**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 SMAD 1/5/8 to activate genes involved in vascular morphogenesis.
- ALK1/BMP9/BMP10 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.
- 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 preclinical studies, dalantercept demonstrated anti-angiogenic activity in a xenograft model of renal cell carcinoma.
- In a completed Phase 1 study in 37 patients with advanced solid tumors, dalantercept monotherapy demonstrated anti-tumor activity and the safety profile was generally non-overlapping with VEGF TrkIs.

**Summary of Results from Part 1**

- Part 1 of this Phase 2 study enrolled 29 patients and assessed the safety and tolerability of dalantercept plus axitinib in advanced RCC patients who had received 1 prior VEGF TKI and ≤3 lines of prior therapy and determined the recommended phase 2 dose level for part 2.
- Daldantercept (0.6, 0.9, 1.2 mg/kg) subcutaneously QW and axitinib 5 mg PO BID for 21 days cycle.
- Most common adverse events (≥31%) included fatigue, diarrhea, dysphonia, peripheral edema, decreased appetite, epistaxis, hypertension, nausea, hand-foot syndrome, arthritis, increased creatinine, and cough.
- There were no grade 4/5 drug-related adverse events.
- Based on the preliminary activity and safety data, the dalantercept 0.9 mg/kg dose level was selected as the RP2D in part 2 of this study.
- Dalantercept axitinib 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, response duration, disease control rate, and pharmacodynamic biomarkers in serum and tumor samples.
- Response to treatment is determined every 6 weeks, according to RECIST v1.1.

**Dalantercept 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 in 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, response duration, 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 DART Part 2 Eligibility Criteria**

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

**References**