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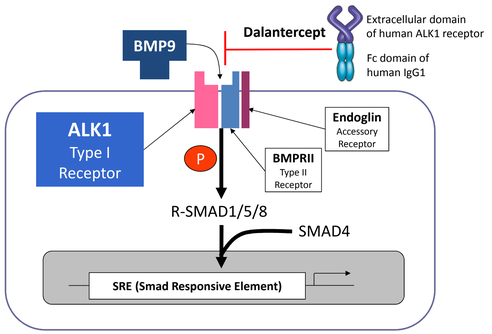
A Phase 2 Randomized Study of Dalantercept Plus Axitinib Versus Placebo Plus Axitinib in Advanced Renal Cell Carcinoma: Results from the Part 1 Dose Escalation and Expansion Cohorts

Michael B. Atkins[1], Martin H. Voss[2], Elizabeth R. Plimack[3], Brian I. Rini[4], Robert Alter[5], Nancy A. Dawson[1], J. Thaddeus Beck[6], Rupal S. Bhatt[7], Kristen M. Pappas[8], Dawn Wilson[8], Ty McClure[8], Ravi Kumar[8], Kenneth M. Attie[8], Matthew L. Sherman[8], Shuchi S. Pandya[8]

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

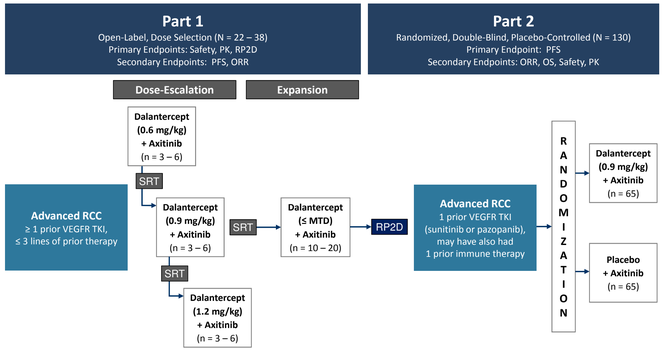


Study Rationale

- The activity of agents that target the vascular endothelial growth factor (VEGF) pathway in metastatic renal cell cancer (mRCC) may be enhanced by combining with dalantercept to improve outcomes for patients.
- 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 mRCC 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.
- 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.
- The safety review team (SRT) reviewed the safety data prior to each dose escalation and the expansion.
- 10 – 20 additional patients were enrolled in an expansion cohort at the maximum tolerated dose (MTD) to further characterize safety and pharmacokinetics.



Key Eligibility Criteria (Part 1)

- Advanced, predominantly clear cell RCC
- Measureable disease according to RECIST 1.1
- ≥ 1 prior VEGFR TKI and ≤ 3 lines of prior therapy
- ECOG performance status grade 0 – 1
- No anti-coagulation therapy, with the exception of low dose aspirin
- No prior axitinib or therapies targeting the ALK1 pathway

Results (Part 1)

- As of May 2014, 26 patients had enrolled in Part 1 (6 at 0.6 mg/kg, 6 at 0.9 mg/kg, and 14 at 1.2 mg/kg).
- No DLTs were reported in escalation cohorts 1 – 3.
- Based on cumulative safety data, the SRT decided to expand at the 1.2 mg/kg dose level.
- 9 patients were enrolled in the 1.2 mg/kg expansion.
  - 1 patient experienced grade 3 abdominal and back pain (DLT).
  - 3 patients at 1.2 mg/kg discontinued due to edema related AEs.
- Enrollment to the expansion at 0.9 mg/kg is ongoing.
- There were no treatment related deaths.
- PK analyses suggest co-administration of dalantercept and axitinib does not effect the individual drug exposure of either agent.
- Based upon the frequency and severity of edema related events at 1.2 mg/kg, the 0.9 mg/kg dose level was selected as the RP2D.

Patient Demographics

Demographic	0.6 mg/kg (N = 6)	0.9 mg/kg (N = 6)	1.2 mg/kg (N =14)	Overall n (%) (N = 26)
Median age (yrs.)	64.5	57.5	60.5	59.5
Gender				
Male	5	4	11	20 (76.9)
Female	1	2	3	6 (23.1)
ECOG				
0	3	4	7	14 (53.8)
1	3	2	7	12 (46.2)
Prior nephrectomy	6	6	14	26 (100)
Sites of disease				
1	1	3	5	9 (34.6)
2	1	3	6	10 (38.5)
≥ 3	4	0	3	7 (26.9)
Number of prior therapies				
1	2	2	9	13 (50.0)
≥ 2	4	4	5	13 (50.0)
Prior systemic therapies				
Sunitinib	4	4	7	15 (57.7)
Pazopanib	1	3	7	11 (42.3)
Evero- / temsirolimus	3	4	4	11 (42.3)
Sorafenib	1	0	1	2 (7.7)
Bevacizumab	1	1	0	2 (7.7)
Nivolumab	1	0	1	2 (7.7)
Interleukin-2	1	0	0	1 (3.8)

Treatment Emergent Adverse Events Regardless of Attribution (≥ 5 patients)

Preferred Term	0.6 mg/kg (N = 6)		0.9 mg/kg (N = 6)		1.2 mg/kg (N = 14)		Overall (N = 26)	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Any AE	5 (83.3)	3 (50.0)	4 (66.7)	1 (16.7)	14 (100)	6 (42.9)	23 (88.5)	10 (38.5)
Fatigue	3 (50.0)	1 (16.7)	3 (50.0)	0	11 (78.6)	0	17 (65.4)	1 (3.8)
Diarrhea	3 (50.0)	1 (16.7)	3 (50.0)	0	8 (57.1)	2 (14.3)	14 (53.8)	3 (11.5)
Creatinine incr.	0	0	1 (16.7)	0	8 (57.1)	0	9 (34.6)	0
Edema peripheral	0	0	2 (33.3)	0	7 (50.0)	0	9 (34.6)	0
Dysphonia	3 (50.0)	0	2 (33.3)	0	3 (21.4)	0	8 (30.8)	0
Epistaxis	0	0	1 (16.7)	0	7 (50.0)	0	8 (30.8)	0
Nausea	2 (33.3)	0	3 (50.0)	0	3 (21.4)	0	8 (30.8)	0
Cough	0	0	3 (50.0)	0	4 (28.6)	0	7 (26.9)	0
Hypertension	1 (16.7)	0	2 (33.3)	0	4 (28.6)	1 (7.1)	7 (26.9)	1 (3.8)
Anaemia	0	0	1 (16.7)	0	5 (35.7)	0	6 (23.1)	0
Arthralgia	1 (16.7)	0	2 (33.3)	0	3 (21.4)	0	6 (23.1)	0
ALK phos incr.	3 (50.0)	0	0	0	3 (21.4)	1 (7.1)	6 (23.1)	1 (3.8)
Constipation	1 (16.7)	0	3 (50.0)	0	2 (14.3)	0	6 (23.1)	0
Thrombocytopenia	0	0	2 (33.3)	0	4 (28.6)	0	6 (23.1)	0
ALT increase	1 (16.7)	0	0	0	4 (28.6)	1 (7.1)	5 (19.2)	1 (3.8)
Palmar-plantar erythrodysesthesia	0	0	1 (16.7)	0	4 (28.6)	0	5 (19.2)	0

Objective Response Rate Analyses RECIST 1.1*

Endpoint	0.6 mg/kg (N = 4)	0.9 mg/kg (N = 4)	1.2 mg/kg (N = 12)	Overall (N = 20)
Partial Response, n (%)	2 (50.0)	1 (25.0)	2 (16.7)	5 (25.0)
Stable Disease, n (%)	0	3 (75.0)	7 (58.3)	10 (50.0)
Disease Control Rate ≥ 6 cycles, n (%)	2 (50.0)	2(50.0)	7 (58.3)	11 (55.0)
Progressive Disease, n (%)	2 (50.0)	0	3 (25.0)	5 (25.0)

Response Rate Analyses Based on Number of Prior Therapies*

Endpoint	1 Prior Therapy (N = 12)	≥ 2 Prior Therapies (N = 8)
Partial Response, n (%)	2 (16.7)	3 (37.5)
Stable Disease, n (%)	7 (58.3)	3 (37.5)
Disease Control Rate ≥ 6 cycles, n (%)	6 (50.0)	5 (62.5)
Progressive Disease, n (%)	3 (25.0)	2 (25.0)

* 6 patients who were either recently enrolled and had not yet undergone restaging imaging (n=4), ineligible (n=1), or came off due to an unrelated adverse event without restaging imaging (n=1) were not included in these analyses.

Individual Patients with Partial Reponses to Dalantercept + Axitinib

Subject	Dalantercept Dose Level (mg/kg)	Prior Therapies	Best Response to Last Therapy	Duration on Last Therapy (months)	Duration on Dalantercept + Axitinib (months)
0101	0.6	• sunitinib	SD	9.0	8.1
0102	0.6	• interleukin-2 • sunitinib • everolimus	SD	4.9	7.0
0201	0.9	• sunitinib • temsirolimus • bevacizumab	PD	1.0	10.4 +
0805	1.2	• sunitinib • nivolumab	SD	7.0	6.2 +
0806	1.2	• pazopanib	SD	23.5	6.7 +

+ active on treatment

Conclusions and Discussion

- In this pretreated mRCC population, the combination of dalantercept and axitinib was well tolerated.
- The most frequent adverse events were generally low grade and included fatigue, diarrhea, elevated creatinine, peripheral edema, dysphonia, epistaxis, nausea, cough, and hypertension.
- 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 dose level in part 2 of this study.
- Common toxicities associated with axitinib, such as diarrhea, hypertension, PPE, and proteinuria occurred with expected frequency and severity.
- Dalantercept and axitinib demonstrated encouraging preliminary activity including partial responses (25%) and disease control (75%) in patients with 1 to 3 prior lines of therapy.
- Part 2 is a Phase 2 multi-center, randomized, placebo-controlled study of dalantercept + axitinib vs. placebo + axitinib in mRCC patients who have received one VEGFR TKI +/- immune therapy.
- In Part 2, 130 patients, randomized 1:1, will be enrolled at approximately 40 centers in the US. PFS is the primary endpoint.
- Study design details are at www.clinicaltrials.gov/show/NCT01727336.

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