Rash and Efficacy in Anaplastic Lymphoma Kinase Positive (ALK+) Non-Small Cell Lung Cancer Patients Treated with Ensartinib

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BACKGROUND

• Ensartinib is a potent ALK small-molecule tyrosine kinase inhibitor (TKI).
• Ensartinib has additional activity against MET, ABL, AXL, EphA2, LTK, ROS1, and cKIT.
• Ensartinib has demonstrated significant preclinical antitumor activity in both ALK TKI-naïve and ALK TKI-resistant models of ALK rearranged non-small cell lung cancer (NSCLC).
• Ensartinib was generally well tolerated, with rash being the most common related adverse event (AE).

SKIN TOXICITY AND TKIs

• Skin toxicity is a class-specific side effect of TKIs, specifically of epidermal growth factor receptor (EGFR) TKIs.
• Although skin rash is considered an AE, it’s presence and severity of skin rash are associated with improved clinical efficacy in patients receiving EGFR TKIs.
• EGFR TKI skin toxicity is typically manifested as papulopustular rash with nail fusuring. It is related to the initiation of wild-type EGFR in the skin, which is crucial for the normal development and physiology of the epidermis.
• ALK TKIs normally have less skin toxicity than EGFR TKIs.

• Ensartinib-related rash has been described as different than EGFR TKI rash in its pathogenesis, presentation, and evolution. It is possibly immune mediated and presents as a "benign type" of rash in appearance (without the discomfort) that tends to wane while the patient is receiving treatment.

• This posthoc analysis of a phase 1/2 dose escalation and expansion study of ensartinib (eXalt2) was conducted to determine the relationship between rash and clinical benefit in patients treated with ensartinib 225 mg/d and to define its optimal management.

METHODS

Figure 1. eXalt2 Study Design

RESULTS

Table 1. Demographics by Rash Group (eXalt2 Study)

<table>
<thead>
<tr>
<th>Rash Group</th>
<th>N</th>
<th>Race</th>
<th>Sex</th>
<th>ECOG PS</th>
<th>ALK status</th>
<th>ALK TKIs</th>
<th>Prior ALK TKI treatment, n (%)</th>
<th>No</th>
<th>Yes</th>
<th>Prior chemotherapy treatment, n (%)</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rash</td>
<td>36</td>
<td>16 (64)</td>
<td>22 (61)</td>
<td>2 (5.6)</td>
<td>23 (63)</td>
<td>15 (42)</td>
<td>23 (63)</td>
<td>2 (5.6)</td>
<td>1 (2.8)</td>
<td>30 (83)</td>
<td>6 (17)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>38</td>
<td>12 (32)</td>
<td>26 (68)</td>
<td>2 (5.3)</td>
<td>15 (39)</td>
<td>23 (61)</td>
<td>26 (68)</td>
<td>2 (5.3)</td>
<td>1 (2.6)</td>
<td>31 (81)</td>
<td>9 (24)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Pooled Efficacy in 1L, 2L, and 3L Patients Treated with Ensartinib 225 mg QD

<table>
<thead>
<tr>
<th>ORR, n (%)</th>
<th>mPFS (95% CI), months</th>
<th>P1.14-32</th>
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<tr>
<td>No Rash</td>
<td>0.72 (0.38-1.39)</td>
<td>0.06</td>
</tr>
<tr>
<td>Rash</td>
<td>0.49 (0.25-0.94)</td>
<td>0.03</td>
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CONCLUSIONS

• Ensartinib has shown promising activity in patients with ALK+ NSCLC, including patients previously treated with ALK TKIs.
• Ensartinib is well tolerated, with mild to moderate rash being the most common drug-related AE at 225 mg QD (recommended phase 2 dose).
• The ensartinib-related rash is clinically distinct from the typical EGFR TKI-related rash.
• The rash was manageable with topical treatments; it was transient and required discontinuation in only 2% of patients.
• Despite dose reduction in 10% of the patients, rash was potentially associated with better clinical benefit from ensartinib in a mixed population of ALK+ patients in first or greater lines of treatment.

ACKNOWLEDGMENTS

The authors thank the patients and their families for participation in the study. Medical writing and editorial assistance was provided by Schweitzer, PharmD, PCC, of Chirag Medical Communications, Hamilton, NJ, USA, and funded by Xcovery.

REFERENCES