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The DART Study Part 1: Updated Results of Dalantercept plus Axitinib in Advanced Renal Cell Carcinoma

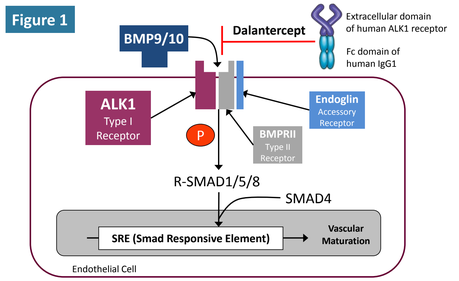
Martin H. Voss[1], Elizabeth R. Plimack[2], Brian I. Rini[3], Rupal S. Bhatt[4] Robert Alter[5], J. Thaddeus Beck[6], Kristen M. Pappas[7], Dawn Wilson[7], Xiaosha Zhang[7], J. Sun[7], Chad E. Glasser[7], Matthew L. Sherman[7], Shuchi S. Pandya[7] , Michael B. Atkins[8]

[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]Beth Israel Deaconess Medical Center, Boston, MA; [5]John Theurer Cancer Center, Hackensack, NJ; [6]Highlands Oncology Group, Fayetteville, AR; [7]Acceleron Pharma, Cambridge, MA; [8]Georgetown University Lombardi Comprehensive Cancer Center, Washington, DC

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/BMP9/10 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 is an ALK1 receptor fusion protein that binds to BMP9 and BMP10 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 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.
- Based on *in vivo* data, dalantercept may enhance and prolong the activity of agents that target the VEGF pathway in advanced RCC.
- 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 advanced RCC.[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 (mPFS) was 4.8 months and the median overall survival was 15.2 months.[9,10,11]

Key Eligibility Criteria

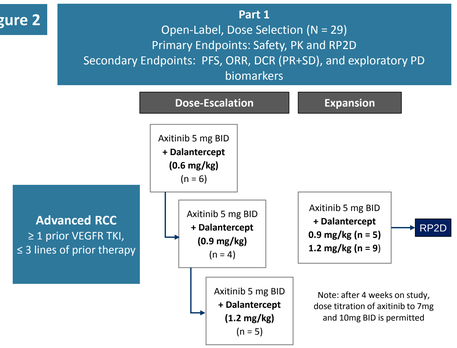
- Advanced clear cell RCC
- ≥ 1 prior VEGFR TKI and ≤ 3 lines of prior therapy
- No prior axitinib or therapies targeting the ALK1 pathway
- Stable, treated CNS disease permitted
- ECOG performance status 0 – 1

Study Design

- 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 of the combination.
- Tumor response was assessed for all patients who met eligibility, received study drugs, and had at least 1 post-treatment scan.
- PFS was assessed for all patients who received study drugs.

Study Schema

Figure 2



Safety Results

- As of June 03, 2015, a total of 29 patients were enrolled, including 18 patients (62.1%) who had 2 or more prior lines of therapy.
- There were no dose limiting toxicities in the dose escalation cohorts, no grade 4/5 drug related adverse events, and no serious bleeding events.
- Three patients at the 1.2 mg/kg dalantercept dose level discontinued therapy due to edema related adverse events.
- Telangiectasias, an on-target effect of ALK1 pathway inhibition, were documented in 6 patients (20.7%) at the 0.9 and 1.2 mg/kg dose levels.
- Axitinib was titrated to 7 mg or 8 mg in 5 patients (17.2%) and 3 patients maintained this dose > 3 months with a best response of stable disease.
- 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.

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)
Number of disease sites	1	1	0	2	3 (10.3)
	≥ 2	5	9	12	26 (89.7)
MSKCC risk category	Favorable	1	6	7	14 (48.3)
	Intermediate	5	3	7	15 (51.7)
	Poor	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 patients)

Preferred Term	0.6 mg/kg (N = 6)		0.9 mg/kg (N = 9)		1.2 mg/kg (N = 14)		Overall (N = 29)	
	Grade 1-3 n (%)	Grade 3* n (%)	Grade 1-3 n (%)	Grade 3* n (%)	Grade 1-3 n (%)	Grade 3* n (%)	Grade 1-3 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)	2 (33.3)	5 (55.6)	1 (11.1)	9 (64.3)	1 (7.1)	18 (62.1)	4 (13.8)
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
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)
Nausea	2 (33.3)	0	5 (55.6)	0	3 (21.4)	0	10 (34.5)	0
Hand-foot syndrome	1 (16.7)	0	4 (44.4)	0	5 (35.7)	0	10 (34.5)	0
Arthralgia	1 (16.7)	0	4 (44.4)	0	4 (28.6)	0	9 (31.0)	0
Creatinine increase	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
Hypothyroidism	1 (16.7)	0	3 (33.3)	0	4 (28.6)	0	8 (27.6)	0
Weight decreased	2 (33.3)	0	1 (11.1)	0	5 (35.7)	1 (7.1)	8 (27.6)	1 (3.4)
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
Headache	1 (16.7)	0	3 (33.3)	0	3 (21.4)	0	7 (24.1)	0
Pericardial effusion	0	0	3 (33.3)	0	4 (28.6)	0	7 (24.1)	0

* No grade 4/5 related adverse events

Response Rates (RECIST v1.1)

As of 03 June 2015

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)

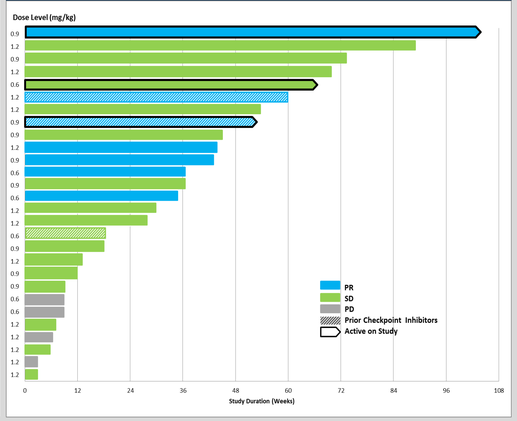
Note: 1 pt. not evaluable for response based upon ineligibility

Best Overall Response (RECIST v1.1)

As of 03 June 2015

Treatment Duration

As of 03 June 2015



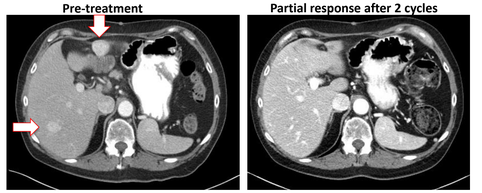
Survival Analyses

As of 03 June 2015

Endpoint	0.9 mg/kg (N = 9)	Overall (N = 29)
Median Progression Free Survival (months)	NR	8.3
12 month progression free survival rate* (%)	50%	39%
12 month overall survival rate* (%)	89%	75%

Analysis includes all patients who received study drugs (n=29)
NR= not reached, *Assessed by Kaplan Meier Method

Durable Partial Response in 4th Line Patient



- Patient progressed on 3 prior therapies: sunitinib (9 months), temsirolimus (1.5 months), and bevacizumab (< 2 weeks). Patient remains on dalantercept 0.9 mg/kg and axitinib 5 mg BID for over 2 years with a partial response

Conclusions and Discussion

- In this pretreated advanced RCC population, the combination of dalantercept and axitinib was well tolerated with a generally non-overlapping safety profile.
- 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.
- 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) .[10,11]
- In the ongoing Part 2 of the DART study, patients are randomized 1:1 to dalantercept plus axitinib vs. placebo plus axitinib .
- DART study details are at https://clinicaltrials.gov/ct2/show/NCT01727336.

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