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The DART Study: Part 1 results of dose escalation and expansion cohorts of dalantercept plus axitinib in advanced renal cell carcinoma

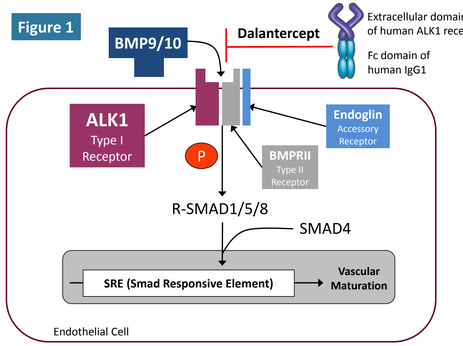
Martin H. Voss[1], Elizabeth R. Plimack[2], Brian I. Rini[3], Michael B. Atkins[4], Robert Alter[5], Rupal S. Bhatt[6], J. Thaddeus Beck[7], Kristen M. Pappas[8], Dawn Wilson[8], Xiaosha Zhang[8], Matthew L. Sherman[8], Shuchi S. Pandya[8]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Fox Chase Cancer Center, Philadelphia, PA; [3]Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH; [4]Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC; [5]John Theurer Cancer Center, Hackensack, NJ; [6]Beth Israel Deaconess Medical Center, Boston, MA; [7]Highlands Oncology Group, Fayetteville, AR; [8]Acceleron Pharma, Cambridge, MA

Dalantercept 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 signaling promotes vascular stabilization and maturation which are downstream events from the proliferative stages of angiogenesis that are driven primarily by vascular endothelial growth factor (VEGF).[3]
- Dalantercept is an ALK1 receptor-Fc fusion protein that binds with high affinity to BMP9 and BMP10 and thereby 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*.[4]
- In preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity.[4,5,6]

Figure 1



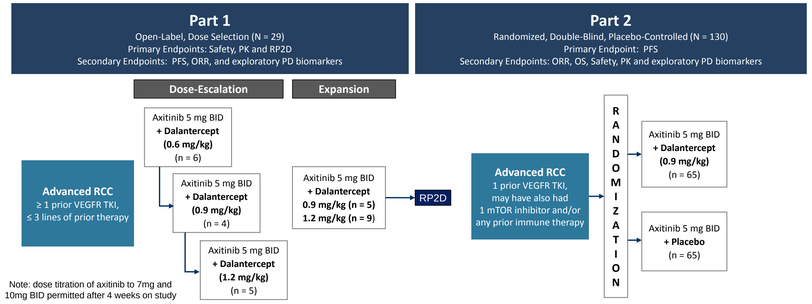
Study Rationale

- Advanced clear cell renal cell cancer (RCC) is highly dependent upon tumor angiogenesis and is responsive to agents that target the VEGF pathway.
- The efficacy of anti-VEGF therapies is limited in duration.
- Based on *in vivo* data, dalantercept may enhance and prolong the activity of agents that target the VEGF pathway in advanced RCC.
- Dual angiogenic blockade with dalantercept and a VEGFR TKI in murine RCC models (786-O and A498) resulted in greater tumor growth inhibition compared to either agent alone.[6]
- In a phase 1 study, dalantercept monotherapy demonstrated anti-tumor activity in patients with advanced solid tumors.[7]
- Axitinib is a VEGFR TKI currently approved for 2nd line mRCC.[8]
- In the AXIS phase 3 study, in the large subgroup of sunitinib-refractory patients treated with axitinib, the objective response rate was 11.3%, the median progression-free survival was 4.8 months and the median overall survival was 15.2 months.[9,10,11]

Study Design and Schema

- Part 1 of this phase 2 study assessed the safety and tolerability of dalantercept plus axitinib in advanced RCC patients who had ≥ 1 prior VEGFR TKI and ≤ 3 lines of prior therapy and to determine the recommended phase 2 dose level (RP2D) for part 2. (Figure 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.
- Imaging occurred every two cycles (6 week intervals) and was assessed by RECIST v1.1.
- A safety review team (SRT) reviewed safety data for all patients who received study drugs prior to each dose escalation and during the expansion.
- Additional patients were enrolled in expansion cohorts at 0.9 and 1.2 mg/kg to further characterize safety and pharmacokinetics.
- Tumor response and progression free survival (PFS) assessments included all patients who met eligibility, received study drugs, and had at least 1 post-tx scan.

Figure 2



Key Eligibility Criteria (Part 1)

- Advanced, predominantly clear cell RCC
- Measureable disease according to RECIST v1.1
- ≥ 1 prior VEGFR TKI and ≤ 3 lines of prior therapy
- No prior axitinib or therapies targeting the ALK1 pathway
- Stable, treated CNS disease permitted
- ECOG performance status grade 0 – 1

Safety Results (Part 1)

- As of January 16, 2015, a total of 29 patients were enrolled.
- 15 patients were enrolled in Part 1 dose escalation cohorts (6 at 0.6 mg/kg, 4 at 0.9 mg/kg, and 5 at 1.2 mg/kg).
- PK analyses suggested co-administration of dalantercept and axitinib does not affect the individual drug exposure of either agent.
- There were no grade 4/5 drug related adverse events.
- Telangiectasias, an on-target effect of ALK1 pathway inhibition, were documented in 5 patients (17.2%) at the 0.9 and 1.2 mg/kg dose levels.
- There were no serious bleeding events. Low grade epistaxis and gingival bleeding were reported in 34.5% and 13.8% of patients respectively.
- The SRT expanded the 1.2 mg/kg dose level to include 9 additional patients. More edema related events including peripheral edema, asymptomatic pericardial effusion, and pleural effusion were observed and the SRT expanded the 0.9 mg/kg dose level to include 5 additional patients.
- The 0.9 mg/kg dose level was overall well-tolerated with fewer edema related events and was selected as the RP2D for Part 2.

Patient Demographics

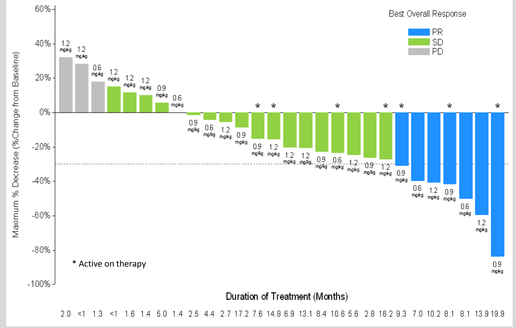
Demographic		0.6 mg/kg (N = 6)	0.9 mg/kg (N = 9)	1.2 mg/kg (N =14)	Overall n (%) (N = 29)
Median age (years)		64.5	56.0	60.5	59.0
Gender	Male	5	7	11	23 (79.3)
	Female	1	2	3	6 (20.7)
ECOG	0	3	5	7	15 (51.7)
	1	3	4	7	14 (48.3)
Prior nephrectomy	Yes	6	8	14	28 (96.6)
	No	0	1	0	1 (3.4)
Sites of disease	1	1	0	3	4 (13.8)
	≥ 2	5	9	11	25 (86.2)
MSKCC risk category	Favorable	1	6	7	14 (48.3)
	Intermediate	5	3	7	15 (51.7)
	Unfavorable	0	0	0	0
Number of prior therapies	1	2	2	7	11 (37.9)
	≥ 2	4	7	7	18 (62.1)
Prior systemic therapies	Sunitinib	4	6	7	17 (58.6)
	Pazopanib	1	5	8	14 (48.3)
	mTOR inhibitors	3	5	4	12 (41.4)
	Nivolumab	1	1	1	3 (10.3)
	Sorafenib	1	0	1	2 (6.9)
	Bevacizumab	1	1	0	2 (6.9)
	Interleukin-2	1	0	1	2 (6.9)
	Ipilimumab	0	1	0	1 (3.4)

Treatment Emergent Adverse Events Regardless of Attribution (≥ 7 subjects)

Preferred Term	0.6 mg/kg (N = 6)		0.9 mg/kg (N = 9)		1.2 mg/kg (N = 14)		Overall (N = 29)	
	All grades n (%)	Grade 3* n (%)	All grades n (%)	Grade 3* n (%)	All grades n (%)	Grade 3* n (%)	All grades n (%)	Grade 3* n (%)
Fatigue	5 (83.3)	1 (16.7)	6 (66.7)	0	10 (71.4)	0	21 (72.4)	1 (3.4)
Diarrhea	4 (66.7)	1 (16.7)	6 (66.7)	1 (11.1)	9 (64.3)	1 (7.1)	19 (65.5)	3 (10.3)
Dysphonia	4 (66.7)	0	3 (33.3)	0	6 (42.9)	0	13 (44.8)	0
Peripheral edema	0	0	4 (44.4)	0	8 (57.1)	0	12 (41.4)	0
Nausea	2 (33.3)	0	5 (55.6)	0	4 (28.6)	0	11 (37.9)	0
Decreased appetite	3 (50.0)	0	2 (22.2)	0	5 (35.7)	0	10 (34.5)	0
Epistaxis	1 (16.7)	0	2 (22.2)	0	7 (50.0)	0	10 (34.5)	0
Hypertension	2 (33.3)	0	4 (44.4)	0	4 (28.6)	1 (7.1)	10 (34.5)	1 (3.4)
Arthralgia	1 (16.7)	0	4 (44.4)	0	4 (28.6)	0	9 (31.0)	0
Incr. creatinine	0	0	1 (11.1)	0	8 (57.1)	0	9 (31.0)	0
Cough	1 (16.7)	0	4 (44.4)	0	4 (28.6)	0	9 (31.0)	0
Hand-foot-syndrome	1 (16.7)	0	4 (44.4)	0	4 (28.6)	0	9 (31.0)	0
Headache	1 (16.7)	0	4 (44.4)	0	3 (21.4)	0	8 (27.6)	0
Abdominal pain	1 (16.7)	0	2 (22.2)	0	4 (28.6)	1 (7.1)	7 (24.1)	1 (3.4)
Constipation	2 (33.3)	0	3 (33.3)	0	2 (14.3)	0	7 (24.1)	0
Pericardial effusion	0	0	3 (33.3)	0	4 (28.6)	0	7 (24.1)	0
Weight decreased	2 (33.3)	0	0	0	5 (35.7)	1 (7.1)	7 (24.1)	1 (3.4)

* Note: There were no grade 4/5 drug related adverse events

Best Overall Response and Duration on Therapy



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

Progression Free Survival (PFS)

Endpoint	0.6 mg/kg (N = 6)	0.9 mg/kg (N = 9)	1.2 mg/kg (N = 14)	Overall (N = 29)
Median PFS, months (95% CI)	5.5	NR	6.9	8.3 (4.1 – NR)

NR: not reached

Conclusions and Discussion

- In this pretreated advanced RCC population, the combination of dalantercept and axitinib is well tolerated with a generally non-overlapping safety profile.
- Based upon the edema events at the 1.2 mg/kg dose level and preliminary activity and safety data at the 0.9 mg/kg dose level, dalantercept 0.9 mg/kg was selected as the RP2D in part 2 of this study.
- The combination of dalantercept and axitinib is 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.
- The preliminary median PFS of 8.3 months in all dose levels combined is encouraging.
- The randomized Part 2 of the DART study is actively enrolling patients who have received one VEGFR TKI and may have received 1 prior mTOR inhibitor and/or any number of prior immune therapies.
- DART study details are at https://clinicaltrials.gov/ct2/show/NCT01727336.

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