A Phase 1b Trial of Cirmtuzumab and Paclitaxel in Locally Advanced /Unresectable or Metastatic Her2 Negative Breast Cancer

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Table 1: Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>30 to 59 years</td>
</tr>
<tr>
<td>Safety-evaluable patients</td>
<td>8</td>
</tr>
<tr>
<td>Patients with locally advanced, unresectable or metastatic breast cancer</td>
<td>7</td>
</tr>
<tr>
<td>Prior lines of therapy allowed</td>
<td>Any number</td>
</tr>
<tr>
<td>Study treatment</td>
<td>Fixed dose 600mg cirmtuzumab given days 1 and 8 of each subsequent 28 day cycle. Paclitaxel was given weekly at a dose of 80mg/m²</td>
</tr>
</tbody>
</table>

METHODS

The primary aim of this trial was to determine the safety of cirmtuzumab and weekly paclitaxel in patients with advanced Her2 negative breast cancer based upon dose limiting toxicities (DLTs) in the first cycle of treatment. Secondary endpoints were clinical activity, pharmacokinetics and correlative biomarkers on tumor specimens. Eligible patients were those with locally advanced, unresectable or metastatic Her2 negative breast cancer who had not previously received paclitaxel in the metastatic setting, had not developed metastatic disease within 6 months of the last dose of adjuvant paclitaxel and had ECOG performance status of 0-2, and had adequate laboratory parameters. Any number of prior lines of therapy were allowed. Study treatment included fixed dose 600mg cirmtuzumab given days 1 and 8 of each subsequent 28 day cycle. Paclitaxel was given weekly at a dose of 80mg/m². Patients were evaluated in dose cohorts of 5 for 25 evaluable patients.

RESULTS

• Preliminary pharmacokinetic results are consistent with sustained tumor activity of cirmtuzumab in combination with paclitaxel.
• Responses to therapy have been observed (4/7 partial responses).
• Adverse event assessment indicates no new safety signals of the combination compared to that of paclitaxel alone.

CONCLUSIONS

• Preliminary results indicate that the combination of fixed dose cirmtuzumab and paclitaxel is safe and well tolerated in patients with locally advanced or metastatic breast cancer.
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• Responses to therapy have been observed (4/7 partial responses).
• Preliminary pharmacokinetic results are consistent with sustained potentially therapeutic levels of cirmtuzumab.
• One patient was maintained on cirmtuzumab monotherapy with stable disease for 30 weeks after discontinuation of paclitaxel.

Figure 1: % Tumor Volume Reduction by Week of Therapy

Figure 2: Best Tumor Response by Patient and % Tumor Volume Reduction

Table 2: Most Common Adverse Events (all paclitaxel related)

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Neutropenic count</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypothalamus-pituitary axis disruptions</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
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</tbody>
</table>

Table 3: ≥ Grade 3 Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
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<td>0</td>
</tr>
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<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2 & 3: Safety Data

Table 3: ≥ Grade 3 Adverse Events

Figure 3: BROR2 Response Scans at Start of Therapy and at Cycle 6

Figure 4: Pretreatment ROR1 IHC

Figure 5: Pharmacokinetic Data

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<table>
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<td>Mean concentration of cirmtuzumab at 8 weeks in plasma of all patients analyzed (n=8) was 58 mcg/ml (range 42-70, median 59 mcg/ml)</td>
<td></td>
</tr>
</tbody>
</table>

Tables 2 & 3: Safety Data

Figure 5: Cirmtuzumab concentration in plasma of representative patients.

Cirmtuzumab Concentration in Plasma of Representative Patients

BROR1-09: mAb Conc. (mcg/ml)

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