A Phase 1b Study of the Anti-Cancer Stem Cell Agent Demczumab (DEM, anti-DLL4) and Gemcitabine (GEM) with or without Nab-Paclitaxel in Patients with Pancreatic Cancer

**Background**

There is accumulating evidence that the cell types within tumors are heterogeneous and that heterogeneity is a subset of the property that contributes to growth and progression in more differentiated progeny. These cells, called Cancer Stem Cells (CSCs) or tumor initiating cells, drive tumor growth and progression. Disease recurrence and treatment failure can therefore be attributed not only to a lack of effective chemotherapeutics but also to the presence of cancer stem cells that are resistant to chemotherapeutic agents. Preclinical evidence suggests that targeting CSCs would provide a more durable clinical benefit than conventional chemotherapy. This study assessed the safety and antitumor activity of Demczumab (DEM) in xenograft models of pancreatic cancer, and the potential of DEM in combination with chemotherapy. The study aimed to determine the maximum tolerated dose (MTD) of DEM and the dose levels at which the combination of DEM with chemotherapy could be administered.

**Patient Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall (n=56)</th>
<th>GEM (n=28)</th>
<th>DEM/DEM + Paclitaxel (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>65</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>31/25</td>
<td>17/11</td>
<td>14/14</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>Yes</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>Yes</td>
<td>68%</td>
<td>68%</td>
</tr>
<tr>
<td>Locally advanced/locoregional/metastatic</td>
<td>Yes</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Effect of Notch Pathway Gene Expression in Whole Blood (By DEM Dose Cohort)**

<table>
<thead>
<tr>
<th>DEM/DEM + Paclitaxel</th>
<th>GEM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLL4 expression level</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Notch1 expression level</td>
<td>0.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Nonclinical Xenograft Data**

- **Activity of Anti-DLL4 in Combination with GEM vs. GEM + Nab-Paclitaxel in a Patient Derived Pancreatic Xenograft (OMP-PN-315)**
- **Related AEs >15% Pts (n=56)**
- **RECIST Best Overall Response (n=56)**
- **Progression-Free Survival**
- **Survival**

**Methods**

This is an open-label, Phase 1b dose escalation study of DEM plus chemotherapy with or without Nab-Paclitaxel in patients with pancreatic cancer. The study enrolled 56 patients with advanced or metastatic disease who had exhausted all prior standard of care with at least one line for gemcitabine-based chemotherapy including gemcitabine plus Nab-Paclitaxel. The study was designed to assess the safety, tolerability, and antitumor activity of DEM and the combination of DEM with nab-paclitaxel. The primary endpoints were the determination of the maximum tolerated dose (MTD) of DEM and the dose levels at which the combination of DEM with chemotherapy could be administered. The study also aimed to determine the overall survival and progression-free survival rates of patients treated with DEM plus chemotherapy.

**Summary**

- This is an ongoing Phase 1b dose escalation study of demczumab, a cancer stem cell targeting monoclonal antibody (targeting the DLL4 ligand in the Notch pathway) plus gemcitabine with or without nab-paclitaxel in 17 pancreatic cancer patients. Demczumab and gemcitabine with or without nab-paclitaxel were generally well tolerated with fatigue, nausea and vomiting being the most common drug related toxicities.
- Demczumab + gemcitabine + nab-paclitaxel (n=13) was generally well tolerated with fatigue, nausea and vomiting being the most common drug-related toxicities. The hypotension was managed with carvedilol. Grade 2-3 pulmonary hypertension occurred in 2 patients and Grade 2 heart failure occurred in 1 patient receiving demczumab for greater than 10 days, but none of the patients treated with trucuncated demczumab developed pulmonary hypertension or heart failure.
- Patients are being followed with cardiac monitoring using B-type natriuretic peptide (BNP) and echocardiography. BNP appears to be a early indicator of cardiotoxicity. In addition, a cardioprotective medication (i.e., an angiotension-converting enzyme inhibitor or candesartan) was administered to patients with rising BNP and this strategy appears to prevent cardiotoxicity.
- Trucuncated demczumab therapy (i.e. 70 days of therapy) appears to prevent the onset of late cardiotoxicity, as none of the patients treated in this manner developed heart failure or pulmonary hypertension.
- Fourteen of the 32 (48%) evaluable patients who received DEM+gemcitabine had a RECIST partial response and 11 had stable disease resulting in a clinical benefit rate of 85%. The Kaplan-Meier estimated median progression-free survival was 9.0 months (4.4 – not reached) and the Kaplan-Meier estimated overall survival was 15.5 months (6.5 – 24.2) for the patients who received DEM+gemcitabine.
- A randomized Phase 2 trial (YOSEMT) in 41 late pancreatic cancer is ongoing. The trucutaneous dose of demczumab for the Phase 2 study is 3.5 mg/kg once every 2 weeks.

**Reversible Cardiopulmonary Toxicity** (Any Grade) (N=56)

- **% Change in RECIST Target Lesion Size**
- **Exploratory DLL4 Expression Biomarker Analyses**

**Overall Survival Exploratory Biomarker Analyses**

**Truncated Patients (n = 15)**

**Figure:**

- **Days Post Treatment**
- **Tumor Volume, mm3**
  - Control mAb
  - Gemcitabine
  - Gem+Nab-Pac
  - Anti-DLL4+Gem/Nab-Pac
  - Chemo+/-mAb
  - Chemo only

**Graph:**

- **Days Post Treatment vs. Tumor Volume**
  - Control mAb
  - Gemcitabine
  - Gem+Nab-Pac
  - Anti-DLL4+Gem/Nab-Pac
  - Chemo+/-mAb
  - Chemo only