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Clinical Trial Results

A Phase Ib, Open-Label Study of Dalantercept, an Activin Receptor-Like Kinase 1 Ligand Trap, plus Sorafenib in Advanced Hepatocellular Carcinoma

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT02024087
- **Sponsor(s):** Acceleron Pharma
- **Principal Investigator:** Ghassan K. Abou-Alfa
- **IRB Approved:** Yes

Lessons Learned

- Patients with hepatocellular carcinoma (HCC) often have limited therapeutic responses to the vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor sorafenib, which is standard of care in advanced HCC. Targeting the activin receptor-like kinase 1 (ALK1) and VEGF pathways simultaneously by combining the ALK1 ligand trap dalantercept with sorafenib may result in more effective angiogenic blockade and delay tumor progression in patients with advanced HCC.
- Although the combination was generally well tolerated, there was no additive antitumor activity with the combination of dalantercept plus sorafenib in patients with advanced HCC. No complete or partial responses were observed, and overall survival ranged from 1.9 to 23.3 months.
- These results suggest that, in this patient population, further development of the possible limited benefits of combination therapy with dalantercept plus sorafenib is not warranted.

Abstract

Background. Targeting the activin receptor-like kinase 1 (ALK1) and vascular endothelial growth factor (VEGF) pathways may result in more effective angiogenic blockade in patients with hepatocellular carcinoma (HCC).

Methods. In this phase Ib study, patients with advanced HCC were enrolled to dose-escalation cohorts, starting at 0.6 mg/kg dalantercept subcutaneously every 3 weeks plus 400 mg sorafenib orally once daily, or to a dose expansion cohort. The primary objective was to determine the safety and tolerability and the dalantercept maximum tolerated dose (MTD) level. Secondary objectives were to assess the preliminary activity and the association of pharmacodynamic biomarkers with tumor response.

Results. A total of 21 patients were enrolled in the study. Five patients received 0.6 mg/kg dalantercept in the first dose escalation cohort. Based on the initial safety results, the dose level was de-escalated to 0.4 mg/kg in the second cohort (n = 6). The MTD was identified as 0.4 mg/kg and used for the dose expansion cohort (n = 10). At this dose level, the combination was generally well tolerated. Overall survival ranged from 1.9 to 23.3 months, and the best overall response was stable disease.

Conclusion. The addition of dalantercept to sorafenib did not improve antitumor activity in patients with HCC. The dalantercept program in this population was discontinued. ***The Oncologist*** 2019;24:161–e70

Discussion

Dalantercept is a soluble ALK1 receptor fusion protein that acts as a ligand trap by binding bone morphogenetic protein 9 and 10, disrupting the formation of mature blood vessels through a mechanism distinct from the VEGF

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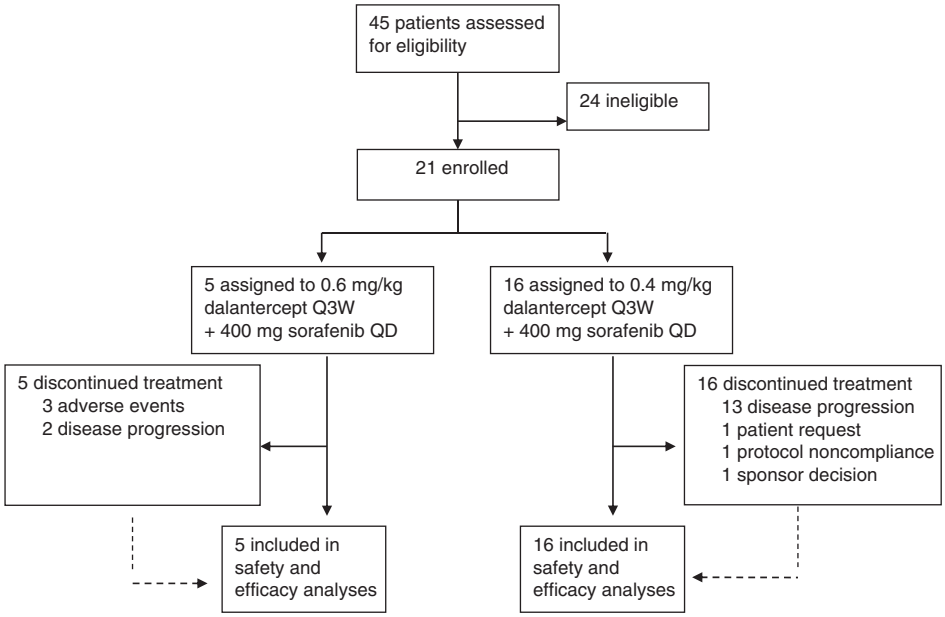

Figure 1. Study design and patient disposition.
Abbreviations: Q3W, every 3 weeks; QD, once daily.

pathway [1,2]. Targeting the ALK1 and VEGF pathways by combining dalantercept and the multikinase and VEGF receptor tyrosine kinase inhibitor (TKI), sorafenib, may result in more effective angiogenic blockade and delay tumor progression in patients with advanced HCC.

Preclinical and early clinical studies suggest that dalantercept in combination with VEGF pathway inhibitors may maximize growth inhibition in tumors that are sensitive to antiangiogenic agents [3,4]. This phase Ib study was designed to determine the maximum tolerated dose of dalantercept in combination with sorafenib for phase II studies. The starting dose level was 0.6 mg/kg dalantercept subcutaneously every 3 weeks (Q3W) plus 400 mg sorafenib orally once daily (QD).

Although dose levels of dalantercept ranging from 0.6 mg/kg to 1.6 mg/kg were generally well tolerated in other clinical studies [5–7], including 0.9 mg/kg in combination with the TKI axitinib [4], in this study the incidence and severity of volume-related events at the 0.6 mg/kg dose level, including peripheral edema (40%), increased weight (60%), and one dose-limiting toxicity, grade 4 hyponatremia, led to the de-escalation of the dalantercept dose level to 0.4 mg/kg.

The combination of 0.4 mg/kg dalantercept Q3W plus 400 mg sorafenib QD was generally well tolerated in the 16 patients treated at this dose level. The safety profile was similar to that reported in other clinical studies [4–7]. The most common treatment-emergent adverse events were constipation, diarrhea, palmar-plantar erythrodysesthesia syndrome, abdominal pain, fatigue, nausea, cough, peripheral edema, and increased lipase. There were no events higher than grade 3 and no study treatment discontinuation due to adverse events reported in this treatment group.

However, antitumor activity was minimal. Overall survival ranged from 1.9 to 23.3 months, and the best overall response was stable disease, reported in 53.3% of patients. In comparison, sorafenib alone in patients with advanced HCC has a median overall survival of 10.7 months (95% confidence interval [CI] 9.4–13.3) and time to progression of 5.5 months (95% CI 4.1–6.9) [8].

Although this combination was generally well tolerated, it did not improve upon the efficacy of sorafenib in patients with advanced HCC. Thus, there are no further clinical studies of this combination planned in patients with HCC.

Trial Information	
Disease	Hepatocellular carcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study - 1	Phase I
Type of Study - 2	3 + 3
Primary Endpoint	Safety
Primary Endpoint	Tolerability
Secondary Endpoint	Efficacy
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Pharmacodynamic
Investigator's Analysis	Level of activity did not meet planned endpoint

Drug Information	
Drug 1	
Generic/Working Name	Dalantercept
Company Name	Acceleron Pharma
Drug Type	Antibody
Drug Class	ALK
Dose	0.6 mg/kg
Route	Other
Schedule of Administration	Subcutaneously every 3 weeks
Drug 2	
Generic/Working Name	Sorafenib
Trade Name	Nexavar
Company Name	Bayer
Drug Type	Biological
Drug Class	Tyrosine kinase inhibitor
Dose	400 mg per flat dose
Route	p.o.
Schedule of Administration	Daily

Dose-Escalation Table				
Dose level	**Dose of drug**	**Dose of drug**	**Number enrolled**	**Number evaluable for toxicity**
1	0.6	400	5	4
2	0.4	400	16	16

Patient Characteristics for Phase I Control	
Number of Patients, Male	14
Number of Patients, Female	7
Stage	IV
Age	Median: 64
Number of Prior Systemic Therapies	0
Performance Status: ECOG	0 — 9 1 — 12 2 — 3 — Unknown —

Primary Assessment Method	
Number of Patients Screened	45
Number of Patients Enrolled	21
Number of Patients Evaluable for Toxicity	21
Number of Patients Evaluated for Efficacy	18
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 0 (0%)
Response Assessment SD	*n* = 10 (56%)
Response Assessment PD	*n* = 8 (44%)4
(Median) Duration Assessments OS	1.9–23.3 months

Serious Adverse Events		
Name	Grade	Attribution
Abdominal pain	3	Unlikely
Atrial fibrillation	3	Unlikely
Pneumonia	3	Unlikely
Acute myocardial infarction	3	Unlikely
Diarrhea	3	Probable
Decreased ejection fraction	3	Probable
Erythema multiforme	3	Possible
Hemoptysis	3	Probable
Hypoglycemia	3	Unlikely
Hyponatremia	3	Probable
Hepatobiliary disease	3	Probable
Pulmonary edema	3	Probable
Pyrexia	3	Probable
Spinal cord compression	3	Unlikely

A serious adverse event was defined as an adverse event regardless of causality that resulted in death, was life threatening, required inpatient hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event that may jeopardize the patient and require medical or surgical intervention. Patients with multiple unique events were counted once per each unique event.

Dose-Limiting Toxicities for Phase I Control				
Dose level	**Number enrolled**	**Number evaluable for toxicity**	**Number with a dose-limiting toxicity**	**Dose-limiting toxicity information**
1	5	4	1	Grade 4 hyponatremia
2	16	16		

Assessment, Analysis, and Discussion	
Completion	**Study completed**
Investigator's Assessment	Level of activity did not meet planned endpoint

Activin receptor-like kinase 1 (ALK1) is a type I receptor of the transforming growth factor beta superfamily that is selectively expressed on the surface of activated endothelial cells [9,10]. When activated by ligands bone morphogenetic protein (BMP) 9 and BMP10, ALK1 signals via phosphorylation [9,11] of the Smad 1/5/8 to activate genes involved in vascular morphogenesis [10]. ALK1/BMP9 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) [11].

Dalantercept is a soluble ALK1 receptor fusion protein that acts as a ligand trap by binding BMP9 and 10, inhibiting signaling through the ALK1 receptor. This disrupts the formation of mature blood vessels through a mechanism that is distinct from the VEGF pathway and impairs basic fibroblast growth factor and VEGF-A-stimulated angiogenesis both in vivo and in vitro [11,12]. In preclinical models, dalantercept displayed potent antitumor activity accompanied by decreased tumor vascularity [12–15]. In a phase I study of dalantercept in 37 patients with advanced solid tumors, dalantercept monotherapy demonstrated antitumor activity. One patient with squamous cell carcinoma of the head and neck had a partial response, and eight patients had prolonged stable disease [7]. Taken together, these results suggest that dalantercept may be effective in hepatocellular carcinoma (HCC).

ALK1 has been detected in the vasculature of many human tumor types, including HCC. BMP9 is overexpressed in HCC compared with normal hepatocytes and is a proliferative and survival factor in HepG2 HCC cells [16,17]. A dalantercept analog (ALK1-Fc) reduced proliferation rates in Huh7, Hep3B, and HepG2 cell lines [17]. In the BEL-7402 preclinical model of HCC, a cell line derived from a primary human tumor from a patient with no prior chemotherapy, dalantercept monotherapy (15 mg/kg three times weekly) completely inhibited tumor growth compared with vehicle. Combination therapy with dalantercept (10 mg/kg twice weekly) plus sorafenib (5–15 mg/kg once daily [QD]) resulted in additive tumor growth inhibition [3]. The processes involved in vascular maturation include vessel stabilization via incorporation of pericytes and other stromal cells, which are commonly downstream of the proliferative stage processes driven by VEGF and other proangiogenic factors. Furthermore, ALK1 expression is elevated in neovascular endothelium during

tumor growth, in contrast to the VEGF/VEGF receptor axis, which is constitutively expressed in new and established blood vessels and in other tissues [18]. In addition, the BMP9/BMP10/ALK1 pathway regulates development of lymphatic vessels [19], which has implications for metastatic spread of tumor cells through lymphatic vasculature [20]. Preclinical and early clinical studies suggest that dalantercept in combination with VEGF pathway inhibitors may maximize growth inhibition in tumors that are sensitive to antiangiogenic agents [3,4]. Further, the safety profile of dalantercept is distinct from that of VEGF tyrosine kinase inhibitors (TKIs), which include fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, and abdominal pain [8]. The most common toxicities with dalantercept include fatigue, peripheral edema, and anemia [7].

Thus, targeting the ALK1 and VEGF pathways simultaneously by combining dalantercept with sorafenib may result in more effective angiogenic blockade and delay tumor progression in patients with HCC.

This study aims to evaluate the safety and tolerability of dalantercept plus sorafenib and to determine the optimal dose of dalantercept in this combination to be studied in phase II trials.

Although dose levels of dalantercept ranging from 0.6 to 1.6 mg/kg were generally well tolerated in other clinical studies [5–7], including 0.9 mg/kg in combination with the TKI axitinib [2], in this study, a dose-limiting toxicity (DLT), grade 4 hyponatremia, occurred at 0.6 mg/kg dose.

Although this DLT was not judged to be related to dalantercept, the Safety Review Team recommended de-escalation of dalantercept from a dose level of 0.6 mg/kg to a dose level of 0.4 mg/kg because of the incidence and severity of volume-related events, including peripheral edema (40%) and increased weight (60%), at the 0.6 mg/kg dose.

No DLTs or AEs higher than grade 3 occurred in the 0.4 mg/kg dose escalation cohort, leading to the determination of 0.4 mg/kg dose level as the maximum tolerated dose. Thus, the expansion cohort was enrolled at this dose level for a total of 16 patients at the 0.4 mg/kg dose level.

The combination of 0.4 mg/kg dalantercept every 3 weeks plus 400 mg sorafenib QD was generally well tolerated, with a safety profile similar to that reported in other clinical studies [4–6]; there were no events higher than grade 3 and no study treatment discontinuation due to adverse events.

However, tumor response at the 0.4 mg/kg dose level was poor; overall survival ranged from 1.9 to 23.3 months, and no patient achieved a complete or partial response.

Disclosures

Ghassan K. Abou-Alfa: Bayer (C/A), Acceleron (RF); **Rebecca A. Miksad**: Flatiron Health (E), Ipsen (C/A); **Stephen Williamson**: Acceleron (RF); **Olugbenga O. Olowokure**: Bayer, Celgene, Bristol-Meyers Squibb (C/A, H); **Matthew L. Sherman**: Acceleron Pharma (E, IP, C/A, OI); **Shuchi S. Pandya**: Acceleron (OI). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Table

Table 1. Demographic and baseline characteristics

Characteristic	0.6 mg/kg dalantercept Q3W + 400 mg sorafenib QD, *n* = 5	0.4 mg/kg dalantercept Q3W + 400 mg sorafenib QD, *n* = 16	Overall, *n* = 21
Sex			
Male	3 (60.0)	11 (68.8)	14 (66.7)
Female	2 (40.0)	5 (31.3)	7 (33.3)
Race			
White	5 (100.0)	11 (68.8)	16 (76.2)
Black	0	3 (18.8)	3 (14.3)
Asian	0	1 (6)	1 (4.8)
Missing	0	1 (6)	1 (4.8)
Median age, years (range)	69.0 (38–83)	63.0 (45–79)	64.0 (38–83)
ECOG status			
0	1 (20.0)	8 (50.0)	9 (42.9)
1	4 (80.0)	8 (50.0)	12 (57.1)

Data are *n* (%) unless otherwise noted.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; Q3W, every 3 weeks; QD, once daily.