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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

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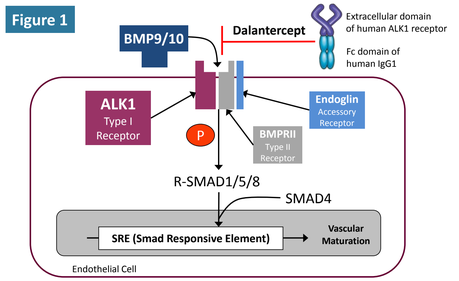
Dalantercept Background

- 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

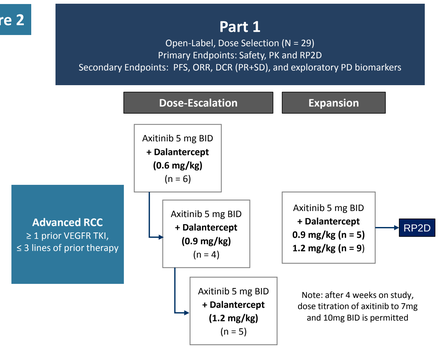
- Advanced clear cell RCC
- ≥ 1 prior VEGFR TKI and ≤ 3 lines of prior therapy
- No prior axitinib or therapies targeting the ALK1 pathway
- Stable, treated CNS disease permitted
- ECOG performance status 0 – 1

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



For details on Part 2 study design, please see Poster TPS4583

NCT01727336

Safety Results

- As of April 14, 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 5 patients (17.2%) 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)	
	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)	5 (55.6)	1 (11.1)	9 (64.3)	1 (7.1)	18 (62.1)	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	3 (21.4)	1 (7.1)	9 (31.0)	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
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
Pericardial effusion	0	0	3 (33.3)	0	4 (28.6)	0	7 (24.1)	0

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

Response Rates (RECIST v1.1)

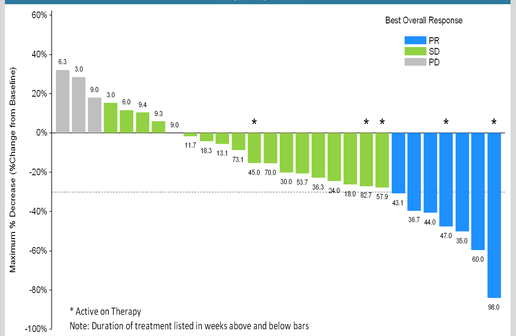
As of 14 Apr 2015

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)
Median PFS (months)	5.5	NR*	6.9	8.3 (4.1-NR)

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

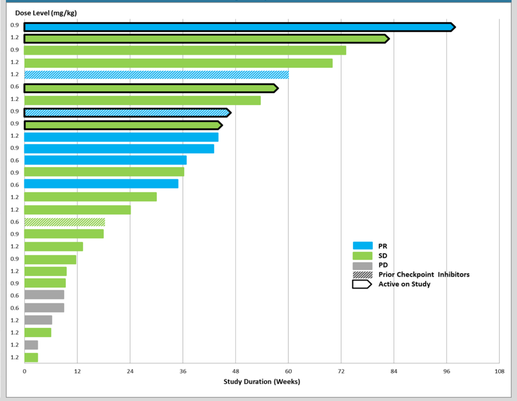
Best Overall Response (RECIST v1.1)

As of 14 Apr 2015



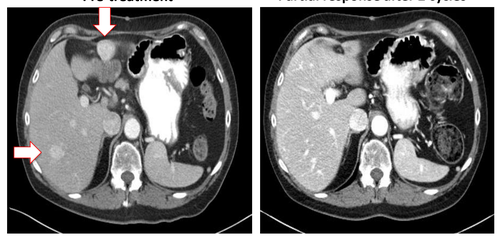
Treatment Duration

As of 14 Apr 2015



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 at 22+ months 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 0.9 mg/kg dose level was selected as the RP2D for Part 2.
- 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 showed clinical activity in all patients previously treated with 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.[10]
- In Part 2 of the DART study, patients are randomized 1:1 to dalantercept plus axitinib vs. placebo plus axitinib (see Poster TPS4583).
- Part 2 is enrolling patients who received 1 VEGFR TKI and may have received 1 prior mTOR inhibitor and/or any number of immune therapies.
- DART study details are at https://clinicaltrials.gov/ct2/show/NCT01727336.

References

1. Seki T, et al. *Circ Res* 2003;93:682-9
2. Shi Y, Massague J. *Cell* 2003;113:685-700
3. Oh SP, et al. *Proc Natl Acad Sci USA* 2000;97:2626-31
4. Mitchell D, et al. *Mol Cancer Ther* 2010;9:379-88
5. Cunha SI, et al. *J Exp Med 2010*;207:85-100
6. Wang X, et al. *AACR Annual Meeting* 2012
7. Bendell JC, et al. *Clin Cancer Res* 2014;20:480-9
8. www.accessdata.fda.gov/drugsatfda_docs/label/2013/202324s001lbl.pdf
9. www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000MedR.pdf
10. Rini BI, et al. *Lancet* 2011; 378: 1931–39
11. Motzer, RJ, et al. *Lancet Oncol* 2013:14:552–62