A Phase I/II Trial of X-396, A Novel ALK Inhibitor, in Patients with Advanced Solid Tumors


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INTRODUCTION

• The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of malignancies
• X-396 is a more potent inhibitor of ALK and less potent inhibitor of MET compared to crizotinib
• X-396 has shown compelling antitumor activity in vivo with a favorable pharmacokinetic and toxicity profile and with a broader therapeutic window than crizotinib
• Pre-clinical data suggest X-396 has the potential to overcome acquired resistance to crizotinib and has CNS penetration
• Based on these promising data, a phase I/II clinical trial is ongoing in the expansion cohort

OBJECTIVES

Primary
• To evaluate the safety/tolerability of X-396
• To determine the maximum tolerated dose (MTD) of X-396 as a single agent

Secondary
• To characterize the preliminary pharmacokinetics (PK) of X-396
• To explore the preliminary biological activity and clinical tumor response after treatment with X-396

EXPLORATORY

• To observe the correlation between PK and clinical endpoints
• To evaluate the status of exploratory biomarkers and correlate with clinical outcome
• To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified

METHODS

Major Inclusion Criteria
• Patients with—Advanced solid tumors (Dose Escalation Phase)—ALK rearranged lung cancer determined by FISH (Expansion Phase)

RESULTS

Based on information as of 20 Oct 2014

Tumor Response to X-396 in Evaluable ALK Positive Lung Cancer Patients

Duration of Treatment (months)

Treatment-Related Toxocities
• Most common drug-related AEs, mostly Grade 1-2, include rash, nausea, vomiting, fatigue, edema and pruritus (see table)
• 2 DLTs observed: fluid overload (200 mg) and rash (250 mg)
• The MTD was not officially reached
• Doses up to 225 mg were generally well-tolerated

Most Common Drug-Related Adverse Events (n=41)

<table>
<thead>
<tr>
<th>AE All Grades (%)</th>
<th>Grade 3/4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>18 (44%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (27%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (22%)</td>
</tr>
<tr>
<td>Edema</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Dry Skin</td>
<td>4 (10%)</td>
</tr>
</tbody>
</table>

Antitumor Activity
• For the 17 evaluable ALK positive lung cancer patients*
—10 patients had PR (59%) and 2 had SD (12%) as best response
—Responses observed in 3 of 4 crizotinib-naive patients and 7 of 13 patients that were previously treated with crizotinib
—Of the 5 patients with PD, 2 were at lower doses (50, 100 mg), 1 (200 mg) had failed prior crizotinib and chemotherapy, and 1 (250 mg) had failed prior crizotinib and ceritinib
—Patient with prior crizotinib and ceritinib had a complete response in retroperitoneal lymph node but progression of bone/CNS metastases
—Responses were observed in patients with CNS metastases
—Duration of response has been from 1.8+ to 16.4+ months

*Evaluated = patient completed 1 cycle and had post baseline response assessment

Demographic Data (n=41)

<table>
<thead>
<tr>
<th></th>
<th>Median Age (Range)</th>
<th>Gender:</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>57</td>
<td></td>
<td>19 (48%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnicity:</td>
</tr>
<tr>
<td>36</td>
<td></td>
<td>Caucasian</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>African American</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECOG PS:</td>
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<tr>
<td>16</td>
<td></td>
<td>16 (39%)</td>
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<tr>
<td></td>
<td></td>
<td>Tumor Type:</td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>33 (80%)</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>18 (40%)</td>
</tr>
</tbody>
</table>

Pharmacokinetics
• Blood drawn on Cycle 1 Days 1 and 22 pre-dose, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours after dosing. Blood samples were also collected before dosing on Days 8 and 15
• t1/2 is ~23 hours at 200 mg
• Trough level observed at 200 mg (~300 nM) is sufficient to completely inhibit most crizotinib resistant mutations, including F1174L, in vitro
• Drug absorption is decreased ~20% in the presence of food

CONCLUSIONS

• X-396 is a novel ALK inhibitor with activity in patients with ALK positive lung cancer
• Responses have been observed in patients with crizotinib naïve NSCLC and in patients with acquired resistance to crizotinib
• Responses have been observed in patients with brain metastases
• Most common drug-related adverse events include rash, nausea, vomiting, fatigue, edema and pruritus but Grade 3/4 are rare
• X-396 is generally well-tolerated at doses up to 225 mg
• Enrollment is ongoing in the expansion cohort

REFERENCES

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

ACKNOWLEDGEMENTS

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