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The DART Study Part 2: A Phase 2 Randomized, Double-Blind Study of Dalantercept plus Axitinib Compared to Placebo plus Axitinib in Patients with Advanced Renal Cell Carcinoma

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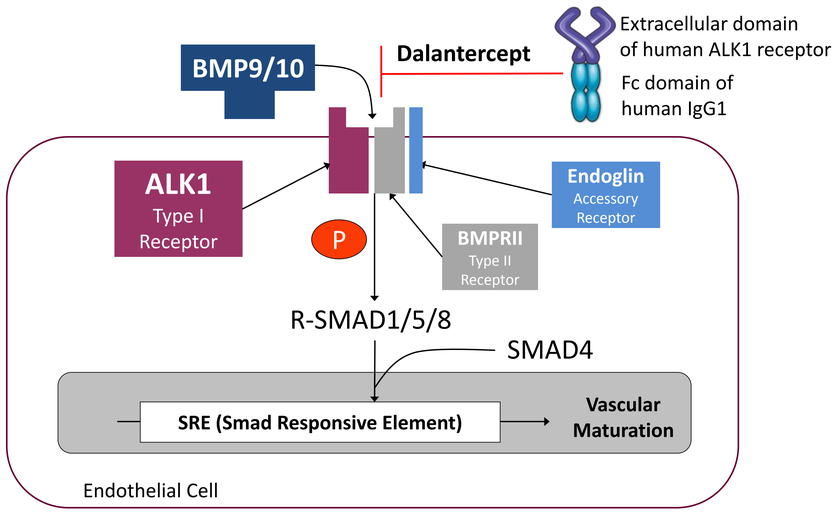
ALK1 Pathway Background

- Activin receptor-like kinase 1 (ALK1) is a type I receptor of the TGFβ superfamily that is selectively expressed on endothelial cells.[1]
- 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.[2] (Figure 1)
- 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).[3]

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*.[4]
- In a variety of preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.[4,5,6]
- In a completed Phase 1 study in 37 patients with advanced solid tumors, dalantercept monotherapy demonstrated anti-tumor activity. The safety profile was generally non-overlapping with VEGFR TKIs, as the most common toxicities included fatigue, peripheral edema, and anemia.[7]

Figure 1: ALK1/BMP9/BMP10 Signaling Pathway



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 VEGFR TKI and ≤ 3 lines of prior therapy and determined the recommended phase 2 dose level for part 2 (see poster 4567).
- Cohorts of 3 – 6 patients each received dalantercept (0.6, 0.9, or 1.2 mg/kg) subcutaneously Q3W and axitinib 5 mg PO BID for a 21 day cycle.
- In this pretreated advanced RCC population, the combination of dalantercept and axitinib was well tolerated.
- Most common adverse events (≥31%) included fatigue, diarrhea, dysphonia, peripheral edema, nausea, decreased appetite, epistaxis, hypertension, arthralgia, increased creatinine, cough, and hand-foot syndrome.
- There were no grade 4/5 drug related adverse events.
- Based upon 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.
- The combination of dalantercept and axitinib was associated with clinically meaningful activity including partial responses (25%) and prolonged disease control (57.1%) in patients with 1 to 3 prior lines of therapy including all patients treated with prior checkpoint inhibitors (N=3; 2 with PR and 1 with SD).
- The preliminary median PFS of 8.3 months in all dose levels combined compares favorably to the historical mPFS with axitinib of 4.8 months in a VEGFR TKI pre-treated advanced RCC population.[8]

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

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

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

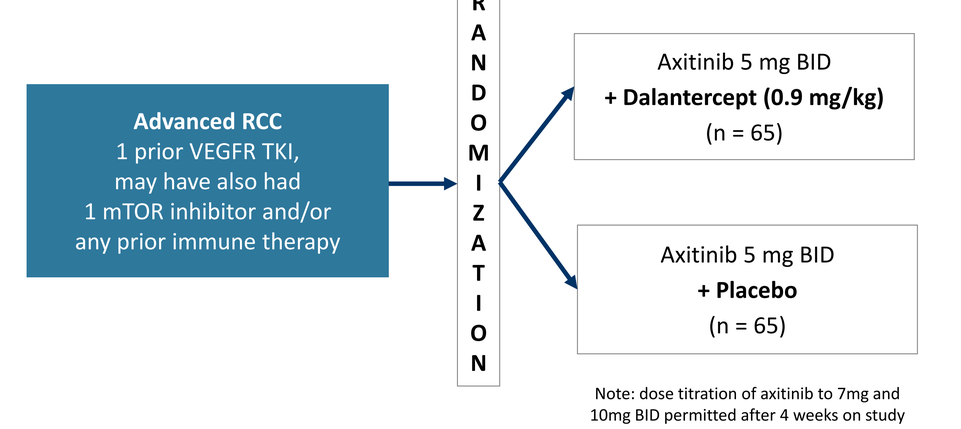
Part 2 Methods

- 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



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.

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