A Phase II/II Study of CR011-vcMMAE, an Antibody-Drug Conjugate, in Patients with Locally Advanced or Metastatic Breast Cancer

Nancy Peacock1, Mansoor Saleh2, Johanna Bendell1, April A.N. Rose3, Zhifeng Dong3, Peter M. Siegel3, Elizabeth Crowley4, Ronit Simantov4, Linda Vahdat5

1Sarah Cannon Research Institute, Nashville, TN; 2Georgia Cancer Specialists, Atlanta, GA; 3Goodman Cancer Centre, McGill University, Montreal, Quebec, Canada; 4CuraGen Corporation, Branford, CT; 5Weill Cornell Medical College, New York, NY

BACKGROUND

- GPNMB (osteoclastin) is a novel glycoprotein expressed in breast cancer, melanoma, and other tumors.
- Pretreatment breast cancer models have demonstrated that GPNMB promotes the migration, invasion, and metastasis of breast cancer. GPNMB is expressed in 25-40% of human breast cancers and is an independent prognostic factor for recurrence of disease.
- GPNMB expression is observed in approximately one third of patients with triple negative (ER-, PR-, HER-2/neu-) disease, and is associated with prognosis in that subset.

CR011-vCMMAE

- A fully-human monoclonal antibody (CR011) was raised against the extracellular domain of GPNMB.
- CR011 is conjugated to the dolastatin-like tubulin inhibitor monomethylauristatin-E (MMAE) via a valine-citrulline-cysteine-linkable

STUDY DESIGN

- Eligibility: Locally advanced or metastatic breast cancer.
- Primary endpoint: Progression-free rate at 12 weeks.
- Secondary endpoints: Tumor shrinkage, including partial responses.

DOSE ESCALATION

- Phase I: Dose Escalation
  - Starting dose: 1.34 mg/kg IV q3w (one dose level below the maximum tolerated dose).
- Phase II: Simon Two-Stage Design
  - Primary endpoint: Progression-free rate at 12 weeks.

DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Age</th>
<th>Median 56 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>33 - 90 yrs</td>
</tr>
</tbody>
</table>

TOXICITY

- Treatment-Emergent Adverse Events, Regardless of Attribution

<table>
<thead>
<tr>
<th>Event</th>
<th>Phase I</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>Nausea</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33%</td>
<td>17%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation</td>
<td>33%</td>
<td>13%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
<td>40%</td>
</tr>
<tr>
<td>Pain</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Cough</td>
<td>33%</td>
<td>17%</td>
</tr>
</tbody>
</table>
| Tumor shrinkage, including partial responses, were noted to 25%

GPNMB EXPRESSION

- In a Phase II study in patients with metastatic melanoma, CR011-vCMMAE 1.88 mg/kg IV q3w has been shown to be active, leading to tumor shrinkage and PFS of 4.4 months.
- We are conducting a Phase III study to evaluate the safety and efficacy of CR011-vCMMAE in patients with heavily pre-treated advanced breast cancer.

METHODS

- Immunohistochemistry for GPNMB was performed on patient biopsy samples from this clinical study and 3 separately obtained tissue microarrays using a polyclonal goat anti-GPNMB antibody (R&D Systems) and a biodconjugated donkey anti-goat secondary antibody (Jackson Immunoresearch Laboratories). Sections were developed with DAB and counterstained with hematoxylin.
- The tissue microarrays consisted of 517 undamaged cores representing 34 normal, 35 DCIS, 161 breast tumor and 47 lymph node metastasis samples independent of this clinical study. Patient samples were represented by multiple (2-4) cores on the array. Cores with ≥ 25% of the tissue expressing GPNMB were considered positive.

DOSE ESCALATION

- Dose Escalation
  - The first two patients enrolled at 1.34 mg/kg had dose limiting worsening of peripheral sensory neuropathy. Both patients had baseline neuropathy.
  - Subsequently, patients with baseline grade 2 or higher neuropathy were excluded.
  - Dose Escalation was re-started at 1.00 mg/kg q3w. 1.88 mg/kg q3w was tolerated and selected for expansion in Phase II.
  - Phase II dosing is ongoing.

Dose (mg/kg/dose) / n / DLT

- Phase I (completed)
  - 1.00 / 3 / 0
  - 1.34 / 6 / 0

- Phase II (ongoing)
  - 1.88 / 4 / -

PT DISPOSITION

- Preliminary data from this ongoing study are presented.
- Data cutoff: April 17, 2009
- Median Duration of Follow-up: 6 weeks

CONCLUSIONS

- CR011-vCMMAE 1.88 mg/kg IV q3w is well-tolerated in patients with advanced breast cancer.
- Peripheral sensory neuropathy was dose-limiting in 2 patients with neuropathy at baseline.
- Tumor shrinkage, including partial responses, palliation of bone pain, and stable disease have been observed in heavily-pretreated patients, including those with triple-negative disease.
- Toxicity in patients with breast cancer is similar to that observed in patients with melanoma. Rash is the most common adverse event reported in patients treated with CR011-vCMMAE.
- GPNMB, the target of CR011-vCMMAE, is specifically expressed in breast cancer tissue as observed in a microarray comprising over 500 core samples.
- Immunohistochemical staining of patient tumor samples for GPNMB expression is ongoing.
- The Phase II portion of the study is currently ongoing and has enrolled 12 patients to date.