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Safety, Pharmacokinetics, Pharmacodynamics, and Antitumor Activity of Dalantercept, an Activin Receptor–like Kinase-1 Ligand Trap, in Patients with Advanced Cancer

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Abstract

Purpose: The angiogenesis inhibitor dalantercept (formerly ACE-041) is a soluble form of activin receptor–like kinase-1 (ALK1) that prevents activation of endogenous ALK1 by bone morphogenetic protein-9 (BMP9) and BMP10 and exhibits antitumor activity in preclinical models. This first-in-human study of dalantercept evaluated its safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity in adults with advanced solid tumors.

Experimental Design: Patients in dose-escalating cohorts received dalantercept subcutaneously at one of seven dose levels (0.1–4.8 mg/kg) every 3 weeks until disease progression. Patients in an expansion cohort received dalantercept at 0.8 or 1.6 mg/kg every 3 weeks until disease progression.

Results: In 37 patients receiving dalantercept, the most common treatment-related adverse events were peripheral edema, fatigue, and anemia. Edema and fluid retention were dose-limiting toxicities and responded to diuretic therapy. No clinically significant, treatment-related hypertension, proteinuria, gross hemorrhage, or gastrointestinal perforations were observed. One patient with refractory squamous cell cancer of the head and neck had a partial response, and 13 patients had stable disease according to RECISTv1.1, eight of whom had prolonged periods ($\geq$12 weeks) of stable disease. Correlative pharmacodynamic markers included tumor metabolic activity and tumor blood flow, which decreased from baseline in 63% and 82% of evaluable patients, respectively, and telangiectasia in eight patients.

Conclusion: Dalantercept was well-tolerated at doses up to 1.6 mg/kg, with a safety profile distinct from inhibitors of the VEGF pathway. Dalantercept displayed promising antitumor activity in patients with advanced refractory cancer, and multiple phase II studies are underway. *Clin Cancer Res; 20(2); 480–9.* ©*2013 AACR.*

Introduction

Tumor growth and metastases are dependent on angiogenesis, the development of new blood vessels from existing vascular networks. Many proangiogenic factors, including VEGF, basic fibroblast-derived growth factor (bFGF), and others, are expressed during tumor angiogenesis by tumor, stromal, and infiltrating myeloid cells (1–4). Identification of angiogenic regulatory pathways has led to the clinical development of anticancer agents that target angiogenesis (1, 5), including monoclonal antibodies against VEGF and small-molecule inhibitors of VEGF receptors and other tyrosine kinases (6, 7). VEGF pathway inhibitors have shown efficacy in diverse tumor types, generally when used in combination with chemotherapy. However, these inhibitors are potentially associated with acquired resistance to treatment due, in part, to induction of other angiogenic pathways (8, 9), and thus there is a need to develop therapeutics directed at novel targets of vascular growth and maturation (4, 10).

Activin receptor–like kinase-1 (ALK1), the *ACVRL1* gene product, is a type I receptor in the transforming growth factor-β (TGFβ) superfamily with high affinity for BMP9 and BMP10 (11). Multiple lines of evidence implicate the BMP9/BMP10/ALK1 pathway as a key regulator of angiogenesis. ALK1-null mice die embryonically due to abnormal vascular development (12, 13), whereas heterozygous loss-of-function mutations in ALK1 cause vascular dysplasia in humans (hereditary hemorrhagic telangiectasia type 2, HHT-2) and mice (14–16). ALK1 expression is normally

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Translational Relevance

Novel targets for antiangiogenic therapy could provide treatment alternatives in patients whose tumors are unresponsive to approved agents such as VEGF pathway inhibitors. An emerging target is the pathway by which bone morphogenetic protein-9 (BMP9) and BMP10 activate the type I receptor activin receptor–like kinase-1 (ALK1) in neovascular endothelium during tumor growth. The present article describes the phase I clinical evaluation of dalantercept, an ALK1 receptor fusion protein that inhibits BMP9/BMP10/ALK1 signaling, in adults with a variety of advanced solid tumors. Consistent with its unique mechanism of action, dalantercept exhibited a safety profile distinct from that of VEGF pathway inhibitors. Dalantercept displayed multiple signs of antitumor activity, including a partial response, long-term stable disease, correlative pharmacodynamic activity as assessed by exploratory functional imaging, and occurrence of a marker (telangiectasia) supportive of the mechanism of dalantercept action. The BMP9/BMP10/ALK1 pathway is a promising target for antiangiogenic cancer therapy.

low in established blood vessels but elevated in neovascular endothelium during tumor growth (17), and ALK1 has been detected in the vasculature of many human tumor types (18). BMP9 and BMP10 have been identified as functional activators of ALK1 in endothelial cells (19), and multiple studies underscore the importance of BMP9 and BMP10 in postnatal vascular remodeling (20), particularly in the maturation phase of angiogenesis (21–23). BMP9 expression is increased dramatically during malignant progression in the RIP1-Tag2 transgenic mouse model of multistep tumorigenesis, and reduced ALK1 gene dosage can inhibit tumor growth and progression in this model by inhibiting angiogenesis (24). In addition, the BMP9/BMP10/ALK1 pathway regulates development of lymphatic vessels (25), with implications for metastatic spread of tumor cells through lymphatic vasculature (26). Together, these findings indicate that inhibitors of BMP9/BMP10/ALK1 signaling may be promising therapeutic candidates for treatment of cancer and related diseases.

Dalantercept (previously known as ACE-041) is a soluble receptor fusion protein consisting of the extracellular domain of human ALK1 linked to the Fc portion of human IgG1. Dalantercept and its murine version, RAP-041, bind with high affinity to BMP9 and BMP10, thereby inhibiting activation of endogenous ALK1 (27). In preclinical models, RAP-041 inhibits maturation of vascular endothelial cells, disrupts vascular development, and displays potent antitumor activity accompanied by decreased tumor vascularity (24, 27). Most notably, RAP-041 inhibits tumor angiogenesis and tumor growth in the RIP1-Tag2 murine model, similar in effect to reduced ALK1 gene dosage (24), and inhibits both vascularity and growth of breast cancer in an orthotopic tumor model (27). Although dalantercept and RAP-041 do not bind VEGF or bFGF (27), RAP-041 can block the angiogenic activity of these proangiogenic factors in multiple model systems (24, 27). The distinct mechanism of action for dalantercept compared with inhibitors of the VEGF pathway may create therapeutic opportunities for dalantercept either in combination with VEGF pathway inhibitors or in patients whose tumors are unresponsive to VEGF inhibition. Here, we report the results of a first-in-human, open-label, phase I study assessing the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of dalantercept in patients with advanced solid tumors.

Materials and Methods

Eligibility criteria

This study (NCT00996957) was approved by local institutional review boards and conducted in accordance with national and local regulations. Written informed consent was obtained before initiation of study-related procedures. Eligible patients were men and nonpregnant women at least 18 years of age with a histologically and/or cytologically confirmed diagnosis of metastatic or unresectable advanced solid tumor or relapsed/refractory multiple myeloma, for which the disease had progressed despite available standard therapies or for which no standard therapy existed. Additional eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 2 and measurability of solid tumors by Response Evaluation Criteria in Solid Tumors (RECISTv1.1). Patients with central nervous system metastases were excluded unless clinically stable for $\geq$3 months after treatment. Patients were also excluded if they had significant cardiac risk (e.g., history of myocardial infarction, unstable angina, pulmonary hypertension, clinically significant arrhythmia, or congestive cardiac failure within one year of study day 1) and/or an ejection fraction of less than 45%.

Study design

This was a phase I, multicenter, open-label, multiple-ascending dose study with a dose-expansion component. During dose-escalation, patients were enrolled sequentially in 7 dose cohorts (0.1, 0.2, 0.4, 0.8, 1.6, 3.2, or 4.8 mg/kg, s.c.; 3–6 patients per cohort). Preclinical studies indicated that dalantercept was well-absorbed after subcutaneous administration and was associated with a prolonged elimination half-life, supporting administration every 3 weeks. Therefore, in the present study, dalantercept was administered subcutaneously once every 3 weeks for up to 4 doses (4 cycles). In the absence of progressive disease, patients were eligible to continue on dalantercept. Selected patients were also eligible for intrapatient dose escalation to a dose level that had been tested and considered to be safe by the Safety Review Team (SRT), which was composed of the principal investigators, the sponsor-designated medical monitor, and an independent cardiologist. Cardiac evaluation was included in safety monitoring, in part, due to angiogenesis involvement in normal cardiac homeostasis

and also due to the known cardiac toxicities of VEGF-based antiangiogenesis therapies.

A minimum of 3 patients completed at least one treatment cycle (3 weeks) at each dalantercept dose level with full review of these data by the SRT before escalation to the next higher dose level. After the final dose of dalantercept, patients were followed for up to 3 months for pharmacokinetic and anti-drug antibody analyses. Once the maximum tolerated dose (MTD) was determined, 12 to 24 additional patients could have been enrolled in the dose expansion cohort and treated at the MTD or lower dose level. The size of the expansion cohort was based on clinical considerations and not statistical power calculations.

Study objectives

The primary objective of the study was to evaluate the safety and tolerability of dalantercept in patients with advanced solid tumors or relapsed/refractory multiple myeloma. Secondary objectives were to identify the MTD, examine the pharmacokinetic profile, and evaluate preliminary antitumor activity and the effect of dalantercept on pharmacodynamic biomarkers.

Dose-limiting toxicity, MTD, and dose modifications

Dose-limiting toxicity (DLT) was defined as any of the following events considered at least possibly related to dalantercept: grade $\geq$3 nonhematologic toxicity as defined by NCI-CTCAEv3.0 (National Cancer Institute Common Terminology Criteria for Adverse Events) with the exception of grade 3 nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis; grade 3 thrombocytopenia with associated bleeding; grade 4 anemia or thrombocytopenia; and grade 4 neutropenia with fever. If a DLT occurred in at least 2 patients in any dose group of 3 to 6 patients within 21 days following a single dose, dose escalation was to be stopped, and the preceding dose level was considered to be the MTD.

Evaluation of safety

Safety endpoints included evaluation of adverse events, physical examination, vital signs, electrocardiogram, echocardiogram, hematology, chemistry, urinalysis, endocrine function, and anti-drug antibodies. Safety analysis was conducted for treatment-emergent adverse events (AE), defined as events that were newly occurring or increasing in severity or frequency during or after study drug administration. Serious adverse events (SAE) were defined by standard criteria. Testing for antidrug antibodies and neutralizing antibodies was conducted by ELISA at baseline and in samples collected at 3-week intervals during dosing and study follow-up.

Pharmacokinetics

Serum samples for determination of pharmacokinetic parameters during the first dosing cycle were collected nominally pre-dose, at 4 and 8 hours, and at 2, 4, 5, 7, 14, and 21 days after dalantercept administration. Additional samples were collected during subsequent dosing cycles. Serum dalantercept concentrations were determined by ELISA, and pharmacokinetic parameters were estimated by noncompartmental analysis of dalantercept concentration data, using actual collection times, with WinNonlin Professional (Pharsight).

Evaluation of antitumor activity

Patients with metastatic or unresectable advanced solid tumors were required to have measurable lesion(s) and must have had a baseline and at least one posttreatment tumor response assessment to be evaluable. Tumor response was evaluated using RECISTv1.1. Restaging scans were conducted at baseline and after every other 21-day cycle (every 6 weeks).

Evaluation of correlative pharmacodynamic markers

Effects of dalantercept on tumor metabolic activity were assessed in 27 of the 37 patients at baseline, at day 15 (middle of cycle 1), and at day 42 (before cycle 3) after initial drug administration. ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) was conducted according to the Netherlands protocol (28). Tumor metabolic activity was measured as maximum percent change in standard uptake value (SUV_{max}) from baseline. Dynamic contrast-enhanced MRI (DCE-MRI) was used to calculate K^{trans}, a composite parameter determined by blood flow, vessel surface area, and vessel permeability (29). Effects of dalantercept on K^{trans} were assessed in 11 of the 37 patients at baseline and at day 15 after initial drug administration. All pharmacodynamic imaging was conducted at the study sites. ^{18}F-FDG PET-CT scans were interpreted locally at the study sites, whereas DCE-MRI scans were interpreted centrally by VirtualScopics.

Statistical analysis

Sample size was sufficient to evaluate safety, tolerability, and pharmacokinetics based on clinical considerations. However, this study was not powered to detect significant changes in pharmacodynamic endpoints. Categoric data were summarized using frequency and percentages, whereas continuous data were summarized by means, median, range, and SD. Evaluable patients were defined as those with complete parametric data for a given endpoint.

Results

General

A total of 37 patients were enrolled between October 2009 and December 2010. Summary demographics and baseline characteristics for these patients are shown in Table 1. Twenty-five patients were enrolled in 7 dose-escalating cohorts (0.1–4.8 mg/kg, s.c., with a treatment cycle of 3 weeks). Twelve patients were enrolled in an expansion cohort at either 1.6 mg/kg (11 patients) or 0.8 mg/kg (1 patient).

Safety

Subcutaneous administration of dalantercept once every 3 weeks was generally well-tolerated. No antidrug

Table 1. Patient demographic and baseline characteristics

Number of patients	37
Male/Female, *n/n*	20/17
Median age, years (min–max)	65 (34–84)
ECOG performance status, *n* (%)	
0	18 (49)
1	19 (51)
Previous systemic therapy (regimens), *n* (%)	
0	1 (3)
1	2 (5)
2	8 (22)
≥3	26 (70)
Prior radiotherapy, *n* (%)	
Yes	25 (68)
No	12 (32)
Tumor type, *n* (%)	
Colorectal	7 (19)
NSCLC	6 (16)
Sarcoma (various)	5 (14)
Head and neck	3 (8)
Ovarian	3 (8)
Pancreatic	2 (5)
Neuroendocrine	3 (8)
Other[a]	8 (22)

[a]Cervical mucinous adenocarcinoma, cholangiocarcinoma, esophageal adenocarcinoma, hepatocellular carcinoma, granulosa cell tumor, salivary duct carcinoma, small-bowel mucinous adenocarcinoma, and carcinoma of unknown origin.

antibodies were detected in any patient. An MTD as defined in the protocol was not determined. Dose escalation was not continued beyond the 4.8 mg/kg dose level due to certain AEs (anemia, peripheral edema, headache, pulmonary congestion) observed at 3.2 and 4.8 mg/kg and a DLT of fluid retention at 4.8 mg/kg. Thus, the expansion cohort was enrolled at 1.6 mg/kg, and all active patients on higher doses were reduced to that dose level.

Table 2 presents treatment-related AEs reported in at least 10% of patients overall in any severity grade or in at least 2 patients with grade ≥3. The majority of AEs were mild (grade 1) or moderate (grade 2). The most frequent AE was peripheral edema (20 patients), primarily in the lower extremities. These events were grade 1 or 2 and were dose-dependent. Peripheral edema tended to occur early during the course of treatment and was readily managed with diuretics.

Another AE possibly associated with fluid retention was congestive cardiac failure (3 patients). Two of the patients with congestive cardiac failure experienced events that were grade 3, were considered probably related to study drug, and were reported as SAEs (Table 2). However, there was no overt evidence of acute cardiac dysfunction, and these 2 patients maintained ejection fractions of 60% and 55% to 57%, respectively. In the third patient with congestive cardiac failure (0.4 mg/kg dose level), the event was grade 1 and considered unrelated to study drug treatment, and ejection fraction measurements from echocardiograms were largely unchanged from baseline in this patient. Taken together, the absence of measurable cardiac dysfunction suggests that pulmonary fluid accumulation was a primary event and noncardiogenic, not secondary to congestive cardiac failure. None of the events associated with fluid retention were characterized by signs or symptoms suggestive of a capillary leak syndrome. As with peripheral edema, these other events associated with fluid retention were readily managed with diuretics, such as furosemide at oral doses of 20 to 40 mg.

A total of 16 (43%) patients experienced AEs of anemia, of which 15 were in the 3 highest dose groups. The severity of anemia in the majority of patients (12 of 16) was grade 1 or 2. The remaining 4 patients had grade 3 anemia. Of these, 1 patient in the 1.6 mg/kg group had anemia that was considered unrelated to study drug, and 3 patients in the 4.8 mg/kg group had anemia considered possibly or definitely related to study drug. There was no evidence of hemorrhage, gastrointestinal blood loss, or hemolysis. Anemia was not associated with treatment-related leukopenia or thrombocytopenia.

Grade 1 telangiectasias occurred in 8 patients distributed among the 3 highest dose groups (Fig. 1). While epistaxis was reported in 9 patients, no bleeding events greater than grade 1 were reported.

SAEs that were possibly or probably related to study drug in 5 patients included fluid overload (2), congestive cardiac failure (2), left ventricular dysfunction, and fatigue. Two of these patients had prior coronary artery disease.

Pharmacokinetics

Mean serum dalantercept concentrations versus time during the first treatment cycle are depicted in Supplementary Fig. S1, and pharmacokinetic parameters for dalantercept during the first treatment cycle are summarized in Table 3. The C_{max} and AUC showed a linear relationship to dose level in the dose range of 0.2 to 4.8 mg/kg. At the lowest dose level (0.1 mg/kg), there were no pharmacokinetic data available for analysis, as 2 patients had limited measurable concentrations and 1 patient had an unresolved predose concentration. The median time to maximum concentration (T_{max}) was 4 to 7 days, and the mean terminal elimination half-life ($T_{1/2}$) of dalantercept was approximately 14 to 18 days. Pharmacokinetic analyses were limited to the first 2 cycles due to sparse sampling in cycle 3 and beyond.

Antitumor activity

Indications of antitumor activity were observed in 14 of 29 evaluable patients (Fig. 2). These included a partial response (33% reduction) by cycle 9 at 0.4 mg/kg in 1 patient with squamous cell carcinoma of the head and neck (SCCHN) who had previously progressed despite receiving radiation therapy, cisplatin, and cetuximab. Thirteen

Table 2. AEs for dalantercept by dose level reported in ≥10% of patients overall with any grade or in at least 2 patients with grade ≥3, by preferred term

	0.1 mg/kg ($n = 3$)		0.2 mg/kg ($n = 3$)		0.4 mg/kg ($n = 3$)		0.8 mg/kg ($n = 4$)		1.6 mg/kg ($n = 15$)		3.2 mg/kg ($n = 6$)		4.8 mg/kg ($n = 3$)		Overall ($n = 37$)	
Preferred term, *n* (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any AE	1 (33)	0	2 (67)	0	3 (100)	1 (33)	4 (100)	0	15 (100)	2 (13)	6 (100)	2 (33)	3 (100)	3 (100)	34 (92)	8 (22)
Edema peripheral	0	0	0	0	1 (33)	0	1 (25)	0	11 (73)	0	6 (100)	0	1 (33)	0	20 (54)	0
Fatigue	0	0	1 (33)	0	2 (67)	1 (33)	1 (25)	0	9 (60)	0	3 (50)	0	1 (33)	0	17 (46)	1 (3)
Anemia	0	0	0	0	0	0	0	0	5 (33)	0	3 (50)	0	3 (100)	3 (100)	11 (30)	3 (8)
Dyspnea	0	0	0	0	0	0	1 (25)	0	7 (47)	1 (7)	2 (33)	0	1 (33)	0	11 (30)	1 (3)
Anorexia	0	0	0	0	1 (33)	0	1 (25)	0	3 (20)	0	4 (67)	0	1 (33)	0	10 (27)	0
Headache	0	0	1 (33)	0	1 (33)	0	0	0	4 (27)	0	2 (33)	0	2 (67)	0	10 (27)	0
Epistaxis	0	0	0	0	0	0	0	0	4 (27)	0	3 (50)	0	2 (67)	0	9 (24)	0
Nausea	0	0	1 (33)	0	0	0	1 (25)	0	2 (13)	0	3 (50)	0	1 (33)	0	8 (22)	0
Pyrexia	0	0	0	0	0	0	0	0	4 (27)	0	1 (17)	0	1 (33)	0	6 (16)	0
Telangiectasia	0	0	0	0	0	0	0	0	3 (20)	0	1 (17)	0	1 (33)	0	5 (14)	0
Cardiac murmur	0	0	0	0	0	0	1 (25)	0	0	0	3 (50)	0	0	0	4 (11)	0
Dizziness	0	0	0	0	0	0	1 (25)	0	2 (13)	0	1 (17)	0	0	0	4 (11)	0
Cardiac failure congestive	0	0	0	0	0	0	0	0	1 (7)	1 (7)	0	0	1 (33)	1 (33)	2 (5)	2 (5)

NOTE: AEs listed are those for which the relationship to dalantercept is indicated as possible, probable, or definite. AEs reported by patients whose dose level was reduced during the study are reported in the dose group to which the patient was initially assigned. No grade 4 or grade 5 treatment-related AEs were reported. Preferred terms are based on MedDRA v12.0, and grades are based on CTCAE v3.

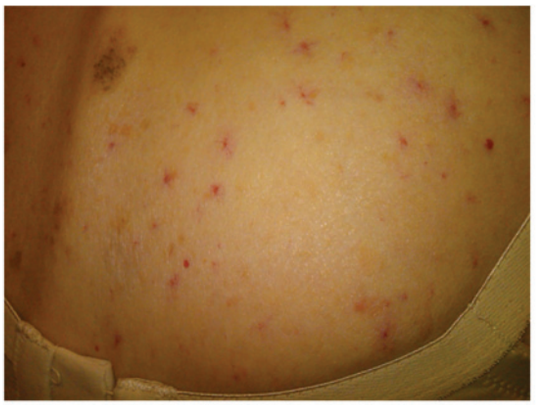

Figure 1. Telangiectasias in a patient with NSCLC after dalantercept treatment at 1.6 mg/kg every 3 weeks.

patients had stable disease per RECISTv1.1. Of these, 8 patients had prolonged periods of stable disease (≥12 weeks) across the dose range (0.2–4.8 mg/kg). A second patient with SCCHN who was refractory to radiation therapy and cetuximab achieved prolonged stable disease/minor response (29% reduction by RECISTv1.1) and received 10 cycles (30 weeks) at 1.6 mg/kg. Additional patients with prolonged stable disease included 3 of 6 patients with non–small cell lung cancer (NSCLC): 1 with nonsquamous NSCLC had 8 cycles (24 weeks) of dalantercept at 0.4 mg/kg, 1 with squamous NSCLC had 6 cycles (18 weeks) of dalantercept at 1.6 mg/kg, and another with squamous NSCLC had 30 cycles (90 weeks) of dalantercept at 3.2/1.6 mg/kg. Prolonged periods of stable disease were also observed in 1 patient each with neuroendocrine carcinoid (6 cycles, 18 weeks at 0.2 mg/kg), granulosa cell tumor (8 cycles, 24 weeks at 1.6 mg/kg), small-bowel mucinous adenocarcinoma (6 cycles, 18 weeks at 1.6 mg/kg), and colorectal adenocarcinoma (9 cycles, 27 weeks at 4.8 mg/kg).

Correlative functional imaging

As measured by ^{18}F-FDG PET-CT, tumor metabolic activity decreased from baseline in 17 (63%) of 27 patients for whom there were evaluable data (Fig. 3). Among patients who exhibited decreased tumor metabolic activity was the SCCHN patient with a partial response, who displayed a 44% reduction in metabolic activity. All 7 patients with prolonged stable disease and evaluable data by PET-CT also had decreased metabolic activity, including the SCCHN patient with stable disease/minor response who displayed a 19% reduction in metabolic activity.

Analysis by DCE-MRI found that 9 (82%) of 11 patients with evaluable data showed reductions in K^{trans} at day 15 compared with baseline, including all 3 patients with stable disease for ≥3 months and for whom DCE-MRI scans were obtained (Supplementary Fig. S2). Similar results were obtained in the 7 patients evaluable at day 43. For example, a patient with NSCLC with evaluable data by DCE-MRI (with squamous histology, stable disease, and 18 weeks of dalantercept treatment) exhibited values for percent change from baseline in median K^{trans} of 30% at day 15 and 37% at day 43.

Discussion

Results from this first-in-human, phase I study of dalantercept in patients with advanced solid tumors indicate that this novel ALK1 fusion protein was well-tolerated with subcutaneous administration at dose levels up to 1.6 mg/kg. The toxicity that limited dose escalation was fluid retention, which was readily managed with diuretic therapy. The most frequently reported AEs were peripheral edema, fatigue, anemia, dyspnea, anorexia, and headache. Fluid retention thought to underlie some of these events may have resulted from inhibition of lymphangiogenesis, given the role of the BMP9/BMP10/ALK1 pathway in this process (25). Of interest, anemia that did not arise from hemolysis or blood loss was observed with dalantercept at the 3 highest dose levels. While the specific mechanism for this anemia is still under investigation, the TGFβ superfamily ligand BMP4

Table 3. Summary of pharmacokinetic parameters for dalantercept after first dose

Dose group [*n*][a]	C_{max}, μg/mL	$T_{1/2}$, d	$AUC_{(0–21d)}$, d × μg/mL	T_{max}, d
0.2 mg/kg [3]	0.71 (0.2)	NR	10.1 (0.9)	7 (6,7)
0.4 mg/kg [3]	1.09 (0.2)	15.9 ($n = 1$)	17.5 (1.7)	6 (4,7)
0.8 mg/kg [4]	3.14 (0.2)	15.9 (7.5)	48.6 (3.6)	6 (5,7)
1.6 mg/kg [15]	9.30 (3.1)	16.0 (4.4)	132 (44.7)	4 (2,7)
3.2 mg/kg [6]	16.1 (5.5)	14.1 (3.1)	229 (48.3)	6 (2,7)
4.8 mg/kg [3]	20.0 (4.0)	18.2 (1.7)	341 (29.4)	4 (2,6)

NOTE: Values are mean (SD) except for T_{max}, in which case median (min–max) are shown.

Abbreviations: $AUC_{(0–21d)}$, area under the concentration–time curve from time 0 to 21 days; C_{max}, maximum observed concentration after subcutaneous injection; NR, not reported; $T_{1/2}$, terminal half-life; T_{max}, time of maximum concentration after subcutaneous injection.

[a]Number of patients per treatment group. Data were not available for all patients for every analysis.

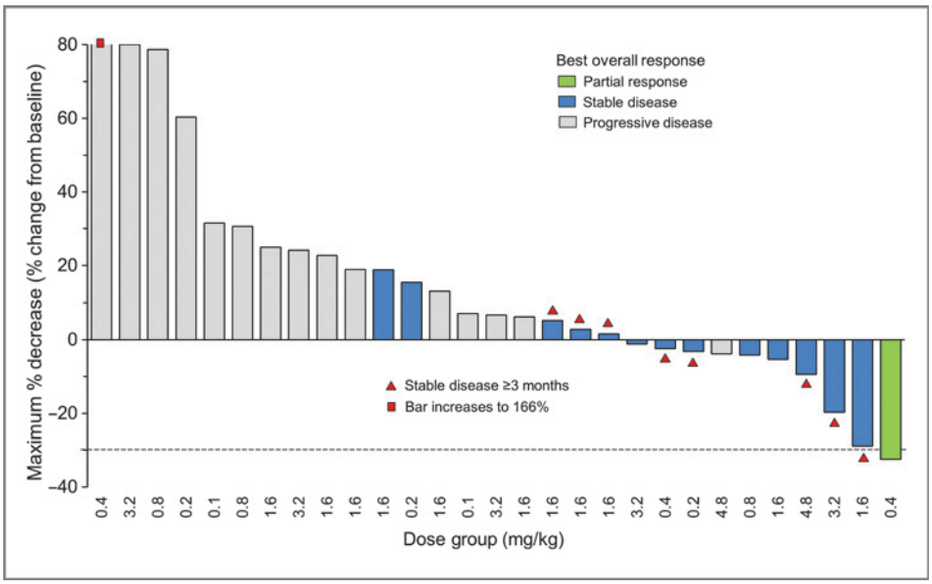

Figure 2. Antitumor activity of dalantercept. Best response measured by RECISTv1.1 and expressed as maximum percent change in tumor size.

stimulates erythropoiesis (30) by activating the same subfamily of transcription factors (Smad1/5/8) through which BMP9/BMP10 signal. Hypoproliferative anemia attributable to proerythroblast suppression is the DLT in patients with cancer receiving anti-endoglin antibody (31), a different inhibitor of the BMP9/BMP10/ALK1 signaling pathway (see below), thereby supporting the view that anemia may be an on-target effect of these dissimilar agents. On the basis of cumulative adverse events observed in the expanded cohort of 1.6 mg/kg, the recommended phase II dose level of dalantercept as monotherapy is 1.2 mg/kg (75% of 1.6 mg/kg) every 3 weeks. In the present study, no clinically relevant hypertension, proteinuria, gastrointestinal perforations, or hemorrhage were observed, and thus the safety profile of dalantercept appears to be distinct from that of VEGF pathway inhibitors (32–35). This result suggests that dalantercept potentially could be administered concurrently with a VEGF pathway inhibitor to achieve enhanced antiangiogenic effect.

Multiple signals of antitumor activity were observed with dalantercept in the present study. One patient with refractory SCCHN had a partial response (33% reduction from baseline by RECISTv1.1), and 8 patients receiving dalantercept had prolonged periods ($\geq$12 weeks) of stable disease. Such effects on tumor size may lag behind functional measures of tumor response, particularly for targeted biologic therapies designed to inhibit tumor progression (36). ^{18}F-FDG PET-CT has been used as a surrogate metric to provide early information about treatment efficacy with cancer therapies that may be primarily cytostatic, including antiangiogenic agents (37). Major determinants of glucose metabolism (^{18}F-FDG uptake) in a tumor include its microvascular supply as well as the number and proliferation rate of viable tumor cells (38). In the present study, tumor metabolic activity was reduced from baseline after dalantercept treatment in more than 60% of patients evaluable by ^{18}F-FDG PET-CT, including all evaluable patients with stable disease. DCE-MRI has also been identified as a potentially useful method for monitoring early tumor response to vascular-targeted therapy (39). As determined by DCE-MRI, dalantercept reduced K^{trans} in more than 80% of evaluable patients, including all 3 with stable disease who were evaluated by DCE-MRI. Although there may be intrapatient variability in measurement of K^{trans} values (40), the changes observed in the present study with dalantercept are interesting and deserve further investigation. Finally, 8 patients distributed among the higher dose groups experienced telangiectasias. This clinical response recapitulates a characteristic feature observed with ALK1 loss-of-function mutations in humans (HHT-2; ref. 14) and therefore represents a marker of pharmacodynamic activity supportive of the mechanism of dalantercept action. Although the above antitumor activity and correlative pharmacodynamic responses require confirmation in a study with sufficient statistical power, they suggest that antitumor effects of dalantercept in patients are accompanied by changes in tumor vasculature.

Diverse agents are under clinical evaluation as modulators of the BMP9/BMP10/ALK1 pathway, an emerging target for antiangiogenic therapy of cancer (41, 42). As described here, dalantercept is a first-in-class soluble receptor fusion protein designed to sequester and inactivate the high-affinity ALK1 ligands BMP9 and BMP10. BMP9 expression in tumors has been proposed as a potential biomarker for selecting patients who might benefit most from such therapy (43). Besides dalantercept, an anti-ALK1 antibody (Pfizer) is undergoing development as a potential antitumor agent (18, 44). Also, in clinical development as an antitumor agent is a chimeric antibody (TRACON) capable of neutralizing endoglin (CD105; ref. 31), a proangiogenic protein in the TGFβ superfamily that binds BMP9/BMP10 (22, 45, 46), with loss-of-function mutations resulting in

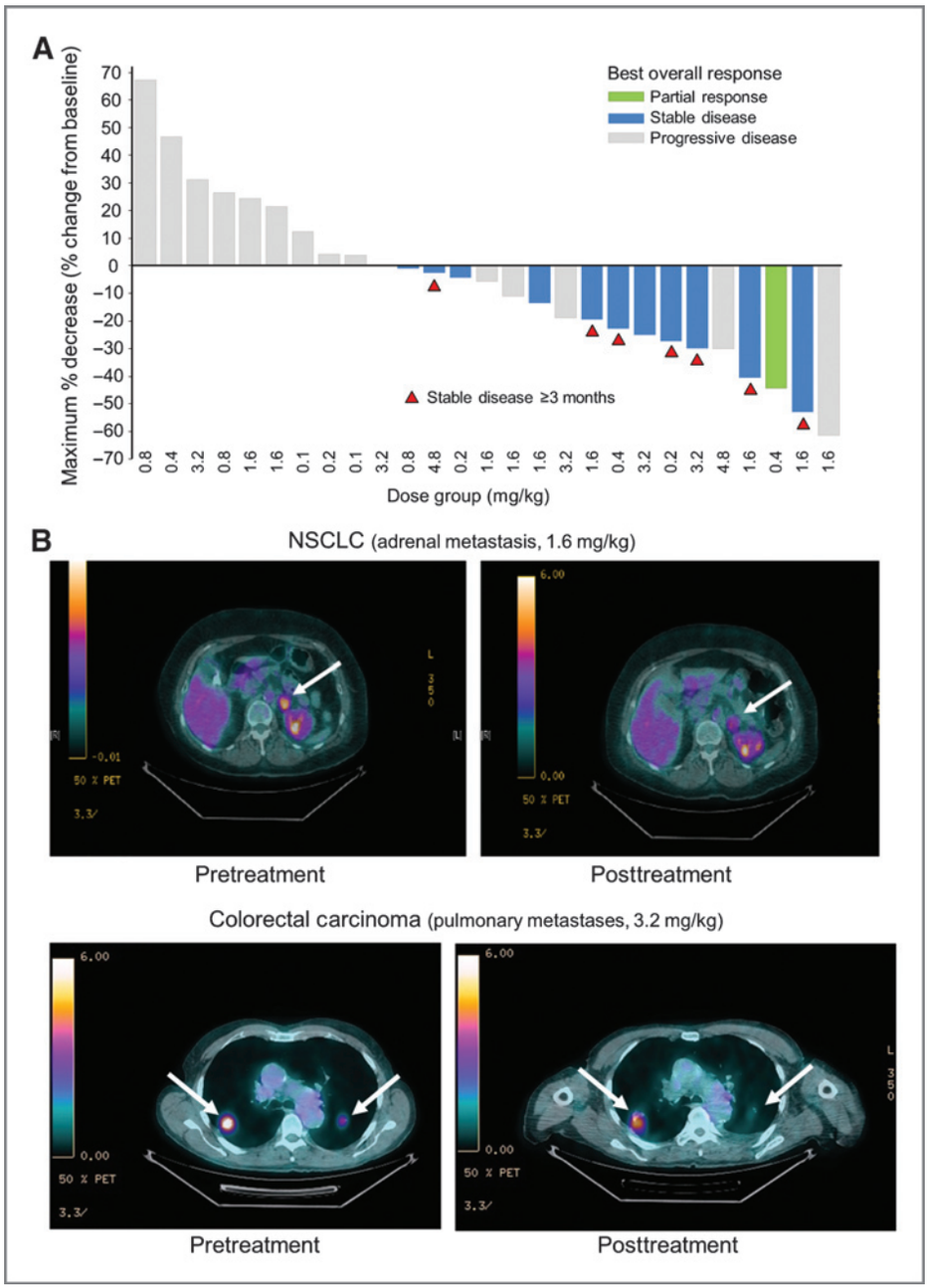

Figure 3. Antitumor pharmacodynamic response to dalantercept as assessed by ^{18}F-FDG PET-CT. A, best response measured as maximum percent change in tumor metabolic activity (SUV_{max}) from baseline. B, top, reduced SUV in adrenal metastasis (arrow) in a patient with NSCLC who received 1.6 mg/kg dalantercept. Bottom, reduced SUV in pulmonary metastases (arrows) in a patient with colorectal carcinoma who received 3.2 mg/kg dalantercept.

another type of vascular dysplasia, HHT-1 (15, 47). In patients with advanced, refractory tumors (31), anti-endoglin antibody was associated with infusion reactions and immunogenicity distinct from effects described for dalantercept in the present study, whereas other adverse effects such as anemia and telangiectasias were observed in both studies. The partial responses, stable disease, and/or pharmacodynamic responses observed in subsets of patients treated with these diverse agents provide encouraging early evidence that the BMP9/BMP10/ALK1 pathway has merit as a therapeutic target for cancer.

In summary, subcutaneous administration of dalantercept, a novel angiogenesis inhibitor, was generally well-tolerated and showed encouraging preliminary anti-cancer activity. These data support future clinical trials evaluating dalantercept as a single agent or in combination with chemotherapy or targeted drugs. Phase II studies with dalantercept are underway in patients with renal cell carcinoma and squamous cell carcinoma of the head and neck, as well as Gynecologic Oncology Group–sponsored trials in endometrial carcinoma and ovarian carcinoma.

Disclosure of Potential Conflicts of Interest

H.I. Hurwitz has received commercial research grants from Acceleron, TRACON, Pfizer, and Genetech/Roche and honoraria from speakers' bureau at Acceleron, TRACON, Genetech, Sanofi, Regeneron, GSK, BMS, and Lilly. G.C. Blobe is a consultant/advisory board member at Acceleron. C.H. Condon is Senior Manager, Clinical Operations in Acceleron Pharma. Y. Yang has ownership interest (including patents) in Acceleron Pharma. K.M. Attie is Vice President, Medical Research in Acceleron Pharma. M.L. Sherman is Chief Medical Officer and has ownership interest (including patents) in Acceleron Pharma. S. Sharma has received commercial research support from Acceleron and has ownership interest (including patents) in Beta Cat Pharmaceuticals, Salarius, and ConverGene. No potential conflicts of interest were disclosed by the other authors.

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