**ALK1 Pathway Background**

- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is selectively expressed on endothelial cells.  
- When activated by ligands bone morphogenetic protein 9 (BMP9) and 10 (BMP10), ALK1 signals via phosphorylation of SMAD1/5/8 to activate genes involved in vascular morphogenesis.  
- ALK1/BMP9/10 signaling promotes vascular stabilization and maturation, which are downstream from the proliferative stages of angiogenesis that are driven primarily by vascular endothelial growth factor (VEGF).

**Dalantercept Background**

- Dalantercept is an ALK1 receptor fusion protein that binds BMP9 and 10 and acts as a ligand trap. (Figure 1)
- Dalantercept inhibits the maturation of vascular cells and impairs basic fibroblast growth factor (bFGF) and VEGF-A stimulated angiogenesis both in vivo and in vitro.  
- In a variety of preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.  
- In a completed Phase 1 study in 37 patients with advanced solid tumors, dalantercept monotherapy demonstrated antitumor activity. The safety profile was generally non-overlapping with VEGFR TKIs, as the most common toxicities included fatigue, peripheral edema, and anemia.  

*Figure 1: ALK1/BMP9/BMP10 Signaling Pathway*

- **Part 1 Results: Tumor Response Data (RECIST 1.1) and Progression Free Survival**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>0.6 mg/kg (N = 6)</th>
<th>0.9 mg/kg (N = 9)</th>
<th>1.2 mg/kg (N = 13)</th>
<th>Overall (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response, n (%)</td>
<td>2 (33.3)</td>
<td>3 (33.3)</td>
<td>2 (15.4)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Stable Disease, n (%)</td>
<td>2 (33.3)</td>
<td>6 (66.7)</td>
<td>9 (69.2)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Progressive Disease, n (%)</td>
<td>2 (33.3)</td>
<td>0</td>
<td>2 (15.4)</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>DCR ≥ 8 months (N = 6), n (%)</td>
<td>3 (50.0)</td>
<td>6 (66.7)</td>
<td>7 (53.8)</td>
<td>16 (57.1)</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.5</td>
<td>NR*</td>
<td>6.9</td>
<td>8.3 (4.1-NR)</td>
</tr>
</tbody>
</table>

*NR: Not reached
Notes: 1 patient not evaluable for response based on ineligibility; mPFS analysis includes all patients who received study drugs (n=29)

**Part 2 Methods**

- Randomized, multi-center, double-blind placebo controlled study in patients with advanced renal cell carcinoma.
- Approximately 130 patients will be enrolled.
- Patients receive dalantercept at 0.9 mg/kg or placebo once every 3 weeks by SC injection and axitinib at a starting dose of 5 mg PO BID on a 21 day cycle.
- Axitinib titration is permitted after 4 weeks on treatment.
- **Primary endpoint:** To determine whether treatment with dalantercept plus axitinib prolongs progression free survival (PFS) compared to placebo plus axitinib in patients with advanced RCC.
- **Secondary endpoints:** To evaluate safety/tolerability, overall survival, objective response rate, duration of response, disease control rate, and pharmacodynamic biomarkers in serum and tumor samples.
- Response to treatment is determined every 6 weeks, according to RECIST v1.1.

**Key Part 2 Eligibility Criteria**

- Advanced clear cell RCC
- Progression of disease following one VEGF receptor TKI for RCC; patients may have also had 1 mTOR inhibitor and/or any prior approved or investigational immune therapies
- No prior axitinib or therapies targeting the ALK1 pathway
- Stable, treated CNS disease permitted
- ECOG performance status 0 – 1

**Part 2 Study Schema**

- Advanced RCC
  - 1 prior VEGF TKI, may have also had 1 mTOR inhibitor and/or any prior immune therapy
- **Randomization**
  - Axitinib 5 mg BID + Dalantercept (0.9 mg/kg) (n = 65)
  - Axitinib 5 mg BID + Placebo (n = 65)

  *Note: dose titration of axitinib to 7mg and 10mg BID permitted after 4 weeks on study*

For details on results from Part 1 of the DART Study, please see poster 4567

NCT01727336

**Summary**

- Dalantercept inhibits signaling through the ALK1 receptor by binding BMP9 and BMP10, and disrupts the formation of mature blood vessels through a mechanism that is distinct from the VEGF pathway.
- Based on the results from Part 1, in this pretreated advanced RCC population, the combination of dalantercept and axitinib is well tolerated with a generally non-overlapping safety profile and is associated with encouraging activity (25% RR, preliminary overall mPFS 8.3 months).
- Part 2 of the DART Study will evaluate whether dalantercept plus axitinib prolongs PFS compared to placebo plus axitinib in patients with advanced RCC.
- Enrollment into Part 1 is complete and Part 2 is actively accruing patients nationwide at approximately 60 sites.
- DART study details including participating sites at can be found at https://clinicaltrials.gov/ct2/show/NCT01727336.

**References**