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A phase II study of ramucirumab (IMC-1121B) in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma☆,☆☆

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HIGHLIGHTS

- Sixty patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma were treated.
- PFS-6 was 25.0% (95% CI: 14.7–37.9%). Best overall response was: partial response 5.0%, stable disease 56.7%, and progressive disease 33.3%.
- Pharmacodynamic analyses revealed increased circulating VEGF-A and PlGF and decreased circulating sVEGFR-2 following initial ramucirumab infusion.

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ABSTRACT

Objective. Vascular endothelial growth factor (VEGF) receptor-mediated signaling contributes to ovarian cancer pathogenesis. Elevated VEGF expression is associated with poor clinical outcomes. We investigated ramucirumab, a fully human anti-VEGFR-2 antibody, in patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Primary endpoints were progression-free survival at 6 months (PFS-6) and confirmed objective response rate (ORR).

Methods. Women who received ≥1 platinum-based chemotherapeutic regimen and had a platinum-free interval of <12 months with measurable disease were eligible. Patients received 8 mg/kg ramucirumab intravenously every 2 weeks.

Results. Sixty patients were treated; one patient remained on study as of September 2013. The median age was 62 years (range: 27–80), and median number of prior regimens was 3. Forty-five (75%) patients had platinum refractory/resistant disease. Thirty-nine patients (65.0%) had serous tumors. PFS-6 was 25.0% (n = 15/60, 95% CI: 14.7–37.9%). Best overall response was: partial response 5.0% (n = 3/60), stable disease 56.7% (n = 34/60), and progressive disease 33.3% (n = 20/60). The most common treatment-emergent adverse events possibly related to study drug were headache (65.0%; 10.0% Grade ≥3), fatigue (56.7%; 3.3% Grade ≥3), diarrhea (28.3%; 1.7% Grade ≥3), hypertension (25.0%; 3.3% Grade ≥3), and nausea (20.0%; no Grade ≥3). Two

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patients experienced intestinal perforations (3.3% Grade ≥3). Pharmacodynamic analyses revealed changes in several circulating VEGF proteins following initial ramucirumab infusion, including increased VEGF-A, PlGF and decreased sVEGFR-2.

Conclusions. Although antitumor activity was observed, the predetermined efficacy endpoints were not met.

Introduction

In 2013, ovarian cancer was the leading cause of death among cancers of the female reproductive system in the United States with approximately 14,000 deaths [1]. The current standards of care for a majority of patients are surgery and platinum-based chemotherapy. However, platinum-resistance develops frequently and investigation of new treatment options remains a priority.

One strategy to limit cancer growth is inhibition of angiogenesis; this is regulated by complex mechanisms and includes the interaction of vascular endothelial growth factors (VEGFs) and the VEGF receptors [2,3]. Interaction of VEGF-A (hereafter referred to as VEGF) with the VEGF Receptor-2 (VEGFR-2) is a critical mediator of angiogenesis and disruption of this interaction inhibits blood vessel formation and tumor growth [4–7]. Given the proof-of-concept provided by the use of the antiangiogenic antibody bevacizumab as a single agent among patients with platinum-resistant and -refractory ovarian cancer [8,9], the use of an investigational antiangiogenic agent as a single agent in this study was deemed appropriate.

Ramucirumab (IMC-1121B; LY3009806) is a fully human IgG1 monoclonal antibody that binds with high affinity to the extracellular domain of the human VEGFR-2 and blocks the interaction of VEGF ligands (VEGF, VEGF-C, and VEGF-D) [10–13]. As a result, ramucirumab inhibits ligand-stimulated activation of VEGFR-2, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells [13] and is being investigated in several types of cancer.

Two phase I studies of ramucirumab evaluated doses ranging from 2 mg/kg/week to 20 mg/kg/3 weeks [10,11]. Thirty-seven patients were enrolled in the first dose-escalation study in which a weekly maximum tolerated dose (MTD) was identified as 13 mg/kg and 30% of patients had confirmed partial response (PR) or stable disease (SD) lasting ≥24 weeks [10]. A second study evaluated every 2- and every 3-week dosing schedules and enrolled 25 patients, 60% of whom had a best response of SD; median duration of SD was 12.7 months and no MTD was identified [11].

We report the results of a phase II study of ramucirumab in patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. The primary objective was to determine the proportion of treated patients without disease progression at 6 months (PFS-6) and the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors Version 1.0 (RECIST v1.0) [14]. Secondary objectives included an analysis of safety and tolerability, progression-free survival (PFS), 1-year survival rate, and overall survival (OS).

Patients and methods

Ethics statement

This trial followed the guiding principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonisation. All patients provided written informed consent. Each institution's Institutional Review Board/Ethics Committee approved the protocol and informed consent form.

Patients

Eligible patients were female, age ≥18 years, with histologically confirmed persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Patients had at least one measureable target lesion as defined by RECIST v1.0 [14], at least one previous platinum-based treatment regimen and performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale. A platinum-free interval of <12 months after last platinum-based therapy, disease progression, or persistent disease during platinum-based therapy was required. Required laboratory parameters included adequate hematopoietic function defined as: absolute neutrophil count $\geq 1.2 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; hemoglobin ≥9 g/dL; adequate renal function defined as: proteinuria ≤1+; serum creatinine ≤1.5 × upper limits of normal (ULN); and adequate hepatic function defined as: bilirubin ≤1.5 × ULN; alanine transaminase and/or aspartate transaminase (ALT or AST) ≤3.0 × ULN (except for patients with liver involvement, for whom ≤5.0 × ULN was acceptable). Adequate coagulation function was required as defined by international normalized ratio ≤1.5 and a partial thromboplastin time ≤1.5 × ULN if not receiving anticoagulation therapy. Patients had discontinued hormonal therapy at least 7 days prior to first dose of study drug and other prior therapies at least 21 days prior to the first dose.

Exclusion criteria included: concurrent active second malignancy; prior non-cytotoxic regimen for recurrent or persistent disease (except as first-line treatment); intraperitoneal chemotherapy or abdominal/pelvic radiation in the prior 3 years for reasons other than ovarian cancer treatment; abdominal surgery within the prior 4 weeks; impending or current bowel obstruction; previous ramucirumab; clinical trial participation within the prior 4 weeks; bleeding diathesis; ongoing infection; brain metastases or leptomeningeal disease; HIV infection; pregnancy or lactation.

Study design

This was a single-arm, open-label, multicenter Phase II study. Ramucirumab was administered at 8 mg/kg via intravenous infusion on days 1 and 15 of a 28-day cycle until disease progression, unacceptable toxicity, or other withdrawal criteria were met. Ramucirumab was discontinued for: Grade ≥3 infusion-related reaction, Grade ≥3 arterial thromboembolic event, Grade ≥3 venous thromboembolic event, Grade ≥3 bleeding (as defined by CTCAE v3.0), or other events resulting in 2 dose level reductions or dose delay for more than 28 days or a decline in ECOG performance status of ≥2 points. Patients could have received a reduced dose of ramucirumab of 6 mg/kg every other week for an initial dose reduction, and a lower 5 mg/kg every-other-week dose (second dose reduction) for grades 3–4, reversible and non-life-threatening adverse events, as well as for symptomatic hypertension responsive to therapy and proteinurea (2–3 g/24 h) requiring postponement of ramucirumab infusion. Primary endpoints were PFS-6 and ORR.

Disease status and antitumor activity

Disease status was defined as follows: platinum refractory: progressive disease while on first-line platinum therapy; primary platinum resistant but not refractory: progressive disease 0 to 6 months after the last dose of first-line platinum therapy; secondary platinum resistant: