Phase Ib Study of the Combination of Balixafortide (a CXCR4 inhibitor) and Eribulin in HER2-Negative Metastatic Breast Cancer Patients

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BACKGROUND AND PURPOSE

Advanced breast is the most common cancer affecting women. Despite advances in targeted therapies and cytotoxic agents, overall survival in metastatic breast cancer (MBC) remains poor.

Balixafortide (PDL103) is a cyclic synthetic peptide and a potent, selective inhibitor of the chemokine receptor CXCR4. CXCR4 is overexpressed in more than 20 human tumor types and its expression is correlated with aggressive metastatic phenotypes and poor prognosis.

CXCR4 inhibitors interfere with several aspects of tumor biology including tumor survival and proliferation, angiogenesis, metastatic spread, and the immunosuppressive tumor microenvironment. CXCR4 inhibition may interfere with the tumor protective microenvironment and enhance the effects of chemotherapeutics and targeted cancer agents.

ATM phase I study investigated the combination of balixafortide with eribulin (Halaven®), an approved non-aurora inhibitor of mitotubule dynamics.

METHODS

Patient Population

A HeNocologically confirmed MBC (AJCC stage IV); Hormonal status: any estrogen (ER) or progesterone (PR); HER2 negative (immunohistochemistry (IHC) 0 or FISH/HER2CEP17 ≤ 2.0) (Table 1)

A Evidence of any CXCR4 expression on tumor cells by IHC; archival tissue (tumor or metastatic site) or a new biopsy of a metastatic site

A Patients (pts) in the 24-week chemotherapy in the metastatic setting and meeting the criteria for eribulin treatment

A A Neutrophil count normal (ANC) >1000/x (Table 1)

Study Design

A Pts received eribulin (1.4 mg/m², x2 on days 1 and 8) with balixafortide (5.5 mg/m², x2 on days 1,5, and 8-10 of 21-cycle phase (Figure 1)

Figure 1: Treatment scheme

RESULTS

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th># of patients (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>59 (37-72)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>0 (10/49), 1 (50/29)</td>
</tr>
<tr>
<td>Biomarker status</td>
<td>1 (20/1), 2 (20/1)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>1 (20/1), 2 (20/1)</td>
</tr>
<tr>
<td>Most common metastatic sites</td>
<td>Bone (15/20), Lung (5/20), lymph nodes (5/20)</td>
</tr>
</tbody>
</table>

Safety and Tolerability

Twenty-one pts were enrolled in this expanded cohort. One pt discontinued therapy after the first treatment due to rapid disease progression. Data from all 21 pts were included in the study analysis (Table 2). The most common AEs related to balixafortide were hematologic-iron deficiency anemia (22/23 pts), neutropenia (22/23 pts), and thrombocytopenia with anemia-thrombocytopenia and invasive infection rates.

Two pts (9%) had grade 3 neutropenia.

5/22 SAEs were considered related to the combination of balixafortide and eribulin: 1 pt reported G3 mucosal inflammation and G4 neutropenia, 1 pt was hospitalized because of mild fever of unknown origin (event resolved in one day), and 1 pt was found to have G4 neutropenia and was diagnosed with pneumonia that responded poorly to antibiotics. This pt received the full treatment schedule for cycle 2. Five days after the last treatment, the pt was hospitalized because of severe respiratory distress and later died of pneumonia.

All SAEs reported in this trial were related to either eribulin alone or the combination of balixafortide and eribulin. No SAEs were related to balixafortide alone.

Table 2: Adverse events reported by 3 or more pts regardless of drug relationship

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eribulin</td>
<td>15 (56%)</td>
<td>3 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Balixafortide</td>
<td>12 (39%)</td>
<td>4 (15%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

RESULTS

Table 3: Tumor response

<table>
<thead>
<tr>
<th>Parameter</th>
<th># of patients (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>PR</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>CR</td>
<td>11 (43%)</td>
</tr>
<tr>
<td>Complete response rate</td>
<td>11 (43%)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Balixafortide (1.4 mg/m²) added to eribulin (1.4 mg/m²) generated a very promising ORR of 38% and OS of 35%, in a population of heavily pretreated MBC patients.

Future studies will evaluate the combination of balixafortide and eribulin in the metastatic setting in patients with advanced breast cancer.

A Further confirmation studies are being considered.

REFERENCES


Andrews et al., Blood 116, 2179, 2011, ASH annual meeting

Figure 2: Best lesion response in expanded dose cohort (5.5 mg/m² balixafortide, 1.4 mg/m² eribulin)

Figure 3: Treatment duration in expanded dose cohort (5.5 mg/m² balixafortide, 1.4 mg/m² eribulin), cycle ≥3 weeks

Figure 4: Time to progression (TTP) in expanded cohort

Table 1: Patient characteristics

Table 2: Adverse events reported by 3 or more pts regardless of drug relationship

Table 3: Tumor response

Table 4: Eribulin 1.4 mg/m² + Balixafortide 5.5 mg/m² (n=21)