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EVOLVING THERAPIES (R BUKOWSKI, SECTION EDITOR)

Activin Receptor Inhibitors—Dalantercept

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Abstract Development of anti-angiogenic therapy including the vascular endothelial growth factor (VEGF) antibodies and VEGF-tyrosine kinase receptors has been a major landmark in cancer therapy leading improvement in survival in several cancers. While anti-angiogenic therapy is effective in some settings, resistance often develops owing to evasive, alternative pathways. Novel targets for anti-angiogenic therapy are urgently required to provide treatment alternatives in patients whose tumors are unresponsive to approved anti-angiogenic agents; one such pathway is the bone morphogenetic proteins (BMP 9 and BMP 10) that activate the type I activin receptor-like kinase-1 (ALK1), which has been implicated in the development of functional vasculature. Dalantercept (ACE-041) is a novel anti-angiogenic agent, which is a soluble form of ALK1, and acts as a ligand trap for BMP 9 and BMP 10, inhibiting their interaction with ALK1, which further disrupts the process of vascular development. This review will discuss the preclinical and clinical development of dalantercept as a novel anti-angiogenic therapy in treating a variety of cancers and its distinct safety profile compared to other anti-VEGF agents. We will also discuss the ongoing and completed studies of dalantercept, including combination studies with other VEGF-directed therapies.

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Introduction

Angiogenesis is crucial for the proliferation of vascular cells and promotion of tumor growth, and several angiogenic growth factors like fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) have been implicated for angiogenesis and tumor progression in a variety of tumors. Inhibition of angiogenesis by targeting these growth factors is a well-established therapeutic strategy in cancer treatment. Several anti-angiogenic agents are currently FDA approved to inhibit angiogenic growth factors, including antibodies targeting VEGF as well as small molecule VEGF-tyrosine kinase inhibitors (VEGF-TKIs) (Table 1).

Despite having efficacy in several tumors, not all patients benefit from anti-VEGF agents as tumors often develop drug resistance to anti-angiogenic agents by secreting alternative cytokines [1, 2]. Development of novel anti-angiogenic agents that can block downstream events in angiogenic process may be effective in tumors resistant to traditional VEGF inhibitors. Activin receptor-like kinase 1 (ALK1) signaling has been shown to be present on the vasculature of several tumor types, regulate the development of mature blood vessels, and represent an attractive therapeutic target in oncology [3•]. Inhibitors of ALK1 can inhibit angiogenesis caused by growth factors such as VEGF or FGF, and several agents are in clinical development.

Dalantercept (ACE-041; Acceleron Pharma, Boston, MA) and PF-03446962 (Pfizer, New York) are activin receptor inhibitors that block ALK1 and are currently in clinical development. Herein, we will review the preclinical and clinical development of dalantercept and its potential role as an anti-angiogenic therapy in selected cancers.

Table 1 Currently approved and novel VEGF inhibitors

Approved agents	Description	Targets	Approved indications
Axitinib (Inlyta)	VEGF TKI	VEGFR1,2,3 PDGFR, c-kit	mRCC
Bevacizumab (Avastin)	Monoclonal antibody	VEGF-A	mCRC, mRCC, GBM, cervical cancer, NSCLC
Pazopanib (Votrient)	VEGF TKI	VEGFR 1,2,3, PDGFR, c-kit	mRCC, advanced soft tissue sarcoma
Ramucirumab (Cyramza)	Monoclonal Ab	VEGFR2	Metastatic gastric/GE junction adenocarcinoma
Regorafenib (Stivarga)	VEGF TKI	VEGFR, PDGFR, FGFR, Flt-3, c-kit, Tie2, Raf	Advanced GIST, mCRC
Sorafenib (Nexavar)	VEGF TKI	VEGFR2,3, PDGFR, Raf, Flt-3, c-kit	mRCC, advanced HCC, advanced thyroid carcinoma
Sunitinib (Sutent)	VEGF TKI	VEGFR1,2,3, PDGFR, Flt-3, c-kit	mRCC, GIST, pNET
Vandetanib (Caprelsa)	VEGF TKI	VEGFR2, EGFR1, RET	Medullary thyroid cancer
Ziv-aflibercept (Zaltrap)	"VEGF Trap"	Decoy receptor, binds to circulating VEGF-A and PLGF	mCRC
Novel Agents	Description	Targets	Completed/ongoing studies
Cediranib (AZD2171)	VEGF TKI	VEGFR1,2,3, PDGFR, FGFR	GBM[1]
Nintedanib	VEGF TKI	VEGFR, PDGFR, FGFR	CRC[2], NSCLC[3], Ovarian CA[4]
Trebananib	Peptibody	Angiopoeitin 1,2	Ovarian CA[5], AML[6], solid tumors[7]
PF03446962	Monoclonal Ab	ALK-1	CRC[8], Solid tumors[9], mesothelioma[10], endometrial[11]
Motesanib (AMG 706)	VEGF TKI	VEGFR1,2, PDGFR, c-kit	NSCLC[12], mCRC[13], Breast[14], solid tumors[15], GIST[16]

mRCC metastatic renal cell carcinoma, *mCRC* metastatic colorectal carcinoma, *GBM* glioblastoma, *NSCLC* non-small cell lung cancer, *GIST* gastrointestinal stromal tumor, *pNET* pancreatic neuroendocrine tumors

ClinicalTrials.gov Indicator: [1] REGAL-NCT00777153, [2] NCT02149108, [3] NCT00806819, [4] NCT10105118, [5] NCT014935050, [5] NCT01281254, [6] NCT01555268, [7] NCT01548482, [8] NCT02116894, [9] NCT01337050, [9] NCT00557856, [10] NCT01486368, [11] NCT01210222, [12] NCT00094835, [13] NCT00101894, [14] NCT01349088, [14] NCT00322400, [15] NCT00448786, [15] NCT00093873, [16] NCT00254267, [16] NCT00089960

Role of Activin Receptor-Like Kinase 1 in Cancer

ALK1 is a type 1 receptor belonging to transforming growth factor beta (TGF-β) expressed on activated endothelial cells and binds to the ligands bone morphogenetic proteins (BMP 9 and 10). Inhibition of ALK1 is a therapeutic strategy aimed at inhibiting capsular development and, hence, tumor progression. The BMP9/BMP10/ALK1 pathway is a promising target for anti-angiogenic cancer therapy. Dalantercept is currently undergoing clinical trials in a variety of tumors.

Pharmacology and Mechanism of Action

Dalantercept is a recombinant fusion protein consisting of extracellular domain of human ALK1 linked to the Fc (hinge, CH2 and CH3 domains) of human immunoglobulin G1(IgG1). Dalantercept functions as a ligand trap, binds with high affinity to BMP 9 and BMP 10, thereby inhibiting the activation of endogenous ALK1 (Fig. 1).

Preclinical Development

Dalantercept and its murine version, RAP-041, bind with high affinity to BMP9 and BMP10, thereby inhibiting the activation of endogenous ALK1 [4]. In preclinical models, RAP-041 inhibits maturation of vascular endothelial cells, disrupts vascular development, and exhibits potent antitumor activity [5, 6]. Dalantercept and its murine version RAP-041 delayed progression of renal cell carcinoma (RCC) cell lines alone and when combined with sunitinib. RAP-041 inhibits vascularity and growth of breast cancer in orthotopic tumor models [4]. RAP-041 exhibited antitumor effects in preclinical models of pancreatic cancer [5].

Clinical Development

First-in-Human Phase 1 Study (A041-01)

The first-in-human study of dalantercept was completed in 37 patients with advanced solid tumors to evaluate its safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity [7•].

Patients with metastatic or unresectable advanced solid tumors or refractory multiple myeloma were eligible and received dalantercept subcutaneously at one of seven dose levels (0.1–4.8 mg/kg) every 3 weeks for a maximum of 4 cycles. Patients without progressive disease and no dose-limiting effects were eligible to continue on dalantercept, and selected patients could have intrapatient dose escalations. Thirty-seven patients were enrolled between October 2009 and December 2010, of which 25 patients were enrolled in 7 dose-escalating

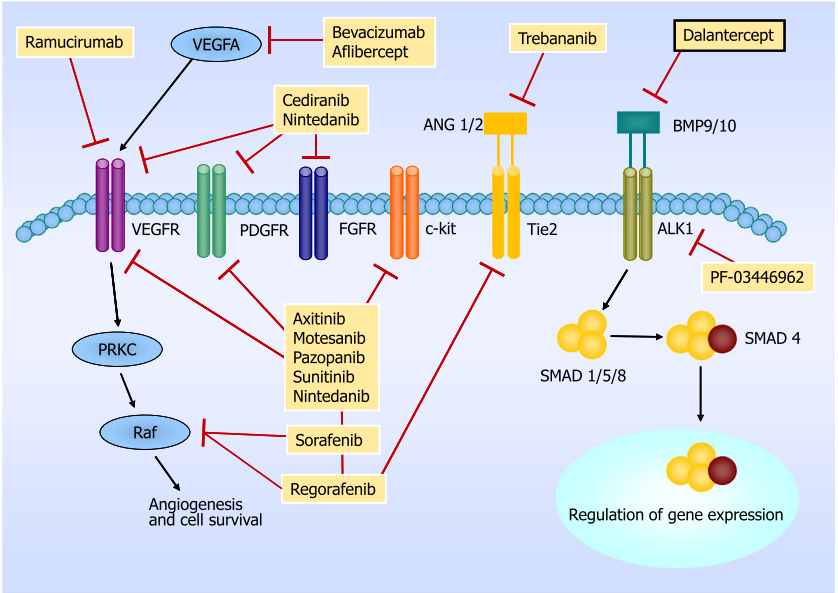

Fig. 1 Dalantercept functions as a ligand trap, binds with high affinity to BMP 9 and BMP 10, thereby inhibiting the activation of endogenous ALK1

cohorts (0.1–4.8 mg/kg), and 12 patients were enrolled in an expansion cohort at either 1.6 mg/kg (11 patients) or 0.8 mg/kg (1 patient).

Pharmacokinetics and Safety

Preliminary analysis of PK data demonstrated a linear relationship to dose level for maximum concentration (*C*max) and area under the concentration-time curve (AUC). The median time to maximum concentration (*T*max) was 4–7 days, and the mean elimination half-life (*T*½) was approximately 14–18 days. These data support the dalantercept dosing frequency of once every 3 weeks. While the maximum tolerated dose (MTD) was not reached, dose escalation was discontinued beyond 4.8 mg/kg due to adverse events (AEs) of anemia, edema, headache, and pulmonary congestion seen at 3.2 and 4.8 mg/kg and a dose-limiting toxicity (DLT) of fluid retention at 4.8 mg/kg. The expansion cohort was enrolled at 1.6 mg/kg, and patients on higher doses were reduced to that dose level. The majority of AEs were grades 1–2, the most frequent being lower extremity peripheral edema in 20 patients occurring early in the treatment course and manageable with diuretics. Another AE associated with fluid retention was congestive cardiac failure in 3 patients, with 2 out of 3 patients experiencing grade 3 events probably related to dalantercept (1.6 and 4.8 mg/kg), but they did not have any overt evidence of cardiac dysfunction. A third patient experienced grade 1 congestive cardiac failure at 0.4 mg/kg dose level of dalantercept, but this was considered unrelated to dalantercept and ejection fraction did not change from baseline. In the absence of overt cardiac dysfunction, the pulmonary fluid accumulation was felt to be non-cardiogenic and there was no evidence of capillary leak syndrome in these patients. Sixteen patients experienced anemia which was grades 1–2 in the majority of patients (12 out of 16) and grade 3 in 3 patients; there was a dose-dependent decrease in red blood cells and hemoglobin levels, with no evidence of hemolysis or hemorrhage. Grade 1 telangiectasias were seen in 8 patients, and epistaxis was the most commonly reported bleeding event, which occurred in 9 patients at the 3 highest dose levels and were grade 1 in severity. There were no grade 2 or higher bleeding events. There was 1 DLT of volume overload at 4.8 mg/kg, but no DLTs at 1.6 mg/kg dosing. No significant, dose-related events of hypertension, gastrointestinal perforation, or proteinuria have been observed in the study to date, indicating a safety profile that appears distinct from VEGF inhibitors.

The increased incidence of edema in over 50 % patients can possibly be explained by the inhibition of lymphangiogenesis by the BMP9/BMP10/ALK1 pathway [4, 6]. BMP10 is known to have a role in adult cardiac development which could explain both edema and congestive heart failure experienced in the study population [8]. Inhibition of this pathway is also a possible mechanism for anemia; of the 11 patients with anemia, none was hemolytic, and of the 3 patients with grades 3–4 anemia, none was receiving high doses raising the possibility of an on-target effect. This is supported by a study with another BMP9/BMP10 inhibitor, anti-endoglin antibody, with proerythroblast suppression and resulting anemia [9]. Telangiectasia present in 14 % of trial patients is possibly explained by inhibition on BMP9 as mutations of BMP9 have been described in patients with hereditary hemorrhagic telangiectasia (HHT) [10].

Antitumor Activity

Dalantercept showed antitumor activity in 14 of 29 evaluable patients, including a partial response (33 % reduction) by

cycle 9 at 0.4 mg/kg in 1 patient with refractory squamous cell carcinoma of the head and neck (SCCHN). Thirteen patients had stable disease of which 8 patients had stable disease for 12 weeks or more; 1 patient with SCCHN showed 29 % reduction in tumor and received 10 cycles at 1.6 mg/kg dose; 3 out of 6 patients with non-small cell lung cancer had stable disease at 8, 6, and 30 cycles, respectively; 1 patient each with neuroendocrine carcinoid (6 cycles), granulosa cell tumor (8 cycles), small-bowel mucinous adenocarcinoma (6 cycles), and colorectal adenocarcinoma (9 cycles) exhibited stable disease as well. Tumor metabolic activity was evaluated using fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan and decreased from baseline in 17 (63 %) of 27 evaluable patients. Seven out of eight patients with prolonged stable disease (SD) who were evaluable for FDG PET-CT showed reduction in metabolic activity, and the patient with a partial response had a 44 % reduction in metabolic activity. Tumor blood flow as measured by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) decreased from baseline in 8 of 12 evaluable patients. The recommended phase 2 dose (RP2D) of dalantercept was determined to be 1.2 m g/kg every 3 weeks based on the AEs seen at dose level 1.6 mg/kg. Based on its mechanism of action, initial safety and activity profile from the aforementioned phase 1 clinical trial, dalantercept is being studied in several studies, alone or in combination with VEGF-TKIs (Table 2).

Single-Agent Dalantercept Phase 2 Studies

Study GOG_0229N (Dalanterept in Endometrial Cancer)

This was a single-arm, two-stage phase 2 study evaluating dalantercept at 1.2 mg/kg in patients with recurrent or persistent endometrial cancer to estimate the number of patients who survived progression free for at least 6 months and those who had objective tumor response. Preliminary results were presented recently [11]. Twenty-eight patients were enrolled, majority of whom had received 1 prior regimen. Most common AEs seen were fatigue, anemia, constipation, and edema; grades 3 and 4 AEs occurred in 39 and 4 % of patients, and there was 1 grade 5 AE of gastric hemorrhage possibly related to dalantercept. There were no objective responses, but SD was seen in 57 % patients; 11 % of patients had PFS >6 months, median PFS was 2.1 months, and median OS was 9.4 months. Overall, these results did not suggest sufficient activity of dalantercept as a single agent to warrant further development in recurrent endometrial cancer.

Study GOG-0170R (Dalantercept in Ovarian Cancer)

This is a single-arm, phase 2 trial evaluating dalantercept at 1.2 mg/kg in patients with recurrent or persistent ovarian cancer. The primary objective is to assess the activity of dalantercept in terms of objective responses, PFS at 6 months, and frequency and severity of adverse events.

Combination Strategies

Since dalantercept targets the alternative angiogenic pathway and blocks common downstream events in the angiogenic process like the later vascular maturation stage, combining it with VEGF-TKIs may help achieve optimal inhibition of the angiogenesis pathway and angiogenically driven tumor progression. Moreover, the dalantercept side-effect profile does not appear to overlap with the toxicity profiles of the VEGF-TKIs. While the incidence of edema was high in the phase I trial with dalantercept [6], and there is a potential concern for

Table 2 Ongoing and completed studies of dalantercept as single agent or in combination with other VEGF Inhibitors

Identifier	Indications	Number	Description	Status
NCT01458392 (A041-03)	Squamous cell carcinoma of the head and neck	45	Single agent Recurrent or metastatic SCCHN previously treated with platinum therapy	Completed
NCT01642082 (GOG-0229N)	Endometrial cancer	28	Single agent Recurrent or persistent endometrial cancer	Completed
NCT01720173 (GOG-0170R)	Ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer	56	Single agent Recurrent or persistent ovarian cancer	Ongoing
NCT01727336 (A041-04)	Renal cell carcinoma	174	Dalantercept and axitinib vs placebo and axitinib Advanced, predominately clear cell disease following up to 3 lines or prior therapy, including 1 VEGF TKI approved for RCC. Must have progressed on either sunitinib or pazopanib	Ongoing
NCT02024087	Hepatocellular carcinoma	20	Dalantercept and sorafenib Locally advanced or metastatic hepatocellular carcinoma, Child-Pugh A	Ongoing

congestive cardiac failure, there were no AES of mucositis, stomatitis, hand foot syndrome, hypertension, neutropenia, or thrombocytopenia. The mechanism of action and safety profile of dalantercept along with promising clinical efficacy in the phase 1 trial [7•] make it an attractive agent to be combined with other VEGF-TKIs for various cancers.

Two combination studies of dalantercept in combination with VEGF-TKIs are currently ongoing in the settings of advanced RCC and hepatocellular carcinoma (HCC), respectively.

Study A041-04(Dalantercept and Axitinib in RCC)

This is a two-part, multi-center, randomized, double-blind, placebo-controlled phase 2 study to evaluate the safety, tolerability, efficacy, and pharmacokinetic profile of dalantercept and axitinib in patients with advanced RCC.

Part 1 (dose-escalation phase): This part assessed the safety and tolerability of dalantercept and axitinib in mRCC patients who had up to 3 prior lines of therapy, including at least 1 approved VEGF TKI, and determined the recommended phase 2 dose (RP2D). Cohorts of 3–6 patients each received dalantercept at dose levels 0.6, 0.9, or 1.2 mg/kg subcutaneously every 3 weeks and axitinib 5 mg orally twice daily.

Interim results from the dose-escalation part were presented recently [12]. Thirteen patients were enrolled in 3 cohorts, 46 % patients had received 2 or more prior treatments, and 15 % had 2 prior VEGF-TKIs. No DLTs were observed. Common dalantercept-related AEs were grades 1–2 diarrhea, fatigue, anemia, arthralgia, creatinine rise, constipation, nausea, dysphonia, headache, and muscle spasms. Axitinib-related AEs were as expected in frequency and severity. Three out of twelve (25 % patients), 2 at 0.6 mg/kg and 1 at 0.9 mg/kg of dalantercept dose, achieved partial responses and were on study for ≥10 cycles (7.5 months); 2 of these had received 3 prior lines of therapies. Six out of eleven (55 %) patients completed at least 6 cycles (4.5 months). These preliminary findings demonstrate that the combination of dalantercept and axitinib is well tolerated and associated with clinical activity in this pretreated advanced RCC population. The R2PD of dalantercept for the part 2 randomized portion of this study is 1.2 mg/kg.

Part 2 (dose-expansion phase): This is the randomized placebo-controlled phase and allows patients to receive an mTOR inhibitor in addition to a VEGF inhibitor. The primary objective is to determine whether the combination of dalantercept and axitinib prolongs PFS compared to axitinib alone, and secondary objectives include evaluation of safety and tolerability of the combination, PFS determination in subgroups of patients with 2 or more prior lines of treatment, overall survival, response rates, and duration of response. In addition, correlation of relevant pharmacodynamic (PD) biomarkers, including BMP9/10, ALK1 in tumor biopsies, and serum with clinical response will be explored. Enrollment is currently ongoing for up to 20 patients.

Study A041-05 (Dalantercept and Sorafenib in HCC)

This is an open-label, multi-center phase 1b study to evaluate the safety, tolerability, PK, PD, preliminary activity, and R2PD of dalantercept and sorafenib. Correlation of PD biomarkers, including BMP9/10, ALK1 in tumor biopsies, and serum with clinical response will also be studied.

The dose level of dalantercept for the first cohort is 0.6 mg/kg every 3 weeks plus sorafenib 400 mg orally daily, and once the MTD is determined, enrollment into the dose-expansion cohort would begin at or below the MTD to further evaluate the safety, tolerability, and PK profile of this combination in advanced/metastatic HCC. Once 10 patients have been evaluated for safety, an additional 10 patients may be enrolled at a current dose level or an intermediate dose level.

Conclusions and Future Directions

Activin receptor inhibitor dalantercept is a promising new anti-angiogenic drug with activity seen in a variety of cancers, as has been described earlier. While there are several anti-VEGF agents currently approved for various tumor types, the development of resistance to these agents is common due to activation of alternative and/or downstream molecular pathways. By targeting the pathways downstream of VEGF pathway, dalantercept provides a potential option to overcome resistance to currently used anti-VEGF agents.

Dalantercept is well tolerated with a distinct side-effect profile compared to other VEGF-targeting agents, making it an attractive choice for combination with these drugs by potentiating their efficacy with non-overlapping toxicities.

Several phase II trials have been completed or are ongoing for the treatment of gynecologic malignancies, HCC, SCCHN, and RCC. These trials will also provide details on potential predictive biomarkers including immunohistochemical and genetic markers of response. The results from these studies would further augment our understanding of the intricacies of the angiogenesis pathway in human cancers and help us devise strategies to integrate dalantercept with existing anti-angiogenic therapies in a variety of cancers.

Compliance With Ethics Guidelines

Conflict of Interest David Gill and Neeraj Agarwal declare that they have no conflict of interest. Shilpa Gupta has received payments for the development of educational presentations from Janssen Pharmaceuticals, Dendreon, and Astellas. Sumanta K. Pal has received consultancy fees from Acceleron.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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