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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☆

Robert A. Burger [a,*], Wei Deng [b], Vicky Makker [c], Yvonne Collins [d], Heidi Gray [e], Robert Debernardo [f], Lainie P. Martin [g], Carol Aghajanian [c]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA 19104, United States of America
[b] NRG Oncology, Clinical Trial Development Division, Biostatistics & Bioinformatics, Roswell Park, Buffalo, NY 14263, United States of America
[c] Department of Medicine, Memorial Sloan Kettering Cancer, New York, NY 10065, United States of America
[d] Department of Obstetrics & Gynecology, University of Illinois at Chicago CCOP, Chicago, IL 60612, United States of America
[e] Dept. of OB/GYN, Washington University School of Medicine, Seattle, WA 98195, United States of America
[f] Department of Obstetrics & Gynecology, Case Western University Hospital, Cleveland, OH 44106, United States of America
[g] Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, United States of America

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.

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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.

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.

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* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Pennsylvania, Perelman Center for Advanced Medicine, South Tower, Room 10-173, 3400 Civic Center Boulevard, Philadelphia, PA 19104, United States of America.
E-mail addresses: robert.burger@uphs.upenn.edu (R.A. Burger), wdeng@gogstats.org (W. Deng), makkerv@mskcc.org (V. Makker), yvonne.collins-md@advocatehealth.com (Y. Collins), hgray@u.washington.edu (H. Gray), debernr@ccf.org (R. Debernardo), lainie.martin@fccc.edu (L.P. Martin), aghajanc@MSKCC.ORG (C. Aghajanian).

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1. 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.

2. Methods

2.1. 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 <12 months for those having received only one prior regimen. Patients were required to have adequate hematologic reserve (absolute neutrophil count [ANC] ≥1500/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 >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 h (urine protein no >1+ by urinalysis or if ≥2+ by urinalysis then <1.0 g in a 24 h 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.

2.2. 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 >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, 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

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