
<td>6 (7%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>22 (24%)</td>
</tr>
<tr>
<td>Edema</td>
<td>8 (9%)</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (7%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (6%)</td>
<td>4 (4%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>9 (10%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (6%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4 (4%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>7 (8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0</td>
<td>10 (11%)</td>
</tr>
</tbody>
</table>

*Note: Information in the database as of 25 January 2017

Phase 2 Trial of Ensartinib in ALK+ NSCLC: Note: Information in the database as of 24 April 2017

• An open-label Phase I/II trial of ensartinib in patients with advanced ALK+ NSCLC

• Recommended dose of 250 mg QD was chosen to move forward

Stage IIIB/IV NSCLC

- ALK+ via FDA approved assay
- No prior ALK TKI or PD-L1/PD-1 inhibitor
- Up to 1 prior chemotherapy

RANDOMIZED

Ensartinib 225 mg by mouth daily

• 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 200 patients are expected to be enrolled

• Study drugs will be given orally daily on a 28-day schedule

PHASE 3 STUDY DESIGN

Figure 1: Study Schematic

Prior Therapy

• ALK TKI Naive

• Prior Crizotinib Only

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 leptomenigeal disease

• Ongoing local systemic therapy (eg, radiation)

• To obtain germline DNA samples for possible pharmacogenomic analysis in an event that results in enrolling patients with known or suspected drug interactions

• Patients who are immunosuppressed

Key Efficacy Endpoints

• Primary endpoint is progression-free survival (PFS) as assessed by independent radiology review using 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

Study Endpoints

• Phosphorylated survival for PFS with 95% confidence interval

• Key Efficacy Endergouts

• Rationale for Phase 3 Study

• Ensartinib has shown promising activity in NSCLC patients that were both ALK+ 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 (most grade 1)

• The study was initiated in June 2016

• 42 sites have been activated as of 22 April 2017

• KlinikaCure, HC Ltd, Tallinn

ENROLLMENT

• 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 intent-to-treat population (n=265)

• A total of 190 PFS events will be required to detect 35% increase in median PFS in patients who receive ensartinib compared with crizotinib

• Sample size of 265 will allow detection of hazard ratios of 0.625 with 50% 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

ACKNOWLEDGMENTS

• The patients and families for their participation in the study

• Participating sites

• Our colleagues at KlinikaCure Holding Company

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References

1. Lawrence et al., American Journal of Pathology 2006; 167: 1341 – 1350
3. Mok et al., Journal of Clinical Oncology 2014; 32: 1015a
4. Lorni et al., Cancer Research 2011; 71: 4529

Figure 2: Locations of eXalt3 Sites

Locations

• Note: Information in the database as of 25 January 2017

• Most Common Drug Related Adverse Event (n=94)

• Fatigue

• Diarrhea

• Nausea

• Vomiting

• Hand-foot syndrome

• Hirsutism

• Edema

• Pruritus

• Arthralgia

• Anemia

• Alopecia

• Rash