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The DART Study: Results from the Dose-Escalation and Expansion Cohorts Evaluating the Combination of Dalantercept plus Axitinib in Advanced Renal Cell Carcinoma

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Abstract

Purpose: Activin receptor-like kinase 1 (ALK1) is a novel target in angiogenesis. Concurrent targeting of ALK1 and VEGF signaling results in augmented inhibition of tumor growth in renal cell carcinoma (RCC) xenograft models. Dalantercept is an ALK1-receptor fusion protein that acts as a ligand trap for bone morphogenetic proteins 9 and 10. The DART Study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of dalantercept plus axitinib in patients with advanced RCC and determined the optimal dose for further testing.

Experimental Design: Patients received dalantercept 0.6, 0.9, or 1.2 mg/kg subcutaneously every 3 weeks plus axitinib 5 mg by mouth twice daily until disease progression or intolerance.

Results: Twenty-nine patients were enrolled in the dose escalation ($n = 15$) and expansion ($n = 14$) cohorts. There were no dose-limiting toxicities or grade 4/5 treatment-related adverse events. In addition to common VEGFR tyrosine kinase inhibitor effects, such as fatigue and diarrhea, commonly seen treatment-related adverse events were peripheral edema, epistaxis, pericardial effusion, and telangiectasia. The objective response rate by RECIST v1.1 was 25% with responses seen at all dose levels. The overall median progression-free survival was 8.3 months.

Conclusions: The combination of dalantercept plus axitinib is well tolerated and associated with clinical activity. On the basis of safety and efficacy results, the 0.9 mg/kg dose level was chosen for further study in a randomized phase II trial of dalantercept plus axitinib versus placebo plus axitinib. *Clin Cancer Res; 23(14); 3557–65. ©2016 AACR.*

Introduction

Renal cell carcinoma (RCC) is the most common malignancy arising from the kidney and accounts for approximately 90% of all cases. Nearly 62,000 new cases and 14,000 deaths from RCC occur each year in the United States (1). Long-term survival beyond 5 years in patients with advanced-stage RCC has historically been <10% (2).

The principal treatment approach involves agents that target VEGF signaling, due to the vast majority of RCC being molecularly driven by functional loss of the von Hippel–Lindau (VHL) protein, ultimately leading to upregulation of VEGF and promotion of tumor angiogenesis. Seven antiangiogenic agents targeting VEGF have been approved for use in RCC in the United States since 2005 (3). Despite these advances, the median progression-free survival (mPFS) in patients receiving a VEGF pathway inhibitor (sunitinib, pazopanib, bevacizumab plus IFNα) in the first-line setting has been limited to approximately 9 to 11 months (4–7). In the second-line setting, VEGF inhibition with the tyrosine kinase inhibitor (TKI) axitinib can still be efficacious, yet again highlighting the relevance of angiogenesis as a key target in this disease. The overall objective response rate (ORR) and mPFS for the total population treated with axitinib monotherapy in a randomized phase III trial was 19% and 6.7 months, respectively (8, 9). However, in patients previously treated with sunitinib, the antitumor effect with axitinib monotherapy was limited to an 11% ORR and mPFS of 4.8 months. Attempts at combining the VEGF pathway inhibitors with other active agents, particularly mTOR inhibitors, have been constrained by compounded toxicity and have failed to improve efficacy in randomized trials, until recently with the combination of lenvatinib plus everolimus showing a benefit compared with either drug alone in a three–arm, randomized, phase II trial (10–14). However, novel agents are still needed, particularly those that may be more suitable for combination with VEGFR-directed TKIs (15, 16).

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Translational Relevance

Despite attempts at combining VEGF pathway inhibitors with other active agents, novel targets for antiangiogenic therapy are still needed, particularly therapies that may be suitable for combination with VEGFR-directed tyrosine kinase inhibitors (TKIs). This report describes the first part of a phase II clinical evaluation of dalantercept plus axitinib in adults with advanced renal cell carcinoma. Dalantercept is an activin receptor-like kinase 1 (ALK1) receptor fusion protein that inhibits bone morphogenetic protein (BMP) 9 and BMP10 signaling through the ALK1 receptor. Consistent with its unique mechanism of action, dalantercept exhibited a safety profile distinct from that of VEGF pathway inhibitors and consistent with that seen in the phase I monotherapy administration. The combination of dalantercept and axitinib displayed evidence of antitumor activity, including objective responses in several pretreated patients. Biomarker analyses were consistent with prior studies of VEGFR-TKIs.

Tumor neovasculature remains of central relevance for developing novel approaches in this disease, and there is interest in targeting non-VEGF–mediated aspects of angiogenesis. Recently, agents cotargeting VEGFR2 with other proangiogenic signaling, such as c-MET, AXL, or FGFR, have demonstrated efficacy in sunitinib-pretreated patients, providing evidence that blocking alternative mechanisms of angiogenesis might enhance the efficacy of VEGF inhibition in patients with RCC (12, 17).

ALK1 is a type I receptor belonging to the TGFβ superfamily that is selectively expressed on the surface of activated endothelial cells and binds with high affinity to the ligands bone morphogenetic proteins (BMP) 9 and 10 (18, 19). Engagement of ALK1 by these ligands induces the Smad1/5/8 intracellular signal cascade (20, 21). ALK1 plays a pivotal role in the development of functionally mature blood vessels and lymphatic vessels (22, 23). As early regulators of angiogenesis, VEGF and FGF do not directly bind to or signal through ALK1, indicating that ALK1 signaling is a critical downstream event, yet distinct from the VEGF and FGF pathways. Loss-of-function mutations in *ACVRL1*, the gene encoding ALK1, leads to a vascular dysplastic syndrome known as hereditary hemorrhagic telangiectasia-2. This autosomal dominant syndrome is characterized by vascular defects, including telangiectasias on the skin and mucosal linings, epistaxis, and in more severe cases, arteriovenous malformations (24–27). ALK1 and its ligand BMP9 are expressed in many human tumor types, including RCC (28, 29). Furthermore, the regulation of developing lymphatic vessels via the BMP9/ALK1 pathway may have implications for the metastatic spread of tumor cells (30–32).

Dalantercept is a soluble receptor fusion protein consisting of the extracellular domain of human ALK1 linked to the Fc portion of the human IgG1. It acts as a ligand trap for BMP9 and BMP10 and impairs vessel maturation and tumor growth in a variety of tumor models (28, 32, 33). In a phase I study in 37 patients with advanced cancer, dalantercept had an acceptable safety profile that was distinct from that of VEGF pathway inhibitors and showed signs of clinical activity across a variety of tumor types (34). Serious and/or severe adverse events (AEs) included dose-dependent anemia and events related to fluid retention. Edema and weight gain were common dose-dependent AEs that responded to diuretic therapy. One patient with squamous cell carcinoma of the head and neck had a partial response, and eight patients experienced prolonged stable disease (34).

On the basis of preclinical data, it is hypothesized that ALK1 pathway inhibition may be additive to VEGF pathway inhibition therapy and may also provide efficacy in the setting of VEGF inhibitor resistance (28, 35). In RCC xenograft mouse models (A498, 786-O), the combination of dalantercept plus sunitinib resulted in significantly longer duration of tumor growth inhibition compared to either agent alone (36). Benefit was also seen when dalantercept was added to sunitinib following the onset of sunitinib resistance in these models (36). Together, these data support the clinical evaluation of dual angiogenic inhibition of the ALK1 and VEGF pathways in patients with advanced RCC.

Materials and Methods

Eligibility criteria

This study (NCT01727336) 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 had to have received at least one prior VEGFR-TKI and up to three prior RCC-directed therapies, and had to have predominantly clear cell histology, measurable disease per response evaluation criteria in solid tumors (RECIST v1.1; ref. 37), and Eastern Cooperative Oncology Group performance status of 0–1. Patients were excluded if they had received prior axitinib or ALK1-directed therapies, in the setting of uncontrolled hypertension ($\geq$150 mm Hg systolic or $\geq$95 mm Hg diastolic; medication permitted), or active cardiac disease. Patients with stable treated central nervous system metastases no longer requiring corticosteroids were permitted to enroll in the study.

Study design

The DART Study (study A041-04) is a two-part, multicenter trial. Part 1 of the study, reported here, was open label and enrolled three to six patients each to three cohorts of dalantercept at 0.6, 0.9, and 1.2 mg/kg subcutaneously every 3 weeks and axitinib 5 mg by mouth twice daily on a 21-day cycle. Patients were allowed to continue therapy until disease progression per investigator assessment according to RECIST v1.1 or unacceptable toxicity. After a minimum of three patients had completed at least 21 days of treatment for dose-limiting toxicity (DLT) assessment, the safety review team (SRT) met to review the safety data prior to escalation to the next dose or expanding a dose level. Once the MTD level was determined by the SRT and the sponsor, up to a total of 20 additional patients could be enrolled at up to two different dose levels at or below the MTD to further evaluate safety, tolerability, and preliminary antitumor activity with predefined safety stopping rules.

Study objectives

The primary objective of part 1 of this study was to evaluate the safety and tolerability of escalating doses of dalantercept in combination with axitinib in patients with advanced RCC to determine the recommended dose level of dalantercept in combination with axitinib for part 2 of this study. The primary

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objective of the ongoing randomized, double-blinded part 2 of this study is to determine whether dalantercept plus axitinib prolongs PFS compared with placebo plus axitinib in patients with advanced RCC.

DLT, MTD, and dose modifications

DLT was defined as any of the following AEs that were considered possibly or probably related to dalantercept: weight gain (due to fluid retention) grade 2 or higher, pulmonary edema grade 2 or higher, bleeding grade 2 or higher, cardiovascular event grade 3 or higher, grade 3 thrombocytopenia with associated bleeding, grade 4 anemia or thrombocytopenia, grade 4 neutropenia with fever, or nonhematologic AE grade 3 or higher. An AE meeting these criteria was defined as a DLT if it occurred within the SRT safety assessment window of the first 29 days on treatment.

Investigators were instructed to follow protocol-defined dose modification guidelines for specific dalantercept-associated AEs related to edema, weight gain, and pulmonary and cardiac toxicities (see Supplementary Table S1). Patients who tolerated axitinib for at least 4 consecutive weeks with no axitinib-related adverse reactions >grade 2 (according to the NCI-CTCAE v4 current active minor version) and stable blood pressure ($\leq$150/90 mm Hg on $\leq$2 concurrent antihypertensive medications) were permitted to have their axitinib dose increased from 5 to 7 mg twice daily, and subsequently from 7 to 10 mg twice daily using the same tolerability and blood pressure criteria as previously established for axitinib (38).

Evaluation of safety

Safety data and DLTs were evaluated by the SRT, which met prior to each dose escalation and periodically during the dose expansion. The SRT was composed of the principal investigator's sponsor-designated medical monitor and an independent medical oncologist. If a DLT occurred in $\geq$2 patients in any dose-level cohort of three to six patients, no further dose escalation was permitted, and a previous or lower intermediate dose level would be defined as the MTD. Serious AEs (SAE) were defined by standard criteria. Testing for antidrug antibodies and neutralizing antibodies was conducted by ELISA at baseline, on study, and study follow-up.

Pharmacokinetics

Serum samples from all patients were collected predose on day 1 of cycles 1, 2, and 3 and used to assess the pharmacokinetic (PK) profile and parameters of dalantercept in combination with axitinib. Serum dalantercept PK parameters in patients dosed with dalantercept alone in previous studies were compared with this study to evaluate potential one-way drug–drug interaction of axitinib on dalantercept (34, 39). PK parameters were estimated using noncompartmental analysis methods and actual collection times using WinNonlin v.5.2.

Evaluation of efficacy endpoints

Patients underwent CT imaging for evaluation of tumor response (RECIST v1.1) approximately every 6 weeks (37). Tumor response was assessed by investigator review for all patients who met eligibility criteria, received study drugs, and had at least one posttreatment scan. PFS was assessed for all patients who received at least one dose of each study drug.

Evaluation of correlative pharmacodynamic biomarkers

Serum samples were collected on day 1 of each cycle, on day 8 of cycle 2, and at the final visit for selected biomarkers associated with angiogenesis [BMP9, soluble endoglin (sEND), VEGF, placental growth factor (PlGF), and VEGFRs (VEGFR2, VEGFR3)] and were evaluated using a Luminex quantitative multiplex immunoassay platform (Myriad RBM). Archived biopsies were evaluated by immunohistochemical tissue staining and laser scanning cytometry for eight tissue biomarkers: ALK1, BMP9, BMP10, CD105, CD31, Id1, pSMAD5, and GDF 5.

Statistical analysis

In the dose-escalation cohorts, a minimum of three patients and up to six patients could be enrolled per cohort prior to dose escalation. After a minimum of three patients in a cohort reached day 29 (the DLT-assessment window), the SRT made sample size revisions based on safety data and could decide to escalate to the next dose level, enroll the remaining patients at the current dose level (to the maximum of six), deescalate to a previously deemed safe dose level (if available), or expand a dose level. RECIST v1.1 was used for tumor response analysis. Kaplan–Meier analysis was used to compute mPFS and overall survival (OS) with 95% confidence intervals (CIs). Descriptive statistics were used to summarize other parameters, such as safety and biomarker data. Paired t tests were used to compare changes in biomarker serum concentrations between visits and dose levels.

Results

General

A total of 29 patients were enrolled between January 2013 and June 2014. Data from all patient visits completed as of February 2, 2016, were included in the analysis. The dose-escalation phase consisted of six patients treated at the 0.6-mg/kg dose level (no toxicities seen), four patients at the 0.9-mg/kg dose level (no toxicities seen), and five patients at the 1.2-mg/kg dose level. The first expansion cohort was opened at 1.2-mg/kg and enrolled nine patients. Although no DLTs were observed, concerns over toxicity observed at this dose level (from both the dose-escalation and expansion cohorts) prompted the SRT to recommend that a second expansion cohort could continue enrolment at the 0.9-mg/kg dose level, and five additional patients were enrolled. Summary demographics and baseline characteristics of these patients are shown in Table 1. The median age of the study population was 59 years and 62% had at least two prior therapies. Sunitinib was the most common prior systemic therapy (59%).

Safety

The combination of dalantercept plus axitinib was generally well tolerated. There were no DLTs, grade 4/5 drug-related AEs, or serious bleeding events in the dose-escalation cohorts ($n = 15$). Common ($\geq$20% overall) dalantercept-related treatment-emergent AEs (TEAEs) included fatigue, diarrhea, peripheral edema, nausea, increased creatinine, epistaxis, pericardial effusion, and telangiectasia (Table 2). Of these TEAEs, greater incidence with higher dose levels of dalantercept was noted for epistaxis, peripheral edema, and creatinine rise. In addition to peripheral edema (31%), other less frequent fluid-related AEs deemed at least possibly related to dalantercept included pericardial effusions (21%) and pleural effusions (14%). All pericardial effusions were

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Table 1. Patient characteristics

	0.6 mg/kg ($n = 6$)	0.9 mg/kg ($n = 9$)	1.2 mg/kg ($n = 14$)	Overall ($n = 29$)
Median age (years)	64.5, *n* (%)	56.0, *n* (%)	60.5, *n* (%)	59.0, *n* (%)
Gender				
Male	5 (83.3)	7 (77.8)	11 (78.6)	23 (79.3)
Female	1 (16.7)	2 (22.2)	3 (21.4)	6 (20.7)
ECOG				
0	3 (50.0)	6 (66.7)	7 (50.0)	16 (55.2)
1	3 (50.0)	3 (33.3)	7 (50.0)	13 (44.8)
Prior nephrectomy				
Yes	6 (100.0)	8 (88.9)	14 (100.0)	28 (96.6)
No	0	1 (11.1)	0	1 (3.4)
Number of disease sites				
1	0	0	2 (14.3)	2 (6.9)
≥2	6 (100.0)	9 (100.0)	12 (85.7)	27 (93.1)
Number of prior therapies				
1	2 (33.3)	2 (22.2)	7 (50.0)	11 (37.9)
≥2	4 (66.7)	7 (77.8)	7 (50.0)	18 (62.1)
Prior systemic therapies				
Sunitinib	4 (66.7)	6 (66.7)	7 (50.0)	17 (58.6)
Pazopanib	1 (16.7)	5 (55.6)	8 (57.1)	14 (48.3)
mTOR inhibitors	3 (50.0)	5 (55.6)	5 (35.7)	13 (44.8)
Nivolumab	1 (16.7)	1 (11.1)	1 (7.1)	3 (10.3)
Sorafenib	1 (16.7)	0	1 (7.1)	2 (6.9)
Bevacizumab	1 (16.7)	1 (11.1)	0	2 (6.9)
Interleukin-2	1 (16.7)	0	1 (7.1)	2 (6.9)
Ipilimumab	0	1 (11.1)	0	1 (3.4)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

asymptomatic and detected incidentally on routine staging scans. No procedural interventions were required for management of these effusions.

Reported treatment-emergent SAEs are listed in Table 3. Per investigator assessment, those that were determined to be related to study treatment were fluid overload, dyspnea, and acute renal failure, all in the 1.2-mg/kg dose level cohort, and pulmonary embolism in the 0.6-mg/kg dose level cohort. All events occurred at least 1 month after the start of treatment. In the study overall, there were four patients (14%) who discontinued due to AEs, all in the 1.2-mg/kg dose level cohort and all occurring at least 1 month after the start of treatment. Telangiectasias, an on-target effect of ALK1 pathway inhibition, were documented in six patients (21%) at the 0.9- and 1.2-mg/kg dose levels. Low-grade (grade 1–2) epistaxis was the most frequent study treatment–related bleeding event, occurring in six patients (21%), and was most frequently reported at the 1.2-mg/kg dose level ($n = 4$). Elevated creatinine (21%) was the most commonly reported study treatment–related laboratory abnormality, occurring in 43% of patients at the 1.2-mg/kg dose level. These data led the SRT to select the 0.9-mg/kg dose level as the recommended phase II dose level for further study.

Pharmacokinetics

Serum dalantercept exposure in patients dosed with dalantercept plus axitinib (Supplementary Table S2) was similar to that observed previously with dalantercept alone, implying there was no drug–drug interaction effect (39).

Antitumor activity

Twenty-eight of the 29 patients were evaluable for radiographic tumor response assessment (Table 4). Seven patients (25.0%) achieved a partial response, 17 (60.7%) had stable disease, and four (14.3%) had progressive disease as their best response. ORR is defined as the proportion of patients who achieved either confirmed complete or partial responses. As no patients achieved confirmed complete response, the confirmed ORR is equal to the partial response rate in this study. Fourteen patients achieved disease control (partial response + stable disease) for >6 months for a disease control rate of 50%. The majority ($n = 5$, 71%) of patients with a partial response had received at least two prior

Table 2. Related TEAEs to dalantercept in ≥10% patients overall

Preferred term	0.6 mg/kg ($n = 6$) *n* (%)	0.9 mg/kg ($n = 9$) *n* (%)	1.2 mg/kg ($n = 14$) *n* (%)	Overall ($n = 29$) *n* (%)
Fatigue	4 (66.7)	5 (55.6)	10 (71.4)	19 (65.5)
Diarrhea	2 (33.3)	4 (44.4)	6 (42.9)	12 (41.4)
Peripheral edema	0	3 (33.3)	6 (42.9)	9 (31.0)
Nausea	2 (33.3)	3 (33.3)	3 (21.4)	8 (27.6)
Blood creatinine increased	0	0	6 (42.9)	6 (20.7)
Epistaxis	1 (16.7)	1 (11.1)	4 (28.6)	6 (20.7)
Pericardial effusion	0	2 (22.2)	4 (28.6)	6 (20.7)
Telangiectasia	0	5 (55.6)	1 (7.1)	6 (20.7)
Arthralgia	0	2 (22.2)	3 (21.4)	5 (17.2)
Decreased appetite	0	0	5 (35.7)	5 (17.2)
Dysphonia	1 (16.7)	1 (11.1)	3 (21.4)	5 (17.2)
Hypothyroidism	0	2 (22.2)	3 (21.4)	5 (17.2)
Weight decreased	1 (16.7)	1 (11.1)	3 (21.4)	5 (17.2)
Abdominal pain	0	1 (11.1)	3 (21.4)	4 (13.8)
Anemia	0	1 (11.1)	3 (21.4)	4 (13.8)
Constipation	1 (16.7)	3 (33.3)	0	4 (13.8)
Gingival bleeding	0	2 (22.2)	2 (14.3)	4 (13.8)
Muscle spasms	2 (33.3)	0	2 (14.3)	4 (13.8)
Palmar-plantar erythrodysesthesia syndrome	0	1 (11.1)	3 (21.4)	4 (13.8)
Pleural effusion	0	1 (11.1)	3 (21.4)	4 (13.8)
Thrombocytopenia	0	1 (11.1)	3 (21.4)	4 (13.8)
Headache	0	1 (11.1)	2 (14.3)	3 (10.3)
Hypertension	0	2 (22.2)	1 (7.1)	3 (10.3)
Hypophosphatemia	1 (16.7)	0	2 (14.3)	3 (10.3)
Rash	0	2 (22.2)	1 (7.1)	3 (10.3)

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Table 3. Treatment-emergent SAEs

Preferred term	0.6 mg/kg ($n = 6$) *n* (%)	0.9 mg/kg ($n = 9$) *n* (%)	1.2 mg/kg ($n = 14$) *n* (%)	Overall ($n = 29$) *n* (%)
Dyspnea[a]	1 (16.7)	0	1 (7.1)	2 (6.9)
Bile duct stenosis	0	0	1 (7.1)	1 (3.4)
Convulsion	0	1 (11.1)	0	1 (3.4)
Fluid overload[a]	0	0	1 (7.1)	1 (3.4)
Gait disturbance	0	0	1 (7.1)	1 (3.4)
Pulmonary embolism[a]	1 (16.7)	0	0	1 (3.4)
Renal failure	0	0	1 (7.1)	1 (3.4)
Renal failure acute[a]	0	0	1 (7.1)	1 (3.4)
Soft tissue injury	0	0	1 (7.1)	1 (3.4)
Transaminases increased	0	0	1 (7.1)	1 (3.4)

[a]Determined to be possibly or probably related to study treatment by the investigator.

therapies. mPFS overall calculated by Kaplan–Meier analysis was 8.3 months (95% CI, 4.1–20.6). The mPFS for the recommended phase II dose level of 0.9 mg/kg was not estimable at the time of report, but exceeds 9.6 months ($n = 9$). The 12-month PFS and OS rates across all cohorts were 39.7% and 75%, respectively (50% and 88.9%, respectively, for the 0.9 mg/kg dose level). The best overall response and duration of treatment are depicted in Fig. 1. The majority of patients (75%) achieved a decrease in target lesion, and 29% of patients remained on therapy for 1 year or longer. One patient with hepatic metastases, previously treated with sunitinib, temsirolimus, and bevacizumab, achieved a durable partial response (>80% tumor shrinkage) lasting >2.5 years. Five patients received prior immune-based therapies, including IL2 ($n = 2$) or nivolumab with or without ipilimumab ($n = 3$). All five of these patients experienced disease control with either a partial response ($n = 3$) or stable disease ($n = 2$). Axitinib was dose escalated per protocol in 10 patients (34.5%).

Exploratory biomarkers

Serum concentrations of BMP9, VEGFR2, and VEGFR3 declined and VEGF and PlGF levels increased over the course of the three initial study visits (Table 5). Decreases in VEGFR2 as well as VEGFR3 were dose dependent (see Supplementary Fig. S1). A decline in VEGFR3, similar to what was previously observed with single-agent dalantercept, occurred in 29 of 29 patients (100%; ref. 39). After cycle 1 of study medication, there was a 73% mean reduction in VEGFR3 compared with baseline ($P < 0.001$). At the cycle 3 visit, there was an 81% mean reduction from baseline ($P < 0.001$); at the end of study when patients were no longer being exposed to axitinib or dalantercept, serum concentrations of VEGFR3 increased significantly in comparison with concentrations at the cycle 3 visit ($P < 0.001$).

Of the 29 tissue samples collected, 60% were from primary kidney tumor specimens. pSMAD5 was the most highly expressed tissue biomarker within the investigated panel (mean: 5.14; minimum–maximum: 3–9, based on a 0–9 scale), while the remaining seven biomarkers had mean and median expression scores of 3.2 or less (see Supplementary Table S3). Because of the small sample size and poor distribution of scores, no correlation between tissue expression levels and tumor response could be made.

Discussion

Angiogenesis is a key driver in the pathophysiology of clear cell RCC, and therefore, novel approaches targeting angiogenic pathways are justified (40). The ALK1 signaling pathway is an attractive target in advanced RCC based upon its role in later stages of angiogenesis, which distinguishes it from the VEGF pathway. The combination strategy of dual angiogenic blockade is especially appealing considering the limited duration of activity of the currently approved VEGF pathway inhibitors due to the development of resistance principally mediated by activation of angiogenic escape pathways (41).

This study demonstrates that the combination of dalantercept plus axitinib is overall well tolerated with a generally nonoverlapping safety profile in patients with previously treated RCC. The majority of AEs were grade 1–2. The side effect profile of dalantercept remained relatively consistent with the phase I monotherapy experience. Although anemia was seen in the phase I monotherapy study of dalantercept, it was not a common AE in this combination study, which may have in part been countered

Table 4. Response data

	0.6 mg/kg ($n = 6$) *n* (%)	0.9 mg/kg ($n = 9$) *n* (%)	1.2 mg/kg ($n = 13$)[a] *n* (%)	Overall ($n = 28$) *n* (%)
Partial response/ORR[b]	2 (33.3)	3 (33.3)	2 (15.4)	7 (25.0)
95% CI	4.3–77.7	7.5–70.1	1.9–45.4	10.7–44.9
Stable disease	2 (33.3)	6 (66.7)	9 (69.2)	17 (60.7)
95% CI	4.3–77.7	29.9–92.5	38.6–90.9	40.6–78.5
Progressive disease	2 (33.3)	0	2 (15.4)	4 (14.3)
95% CI	4.3–77.7	0–33.6	1.9–45.4	4.0–32.7
Disease control rate[c] $\geq$ 6 months	3 (50.0)	5 (55.6)	6 (46.2)	14 (50.0)
95% CI	11.8–88.2	21.2–86.3	19.2–74.9	30.6–69.4

[a]One patient not evaluable for response based upon ineligibility.

[b]ORR is defined as the proportion of patients who achieved either confirmed complete or partial response, as no patients achieved complete response, ORR = partial response in this study.

[c]Disease control rate is defined as the proportion of patients evaluable for response who meet the criteria for complete response, partial response, or stable disease.

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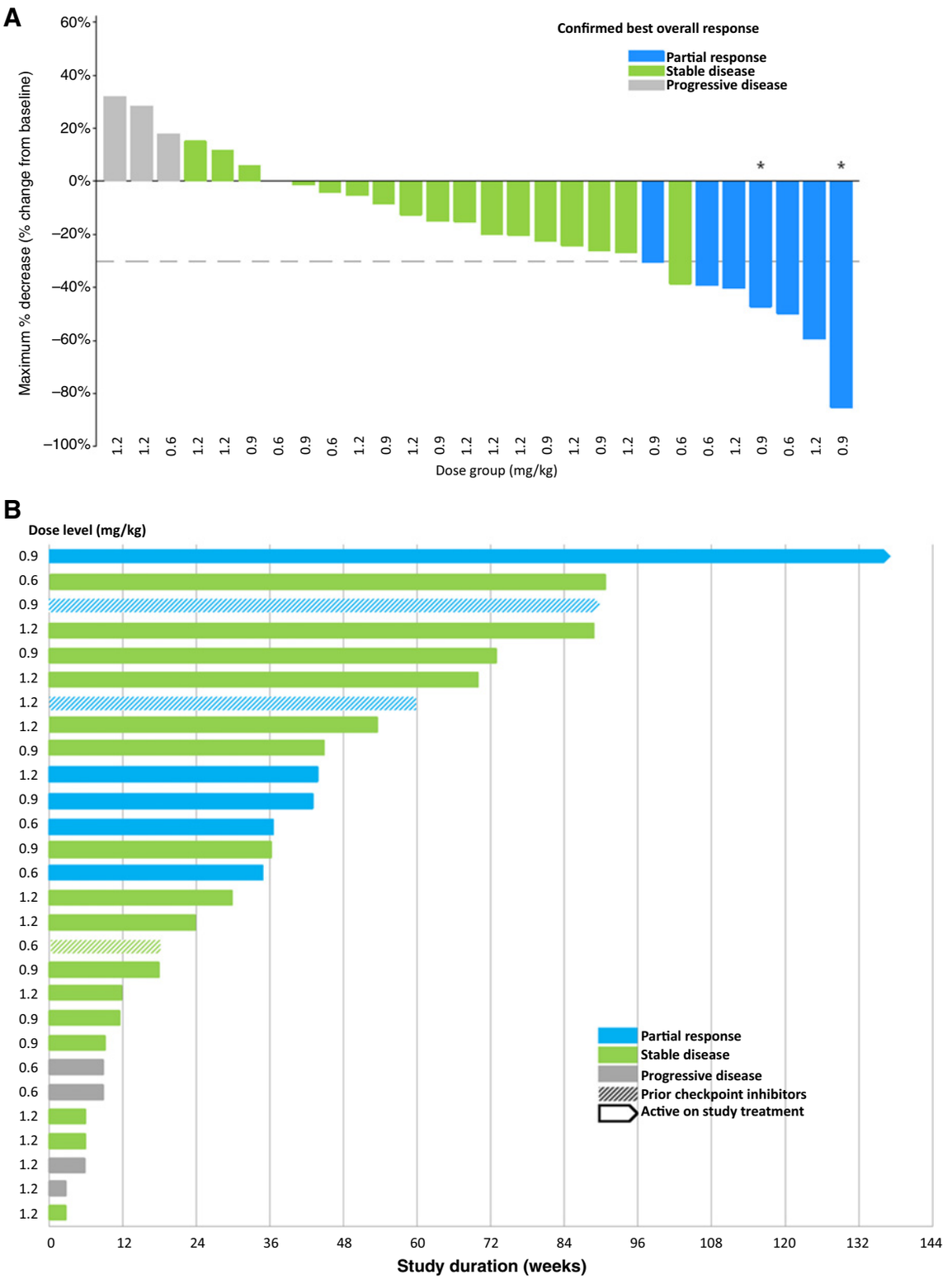

Figure 1.

Antitumor response and durability of dalantercept. **A,** Best response measured by RECIST v1.1 and expressed as a maximum percent change in tumor size. Asterisks denote active on study treatment. **B,** Duration of tumor response. Blue bars, patients with partial response; green bars, stable disease; gray bars, progressive disease; arrows, patients who are active on study treatment; hatched bars, patients treated with prior checkpoint inhibitors.

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Table 5. Serum levels of biomarkers

	Baseline ($n = 29$)	C2D1 ($n = 26$)	C3D1 ($n = 23$)	Last visit ($n = 29$)
BMP9 (pg/mL)				
Mean (SD)	19.4 (12.40)	6.8 (2.46)	7.7 (2.34)	7.9 (2.58)
Median	15	6.8	7.5	7.5
Min–Max	4.6–51.0	2.4–13.0	3.5–14.0	2.1–16.0
P		<0.0001	<0.0001	<0.0001
sEnd (ng/mL)				
Mean (SD)	3.5 (0.82)	3.3 (0.71)	3.2 (0.70)	3.2 (0.65)
Median	3.5	3.4	3.3	3.2
Min–Max	2.2–5.5	2.2–4.7	1.9–4.8	1.5–4.4
P		0.1962	0.1149	0.1058
PlGF (pg/mL)				
Mean (SD)	42.7 (22.92)	93.6 (65.68)	80.2 (43.76)	68.7 (53.36)
Median	33.0	73.0	79.0	51.0
Min–Max	29.0–137.0	29.0–291.0	29.0–213.0	29.0–276.0
P		<0.0001	<0.0001	0.0032
VEGF (pg/mL)				
Mean (SD)	377 (159.1)	494 (261.9)	405 (164.2)	490 (224.4)
Median	360.0	417.5	378.0	439.0
Min–Max	89.0–704.0	147.0–1,120.0	171.0–772.0	189.0–933.0
P		0.0007	0.0027	0.0011
VEGFR2 (ng/mL)				
Mean (SD)	4.8 (1.16)	3.7 (0.69)	3.4 (0.74)	3.9 (1.08)
Median	4.4	3.9	3.4	4.1
Min–Max	3.1–8.1	2.5–5.2	1.9–4.4	2.1–6.1
P		<0.0001	<0.0001	<0.0001
VEGFR3 (ng/mL)				
Mean (SD)	47.0 (23.68)	12.2 (7.88)	9.0 (6.24)	16.0 (10.40)
Median	43.0	9.5	7.9	16.0
Min–Max	20.0–132.0	2.2–35.0	1.4–26.0	1.9–47.0
P		<0.0001	<0.0001	<0.0001

NOTE: *P* values derived from paired *t* tests; each time point compared with baseline.

Abbreviations: Max, maximum; Min, minimum; SD, standard deviation.

by the effect of VEGFR inhibition on stimulating erythropoiesis (42, 43). The overall frequency of fatigue (72%) was greater with the combination of axitinib and dalantercept compared with previously reported monotherapy profiles of either drug; however, these events were limited to grade 1–2 in most patients. Peripheral edema, epistaxis, and increase in creatinine were dose-dependent AEs. The mechanism and host-related risk factors leading to edema remain poorly understood. ALK1 is expressed on lymphatic vessels, and therefore, the inhibition of this pathway may result in impaired lymphatic drainage. PK analyses did not identify drug–drug interactions between axitinib and dalantercept to suggest greater serum exposure to dalantercept due to the presence of axitinib.

Peripheral edema was more common at the 1.2-mg/kg dose level compared with the 0.9-mg/kg dose level (the dose level ultimately chosen for phase II development) and was generally responsive to diuretic therapy (see Supplementary Table S1 for management guidelines). Given the baseline renal impairment of this study population and concurrent AEs associated with axitinib, such as hypertension and diarrhea, the management of edema in some patients at the 1.2-mg/kg dose level was limited by creatinine elevations. VEGF and VEGFRs are expressed in the renal glomeruli. Axitinib and other VEGF pathway inhibitors (such as bevacizumab) are associated with renal impairment usually manifested as elevations of creatinine and proteinuria (44, 45). Proteinuria did not emerge in association with the elevated creatinine events on this study, and the mechanism of renal dysfunction is presently unclear.

Clinical activity was observed in this pretreated population of patients, the majority (62%) of whom had received two or more prior therapies, and we recorded an ORR of 25% and mPFS of 8.3 months. Although it is not possible to say to what extent these findings reflect antitumor effect of axitinib versus the combination, these outcomes compare favorably with the historical ORR of 11% and mPFS of 4.8 months reported for axitinib in patients pretreated with sunitinib (8, 9). The ongoing randomized, placebo-controlled part 2 portion of the DART Study will assess whether the combination of dalantercept plus axitinib achieves superior PFS compared with placebo plus axitinib in patients with advanced RCC previously treated with a VEGF pathway inhibitor. More recent data include the pivotal trial of cabozantinib, a novel multi-TKI targeting VEGFR2, AXL, and MET, which yielded an mPFS of 9.1 months and an ORR of 24% in sunitinib-pretreated patients (46). These data were not available at the time that DART was designed, but conceptually, dalantercept could be studied in combination with other, more novel and recently approved VEGFR-TKI. The biomarker analysis was consistent with prior studies of VEGFR-TKI. A general pattern seen across multiple studies in metastatic and adjuvant therapy is that antiangiogenic therapy is associated with increase in plasma VEGF and PlGF and decrease in VEGFR2 (47–50).

We have identified VEGFR3 as an additional biomarker candidate for antiangiogenic therapy. VEGFR3 is expressed on the cell surface of blood vessels and lymphatics and can be cleaved and act as a sink for the ligands VEGF-C and D. Reduction in VEGFR3 was observed both in this study of dalantercept and axitinib as well as in the prior study of single-agent dalantercept (39). The mechanism by which VEGFR3 is reduced is not known, but our observation of a dose-dependent decrease suggests that this could be a biomarker of target engagement and damage to vascular beds and as such would be of interest for further study in connection with the treatment-induced edema observed with dalantercept. The increase in VEGFR3 seen in patients who were no longer on active treatment supports the hypothesis that levels of this marker correlate with the presence of drug. Further studies with larger sample sizes are needed to investigate whether biomarker changes correlate with clinical response.

In summary, dalantercept plus axitinib demonstrated a favorable safety profile and clinically meaningful antitumor activity in a pretreated population of patients with RCC. The 0.9-mg/kg dose level was selected for further development based on the cumulative safety data and overall activity at this dose level.

Disclosure of Potential Conflicts of Interest

M.H. Voss reports receiving commercial research grants from Bristol-Myers Squibb and Roche/Genentech and is a consultant/advisory board member for Calithera, Exelixis, GlaxoSmithKline, Novartis, and Pfizer. R.S. Bhatt and M.B. Atkins are consultant/advisory board members for Acceleron Pharma. E.R. Plimack is a consultant/advisory board member for Acceleron, Bristol-Myers Squibb, Novartis, and Pfizer. R.S. Alter reports receiving speakers bureau honoraria from Amgen, Astellas, Astra Zeneca, Bayer, Bristol-Myers Squibb, Eisai, Exelixis, Genentech, Janssen, and Novartis and is a consultant/advisory board member for Astellas and Teva. D. Wilson, M. Mutyaba, M.L. Sherman, and S.S. Pandya hold ownership interest (including patents) in Acceleron Pharma. No potential conflicts of interest were disclosed by the other authors.

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The DART Study: Results from the Dose-Escalation and Expansion Cohorts Evaluating the Combination of Dalantercept plus Axitinib in Advanced Renal Cell Carcinoma

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