

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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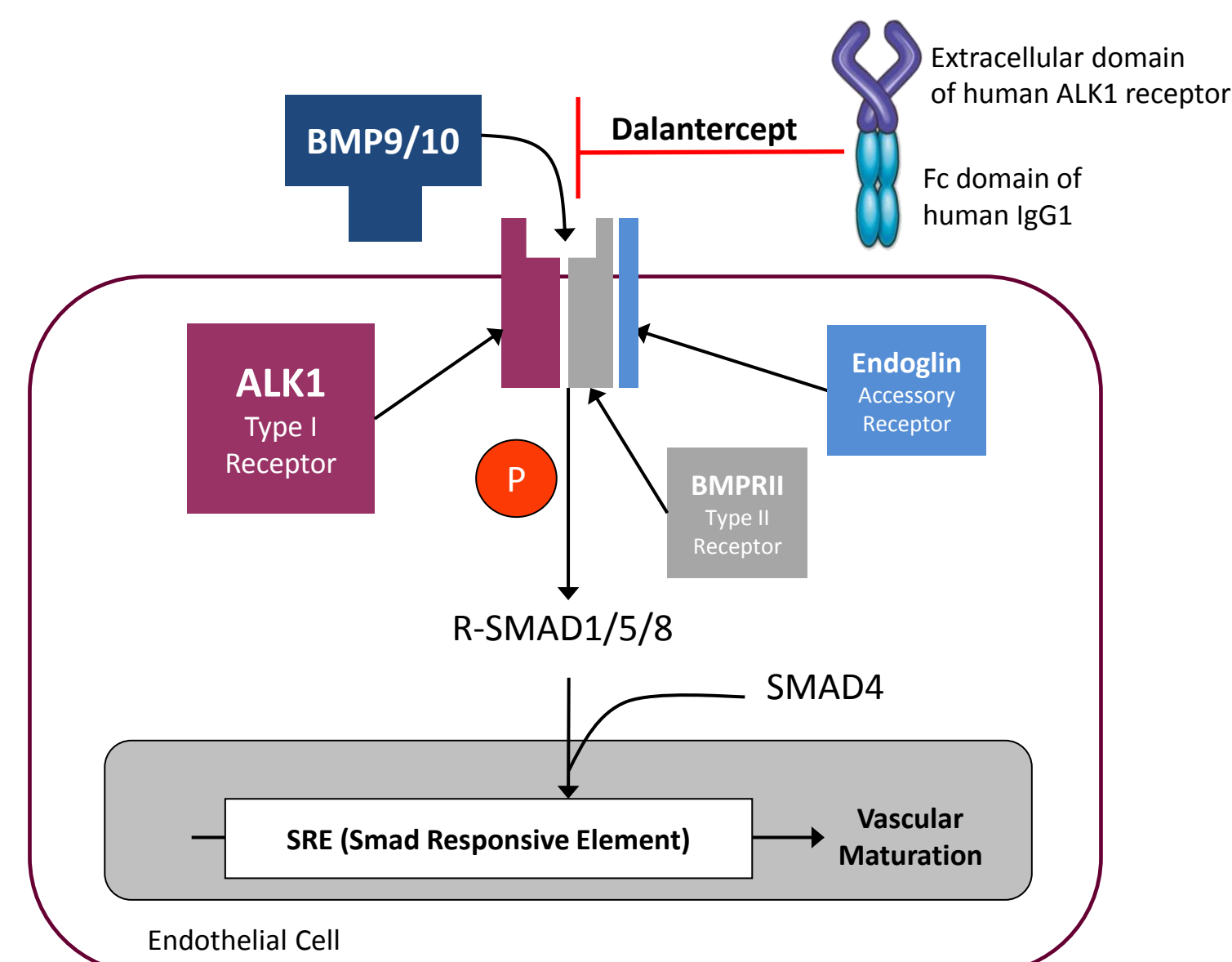
ALK1 Pathway Background

- 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 and the safety profile was generally non-overlapping with VEGFR TKIs.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
- 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, decreased appetite, epistaxis, hypertension, nausea, hand-foot syndrome, arthralgia, increased creatinine, and cough.
- 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.
- Dalantercept plus axitinib achieved a median PFS of 8.3 months and 12 month PFS and OS rates of 39% and 75% which compare favorably to the historical data with axitinib in TKI pre-treated RCC patients (mPFS of 4.8 months, 12 month PFS and OS rates of ~25% and ~58% respectively).^{8,9}

Part 1 Results: Objective Response Rate Analyses RECIST v1.1

| 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) |

Note: 1 patient not evaluable based upon ineligibility

Part 1 Results: Progression Free Survival (PFS) and Overall Survival (OS) As of 03 June 2015

| Endpoint | 0.9 mg/kg (N = 9) | Overall (N = 29) |
|--|-------------------|------------------|
| Median PFS (months) | NR* | 8.3 (4.1-NR) |
| 12 Month Progression Free Survival Rate* (%) | 50% | 39% |
| 12 Month Overall Survival Rate* (%) | 89% | 75% |

Notes: Analysis includes all patients who received study drugs (N=29), NR= not reached, *Assessed by Kaplan-Meier Method.

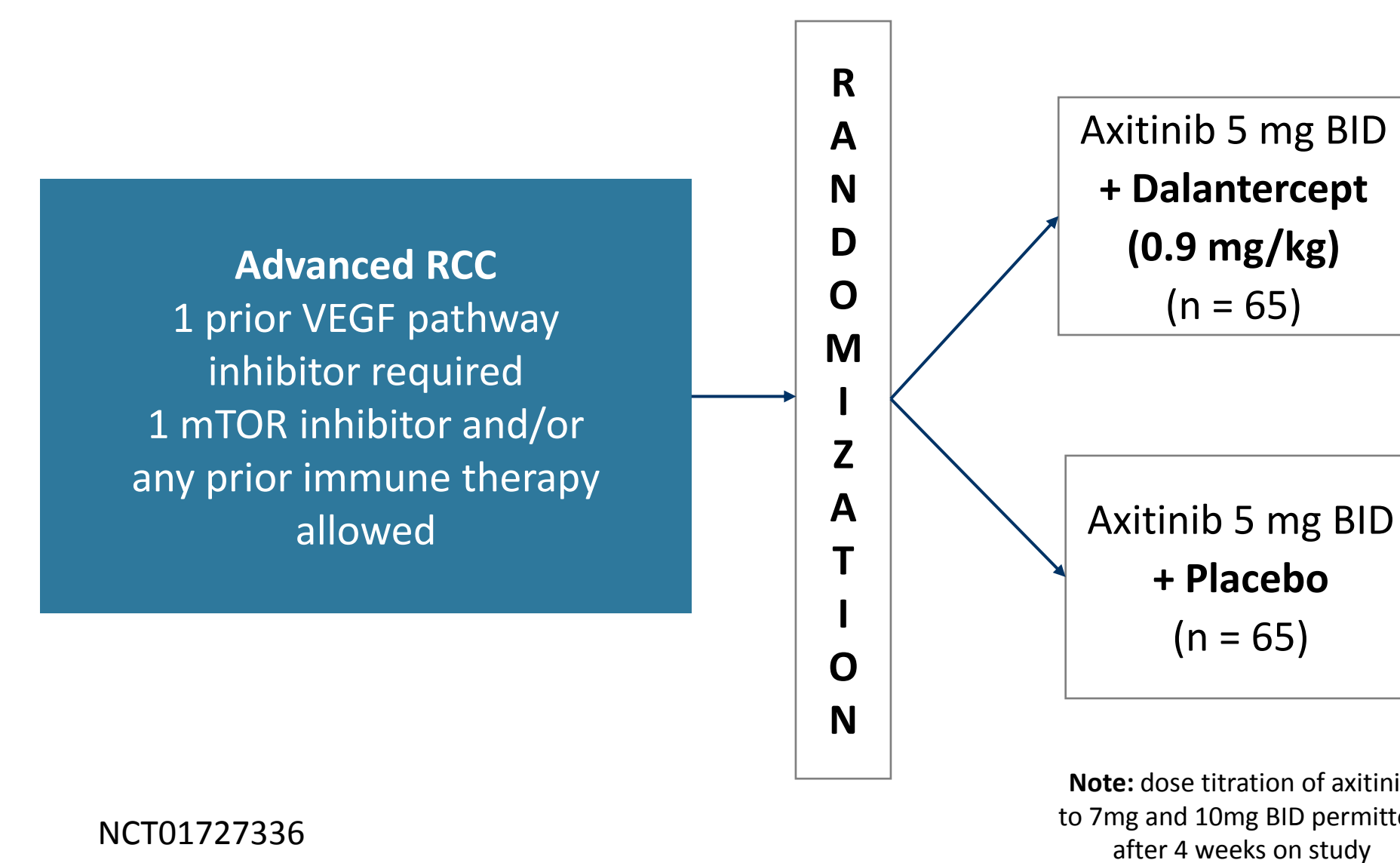
DART Part 2 Methods

- 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.

DART Part 2 Study Schema

DART Part 2

Randomized, Double-Blind, Placebo-Controlled (N = 130)
Primary Endpoint: Progression-free survival
Secondary Endpoints: ORR, DCR (PR + SD), OS, Safety, PK and exploratory PD biomarkers



NCT01727336

Key DART Part 2 Eligibility Criteria

- Advanced clear cell RCC
- Progression of disease following one VEGF pathway inhibitor 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

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 profiles and is associated with encouraging activity (25% ORR, overall median PFS 8.3 months, 12 month OS rate 75%).
- 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

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