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Phase II Evaluation of Dalantercept in the Treatment of Persistent or Recurrent Epithelial Ovarian Cancer: an NRG Oncology/Gynecologic Oncology Group Study

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Abstract

Objective: To determine the efficacy of dalantercept, a soluble ALK1 inhibitor receptor fusion protein, in patients with persistent or recurrent ovarian carcinoma and related malignancies

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AUTHOR CONTRIBUTIONS

All authors provided data, were involved in writing, revision, and approved the final manuscript. Dr Wei Deng performed the statistical analyses of this study

CONFLICT OF INTEREST STATEMENT

Dr. Robert Burger personal fees from Amgen for consulting and travel expenses, Astra Zeneca for consulting and educational training of associates, Tesaro, Genentech, Clovis Oncology, Invitae, Merck, NuCana and VSL Therapeutics for consulting, Roche for staffing international tumor board, Gradalis and Morphotek for Data Monitoring Committee, and Janssen for Data Monitoring Committee and consulting.

Dr. Vicky Makker received money paid to her from Eisai and Merck for consulting fee or honorarium, as well as fees for participation in review activities such as data monitoring boards, statistical analysis and point committees, and the like.

Dr. Lainie Martin received personal fees from Immunogen for Advisory Board, coverage of travel expense for meeting attendance for poster presentation and also Tesaro for serving on the Advisory board.

Dr. Carol Aghajanian received monies from Tesaro, Clovis, Cerulean, Bayer and VentiRx for honorarium and Advisory Board and Mateon Therapeutics for honorarium and steering committee meetings.

All other co-authors have no conflicts of interest to declare.

Methods: Eligibility criteria included measurable disease, 1-2 prior cytotoxic regimens and GOG performance status (PS) ≤ 2. Dalantercept was administered subcutaneously at 1.2 mg/kg every 3 weeks until disease progression or development of unacceptable toxicity. The primary null hypothesis was the probability of response ≤0.10 and the probability of 6-month progression-free survival without receipt of non-protocol therapy (event-free survival at 6 months, EFS6) ≤0.15, using RECIST 1.1 criteria.

Results: The first stage was closed after enrollment of 30 participants with median age of 56.5 years, high-grade serous histology in 76.7%, 2 prior regimens in 46.7%, and platinum-free interval < 6 months in 73.3%. All participants discontinued dalantercept, 24 (80.0%), 5 (16.7%) and 1 (3.3%) due to progression, toxicity, and other reason, respectively. The median number of treatment cycles per patient was 2 (range 1 – 29). There were six treatment-related grade 3 AEs and no grade ≥ 4 AEs. There were no objective responses. EFS6 was reached in 20% (6 out of 30 participants, 90% CI 9.1% to 35.7%).

Conclusions: Though safe, dalantercept as administered had limited efficacy in this patient population overall.

Keywords

dalantercept; ovarian cancer; clinical trial; phase II

INTRODUCTION

The constellation of diseases commonly referred to as “ovarian cancer,” including epithelial ovarian, primary peritoneal and fallopian tube carcinomas, ranks as the third most lethal malignancy affecting women (1). This poor prognosis has been attributed to advanced stage at diagnosis and by ultimate resistance to cytotoxic therapy, the latter reflective of genomic instability and molecular heterogeneity (2, 3).

Anti-vascular endothelial growth factor (VEGF) therapy with bevacizumab has become incorporated in the standard treatment of advanced and recurrent ovarian cancer based on the rationale that angiogenesis is a process central to tumor progression coupled with benefits in long term outcomes demonstrated in multiple phase III trials (4-8). However, tumor angiogenesis is a complex process, involving a proliferative (activation) phase, orchestrated by VEGF and other cytokines, and a non-proliferative (maturation) phase (9). Parallel upstream pathways of the activation phase exist (9, 10), and may in part contribute to progression in patients on treatment with regimens containing bevacizumab. Therefore, agents that block events in the maturation phase of angiogenesis could potentially thwart such escape pathways associated with the earlier stages of microcirculation development. There is evidence that activin receptor-like kinase 1 (ALK1) signaling is critical to this common downstream process.

ALK1 is a member of the TGFβ superfamily (11) expressed in endothelium and essential for the maturation and stabilization of developing blood vessels (12). ALK1 and its active ligands, bone morphogenic proteins (BMPs), are widely expressed in tumor endothelium and tumor tissue, respectively, in multiple solid malignancies, including ovarian cancer (11).

Both BMP9 and BMP10 are known to bind to and signal through the ALK1 receptor and may be important in angiogenic signaling (13).

Dalantercept (ALK1-IgG1) is a fully human fusion protein consisting of the soluble extracellular domain (ECD) of ALK1 linked to a human IgG1Fc domain, including the hinge, CH2 and CH3 domains (14). This fusion protein binds with high affinity to BMP9 and BMP10 and blocks signaling through the endogenous ALK1 receptor. Multiple pre-clinical studies with a murine homologue have demonstrated single agent anti-tumor activity (14). A phase I study in 37 patients with solid tumors including ovarian cancer, demonstrated tolerability and suggested clinical benefit of single agent dalantercept administered subcutaneously every 3 weeks at dose levels ranging from 0.2 to 1.6 mg/kg (15). We conducted a phase II single arm trial primarily to determine the anti-tumor activity of dalantercept in patients with persistent or recurrent ovarian cancer.

METHODS

Eligibility and Exclusion Criteria.

Eligibility criteria included recurrent or persistent ovarian, fallopian tube, or primary peritoneal carcinoma, herein referred to as “ovarian cancer;” measurable disease as defined by RECIST 1.1; at least one “target lesion” to assess response; and one to two prior chemotherapy regimens including front-line platinum-based chemotherapy, with a platinum-free interval less than 12 months for those having received only one prior regimen. Patients were required to have adequate hematologic reserve (absolute neutrophil count [ANC] ≥ 1,500/μL, platelets ≥ 100,000/μL and hemoglobin ≥ 9 g/dL), renal function and electrolytes (serum creatinine ≤1.5 times the institutional upper limit of normal [ULN] and sodium ≥130 mEq/L), hepatic function (serum bilirubin ≤1.5 times the ULN; ALT, AST and alkaline phosphatase ≤ 3 times the ULN; and albumin ≥ 3 g/dL), coagulation parameters(prothrombin time [PT] with international normalized ratio [INR] ≤1.5 times the ULN or with INR between 2 and 3 for patients receiving stable doses of therapeutic anticoagulants; and partial thromboplastin time [PTT] ≤1.5 times the ULN) and cardiac function (left ventricular ejection fraction >50% measured by echocardiogram or multi-gated acquisition [MUGA] scan). A Gynecologic Oncology Group (GOG) performance status (PS) of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours) was required for patients having received one prior regimen and of 0 or 1 (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work) for those having received two prior regimens.

Patients with other malignancies (except non-melanoma skin cancer) evident within three years; prior non-cytotoxic therapy (i.e., immunologic, biologic targeted, or hormonal therapy) for management of recurrent or persistent ovarian cancer; therapeutic paracentesis within four weeks of enrollment; prior therapy with dalantercept or any other anti-ALK1 agent; non-healing wounds, ulcers or bone fractures; history of urinary or gastrointestinal fistula, gastrointestinal perforation or intra-abdominal abscess within six months; dependence on parenteral hydration or nutrition; or CNS disease (including primary brain tumor history, brain metastases, and uncontrolled seizure disorder), were ineligible. Patients

were also excluded for active bleeding or unacceptable bleeding risk (hereditary hemorrhagic telangiectasia, platelet function abnormality, autoimmune or hereditary hemolysis, coagulopathy or tumor involving major vessels); current treatment with full dose aspirin, clopidogrel or direct thrombin inhibitors; 1.0 g or greater proteinuria per 24 hours (urine protein no greater than 1+ by urinalysis or if ≥ 2+ by urinalysis then <1.0 g in a 24 hour collection); peripheral edema ≥ Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 1 within four weeks of enrollment; significant cardiovascular conditions or risks (uncontrolled hypertension; evidence of hypertrophic cardiomyopathy; New York Heart Association Class II or greater congestive heart failure [CHF]; myocardial infarction coronary artery bypass surgery or stent placement, unstable angina, acute coronary syndrome or hospitalization for CHF within 6 months; serious cardiac arrhythmia; QTc interval >450 ms, cardiac arrhythmia requiring medication; or prior anthracycline cumulative dose >450 mg/m^2); clinically significant active pulmonary risk including pulmonary hypertension, pulmonary embolism, or history of pulmonary edema; history of syndrome of inappropriate antidiuretic hormone secretion; history of infection with hepatitis B or C or human immunodeficiency viruses; pregnancy or lactation. All patients provided written informed consent before enrollment.

Study Treatment, Toxicity Monitoring and Treatment Modifications

Study treatment consisted of dalantercept at 1.2 mg/kg (maximum starting dose of 120 mg) subcutaneously once every 21 days (cycle length) until disease progression or unacceptable toxicity. Patients weighing more than 100 kg could be dose escalated based on actual body weight barring unacceptable toxicity during the first two cycles.

Toxicity was monitored with history, physical examination, and laboratory assessment before each treatment cycle, and with echocardiogram or MUGA for left ventricular ejection fraction (LVEF) at baseline, prior to cycle 3 and with any suspicion of pulmonary edema. Adverse events were defined and graded according to CTCAE v4.0.

Treatment modifications were to be made primarily for non-hematologic toxicities (see section 6.2 of the protocol in Supplementary Material), with special attention to those directly related to the mechanism of action for dalantercept. Unless otherwise specified, dalantercept was held for non-hematologic toxicity until resolution in some cases with dose reduction following resolution according to the schedule is shown in Table 1. In general non-hematologic toxicities ≥ grade 3 required a 1 dose level reduction upon resolution. A maximum of three dose reductions was allowed. Patients experiencing toxicity meeting criteria for further dose reduction were to be removed from study therapy. Weight gain of at least 3% due to fluid retention or pulmonary edema at least grade 1 was to be managed with diuretics, with or without cardiac evaluation. Ascites deemed related to dalantercept was to be managed with paracentesis with or without evaluation for disease progression. Dalantercept could be resumed following stable dose therapeutic anticoagulation for a grade 3 venous thromboembolic event (VTE) assuming no evidence of bleeding, excessive bleeding risk or worsening/recurrent VTE. Dalantercept was to be discontinued permanently for a dose delay related to adverse events >3 weeks; a ≥grade 2 decrease in LVEF, arterial

thrombosis, bleeding or gastrointestinal fistula/perforation; a ≥grade 3 cardiac event; or grade 4 VTE.

Assessment of treatment efficacy

The efficacy of dalantercept was evaluated radiographically (and clinically when appropriate) using RECIST 1.1. In general computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen, pelvis and chest was performed at baseline, followed by radiographic assessment of the abdomen and pelvis (and chest if baseline imaging demonstrated evidence of malignancy) every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months, then every 3 months thereafter until confirmation of disease progression. Imaging was also be performed at the discretion of the investigator if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Objective (complete or partial) response required confirmation ≥4 weeks from initial documentation. Vital status after completion of protocol treatment was assessed every 3 months for 2 years, then every 6 months for 3 additional years.

Serum CA-125 levels were required at baseline and prior to each subsequent treatment cycles, but were not utilized in the assessment of antitumor activity; however, for patients with initial CA-125 levels exceeding the ULN, normalization was required in order to consider an objective response to be complete.

Therapy was discontinued in the event of disease progression, unacceptable toxicity, receipt of other anticancer therapy, or patient refusal.

Study design and analytical methods

This single arm phase II trial was to assess the efficacy and toxicity of dalantercept in patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Accounting for the possibility of both tumor eradicating and stabilizing effects of dalantercept and consistent with several trials in the same series reported previously (16-24), the number of patients with objective response by RECIST 1.1 and the number of patients who survived progression-free without having received non-protocol therapy (event-free survival, EFS) at 6 months (EFS6) from enrollment were used as primary endpoints to measure the antitumor activity of dalantercept. The null hypothesis (H_0) was that both the probability of objective response (π_R) is ≤0.10 and the probability of EFS6 (π_S) is ≤0.15; this was determined from an analysis of historical studies based on a similar population. Clinically interesting values for further investigation would be either $\pi_R \geq 0.25$ or $\pi_S \geq 0.35$.

A 2-stage design by Sill et al was used to evaluate the H_0 (29). Stage I accrued 30 patients with a planned accrual range from 22 to 29. Among these 30 patients, if either at least 4 patients had objective response, or at least 7 patients experienced EFS6, then the study would open to a second stage of accrual to further evaluate the agent with medical judgement indicating; otherwise, the study would close and the agent would be declared clinically uninteresting. If 53 patients were accrued cumulatively in stage II, and either more

than 8 patients had objective response or more than 12 patients out of the 53 patients experienced EFS6, then the regimen would be considered worthy for further investigation.

Given an accrual of 30 patients at stage I, if the study proceeded to stage II with a cumulative target accrual of 53 patients with a range from 49 to 56 then, depending on the degree of association between objective response and EFS6, this study had a probability of early termination of 55% to 62%, an average type I error rate at the end of stage II between 7% to 9%, and an average 90% power of detecting the specified clinically significant effect.

Toxicities assessed by CTCAE v4.0 were summarized with descriptive statistics. Secondary endpoints included both progression-free survival (PFS) and overall survival (OS), which were characterized with Kaplan-Meier plots and estimates of median, respectively. The association of PFS with age, performance status or platinum sensitivity was explored by either Cox proportional hazard model or permutation-based log-rank tests with a two-sided test at significance level of 0.05 without adjustment of multiple tests, respectively (30). Statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Study Population

The study population consisted of 30 women, median age 57 (range 35 to 76) years, enrolled from November 2012 to October 2013. All patients were eligible and treated, therefore included in the analyses of both efficacy and toxicity. A description of the cohort according to ethnicity, race and performance status is shown in Table 2. The majority of patients were non-Hispanic white and had a performance status of 0. Baseline disease characteristics are detailed in Table 3. Not unexpectedly, 90% of patients had advanced stage disease, and 76.7% of cancers were of serous histology. Nearly half of patients had received two prior chemotherapy regimens, and 73.3% had cancers demonstrating resistance to last platinum based treatment.

Treatment summary and patient disposition

The data for treatment and outcomes were locked on November 25, 2015. At that time, a total of 158 cycles of dalantercept had been administered, with a median of 2 (range 1- 29) cycles per patient. All of the 30 patients had discontinued therapy, 24 for disease progression, 5 for toxicity, and 1 for other reasons. Dalantercept dose was reduced in 3 (10%) patients – one dose reduction to 0.9 mg/kg in two patients and two dose reductions to 0.68 mg/kg in one patient. Toxicities leading to treatment discontinuation in 5 patients were low platelets; persistent grade 2 ascites and grade 3 fatigue; ascites, fatigue, vomiting and anorexia; and unacceptable side effects according to patient not otherwise specified and leading to voluntary withdrawal from trial participation; abdominal discomfort following paracentesis. One patient discontinued treatment for reasons other than disease progression or toxicity: symptomatic and clinical deterioration.

Adverse events

Table 4 lists the frequency and severity of adverse events according to system organ class for all 30 patients treated with dalantercept. Events of at least grade 2 in severity potentially related to dalantercept or those of any grade probably or definitely related to the investigational agent are shown. There were no grade 4 or grade 5 events. The most frequent grade 2 or greater events were anemia in 14 (46.7%), fatigue in 9 (30.0%), and ascites in 6 (20.0%) patients. Grade 2 or greater edema (in 4, 13.3%), headache (in 3, 10%), dyspnea (in 2, 6.6%), heart failure (in 1, 3.3%), hypertension (in 1, 3.3%), were relatively uncommon. There were no cases reported of grade 2 or greater epistaxis, thromboembolism, proteinuria or injection site reaction.

Efficacy

The anti-tumor activity of dalantercept was evaluated in all 30 patients. With a median follow-up of 24 months, the median PFS for the study population was 1.7 (90% two-sided confidence interval 1.5 to 3.7) months and the median OS was 19.8 (90% two-sided confidence interval 12.4 to 24.4) months.

The best response by RECIST 1.1 was stable disease in 11 (36.7%, 90% two-sided confidence interval 22.1% to 53.3%), including one patient with high grade serous carcinoma who had 29 cycles of study treatment before she was off study treatment due to disease progression. The remaining patients had increasing disease (in 15 [50.0%]) or an indeterminate response (in 4 [13.3%]). There were no objective partial or complete tumor responses.

Six (20%, 90% two-sided confidence interval 9.1% to 35.7%) patients were event free beyond 6 months from enrollment (EFS6). EFS6 was indeterminate in one of the remaining 24 patients classified as a “treatment failure” for the purpose of primary analysis; this patient withdrew consent due to perceived toxicity following cycle 4 and was therefore lost to follow-up. Seven patients out of 30 with EFS6 would have been required for the trial to proceed to a second stage of accrual. Given the lack of objective responses and no more than 6 patients in this first cohort of 30 patients with EFS6 the trial was closed due to insufficient clinical activity.

An exploratory analysis did not support an association of age, GOG performance status or platinum sensitivity with PFS.

DISCUSSION

In this uncontrolled phase II trial, dalantercept demonstrated insufficient efficacy to warrant further investigation as a single agent for patients with recurrent or persistent ovarian cancer. This primary result is consistent with that observed for the two other phase II trials completed in metastatic/recurrent endometrial cancer (26) and squamous cell carcinoma of the head and neck (27). Limited activity in ovarian cancer and other solid tumors demonstrated in these trials challenge the general premise that dalantercept can effectively block the maturation phase of angiogenesis and that such blockade is therapeutically beneficial. Since only 17% of 30 patients in the current study discontinued therapy due to

toxicity, it is unlikely that tolerability was a principal limiting factor. Still, in the current trial, 6 (20%) of patients were progression-free greater than 6 months from study entry without receiving non-protocol therapy. There were no clinical-pathologic factors distinguishing these patients from all others. However, an exploratory study in progress is evaluating tumor and plasma biomarkers for their potential value in prognostication or in predicting efficacy.

Dalantercept as a single agent appears to be well tolerated in patients with advanced malignancies. In the current phase II trial, adverse events were generally grade 1 to grade 2, most commonly anemia, fatigue and ascites. Furthermore, of the 5 patients discontinuing therapy for toxicity, the adverse effects responsible for treatment discontinuation could have been due either to the investigational agent or to underlying malignancy. Events typically associated with anti-VEGF therapy (visceral perforations/fistulae, arterial thromboembolic events, proteinuria and treatment related hypertension) were not reported.

The potential for dalantercept to complement the anti-tumor effects of anti-VEGF therapy has been postulated given distinct mechanisms of action in targeting tumor angiogenesis (as noted in the Introduction) and distinct toxicity profiles. Based on sufficient activity observed in a phase II trial combining dalantercept with axitinib in patients with advanced renal cell carcinoma (28), a randomized phase II placebo-controlled trial of axitinib with or without dalantercept is in progress for renal cell carcinoma (NCT 01727336).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH HIGHLIGHTS

- First ovarian cancer trial targeting the ALK1 receptor signal transduction pathway
- Phase II trial of dalantercept in patients with persistent or recurrent disease
- Insufficient efficacy to warrant further investigation

Table 1.

Dalantercept Dose Reduction Levels

Dose Modification	Dose Level	Maximum Dose
Starting dose level	1.2 mg/kg	120 mg
1 Level reduction	0.9 mg/kg	90 mg
2 Level reduction	0.68 mg/kg	68 mg
3 Level reduction	0.51 mg/kg	51 mg
More than three dose level reductions	Discontinue dalantercept	

Table 2.

Patient Characteristics

Characteristic	No.	%
Ethnicity		
Non-Hispanic	29	96.7
Undeclared	1	3.3
Race		
White	25	83.3
African American	3	10.0
Asian	2	6.7
GOG Performance Status		
0	23	76.7
1	7	23.3

Table 3.

Baseline Disease Characteristics

Characteristic	No.	%
FIGO stage		
I-C	1	3.3
II-A	1	3.3
II-C	1	3.3
III-A	1	3.3
III-B	1	3.3
III-C	18	60.0
IV	7	23.3
Cell type		
Serous	23	76.7
Adenocarcinoma, NOS	3	10.0
Clear cell	2	6.7
Mixed epithelial	1	3.3
Undifferentiated	1	3.3
Tumor grade		
3	29	96.7
Unknown	1	3.3
No. of prior regimens		
1	16	53.3
2	14	46.7
Most recent platinum sensitivity		
PFI < 6 months	22	73.3
PFI ≥ 6 months	8	26.7

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; PFI, platinum-free interval.

Table 4.

Adverse Events (N = 30) Without Regard to Attribution

	Maximum Severity*					
	Grade 1		Grade 2		Grade 3	
Adverse Event	No.	%	No.	%	No.	%
Blood and Lymphatic						
Anemia	7	23.3	13	43.3	1	3.3
Cardiac - Heart Failure	0	0.0	0	0.0	1	3.3
Gastrointestinal						
Abdominal distention	3	10.0	2	6.7	0	0.0
Abdominal pain	8	26.7	5	16.7	2	6.7
Ascites	0	0.0	5	16.7	1	3.3
Bloating	2	6.7	2	6.7	0	0.0
Diarrhea	3	10.0	1	3.3	0	0.0
Nausea	6	20.0	1	3.3	1	3.3
General and administration site	13	43.3	8	26.7	2	6.7
Edema (face, limbs, trunk, localized)	9	30.0	4	13.3	0	0.0
Fatigue	11	36.7	7	23.3	2	6.7
Injection site reaction	1	3.3	0	0.0	0	0.0
Malaise	1	3.3	1	3.3	0	0.0
Immune System						
Allergic reaction	0	0.0	1	3.3	0	0.0
Infections and Infestations - All	0	0.0	2	6.7	2	6.7
Investigations						
Platelet count decreased	5	16.7	1	3.3	0	0.0
Weight gain	8	26.7	0	0.0	0	0.0
Metabolic and Nutrition Disorders						
Anorexia	2	6.7	3	10.0	0	0.0
Dehydration	0	0.0	1	3.3	0	0.0
Hypoalbuminemia	8	26.7	1	3.3	2	6.7
Hyponatremia	4	13.3	0	0.0	1	3.3
Neurologic – Headache	12	40.0	3	10.0	0	0.0
Psychiatric - Insomnia	2	6.7	2	6.7	0	0.0
Respiratory						
Dyspnea	4	13.3	1	3.3	1	3.3
Epistaxis	3	10.0	0	0.0	0	0.0
Skin and Subcutaneous - Telangiectasia	2	6.7	0	0.0	0	0.0
Vascular	2	6.7	0	0.0	0	0.0
Hypertension	2	6.7	1	3.3	0	0.0
Thromboembolic	1	3.3	0	0.0	0	0.0

*The maximum severity of each adverse events per patient, graded according to CTCAE v4.0.