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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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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 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.

Keywords

Angiogenesis; Antiangiogenic; VEGF; Clear cell; Resistant

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 measurable 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 $1.2 \times 10^9/L$; platelets $100 \times 10^9/L$; hemoglobin 9 g/dL ; adequate renal function defined as: proteinuria 1+; serum creatinine $1.5 \times$ upper limits of normal (ULN); and adequate hepatic function defined as: bilirubin $1.5 \times$ ULN; alanine transaminase and/or aspartate transaminase (ALT or AST) $3.0 \times$ ULN (except for patients with liver involvement, for whom $5.0 \times$ ULN was acceptable). Adequate coagulation function was required as defined by international normalized ratio 1.5 and a partial thromboplastin time $1.5 \times$ 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 proteinuria (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: progressive disease either on or within 6 months after second-line (or beyond) platinum therapy; and platinum sensitive: progression-free interval of >6 months from the last platinum dose (any line of therapy). Tumor status was assessed by computerized tomography (CT) scans and/or magnetic resonance imaging every 2 cycles. Direct measurement of palpable or visible lesions was permitted when feasible (RECIST v1.0 Guidelines) [14]. Performance status (ECOG) was assessed on day 1 of each cycle.

Pharmacodynamic assessments

For the assessment of potential pharmacodynamic markers, blood samples were drawn for immunogenicity analysis prior to the initial infusion (obtained within 14 days prior to the first infusion of study therapy), prior to the initial infusions in cycles 2 and 3, and at the 30-day follow-up visit. The following analytes were assayed via electrochemiluminescence assay: VEGF, placental growth factor (PIGF), VEGF-C, VEGF-D, soluble vascular endothelial growth factor receptor-1 (sVEGF Receptor 1; also known as sFlt-1), soluble VEGF Receptor 2 (sVEGF Receptor 2; also known as KDR), angiopoietin-1, angiopoietin-2, basic fibroblast growth factor (bFGF; also known as FGF2), hepatocyte growth factor (HGF), interleukin-12 (IL-12), interleukin-4 (IL-4), interleukin-8 (IL-8), intercellular adhesion molecule-1 (ICAM-1), intercellular adhesion molecule-3 (ICAM-3), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, thrombomodulin, serum amyloid A (SAA), C-reactive protein (CRP), stromal cell-derived factor-1 alpha (SDF 1a), and C-KIT. In addition, platelet factor 4 (PF-4) levels were measured by a capture enzyme-linked immunosorbent assay.

Data and statistical analyses

Efficacy and safety analyses were performed on all enrolled patients who received ramucirumab. The two primary efficacy endpoints were PFS-6 and ORR using RECIST v1.0 criteria. This study had a two-stage design. The null hypothesis was $H_0: \pi_R = 0.10$ and $\pi_S = 0.15$, where π_R is the probability of responding and π_S is the proportion of patients with PFS ≥ 6 months. The alternative analysis was that $\pi_R = 0.25$ and $\pi_S = 0.35$. The sample sizes were 23 and 55 (accumulative) at stage 1 and stage 2, respectively, to achieve 95% power at approximately 10% significant level. Due to the rapid enrollment, 60 patients were enrolled and treated, with rejection of the null hypothesis requiring ≥ 15 patients to be progression-free at 6 months or ≥ 10 patients with complete response or PR.

Secondary endpoints were safety, PFS, OS, and 1-year survival. Kaplan–Meier method was used to estimate the median PFS, 6-month PFS rate (distinct from the primary PFS-6 assessment), median OS, and 1-year survival rate, including 95% confidence intervals (CIs) [15].

Results

Patient demographics and treatment

Seventy-three patients were enrolled (enrollment began August 2008 and the last patient began treatment in September 2009) and 60 patients received at least one dose of ramucirumab. All patients had persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Fifty-two patients were white, five were black (African American), and three patients were Egyptian, Indian, or Jamaican. The median age was 62 years. Twenty-seven patients (45.0%) received ≤ 2 and 24 patients (40.0%) received > 3 regimens of prior therapy. Previous treatments, ECOG status, and degree of platinum resistance are summarized in Table 1. The median number of infusions was 6.5 (range: 1–85).

Toxicity

The most common treatment-emergent adverse events (TEAE) considered at least possibly related to study drug were headache (65.0%; Grade 3/4 10.0%), fatigue (56.7%; Grade 3/4 3.3%), diarrhea (28.3%; Grade 3/4 1.7%), hypertension (25.0%; Grade 3/4 3.3%), and nausea (20.0%; Grade 3/4 0%) and are summarized in Table 2. No patients died while on study drug. Five patients died within 30 days of last dose of study drug (neoplasm progression n = 4, intestinal perforation n = 1). The presence of a large complex pelvic mass present at baseline (probable primary tumor) and an obstructing tumor mass seen in immediate proximity to the perforation (identified during surgery at the time of event) and extensive prior therapy were considered by the investigator to be contributing factors to the grade 5 intestinal perforation.

Twenty-two (36.7%) of the 60 patients who received study drug experienced a treatment-emergent serious adverse event (SAE). There were two patients who had intestinal perforation and three who had small bowel obstruction. One patient experienced Grade 5 intestinal perforation on day 49, approximately 20 days after the last dose of ramucirumab, detailed above, and a second patient experienced Grade 4 intestinal perforation on study days 47–50. A CT scan of this patient showed extensive peritoneal carcinoma. Three patients experienced SAEs of Grade 3 small intestine obstruction, all were considered unrelated to study drug. Each of the following SAEs were experienced by a single patient: Grade 1 mitral valve incompetence; Grade 3 elevated liver enzymes, acute renal failure, peripheral edema, thrombocytopenia, neuralgia, deep vein thrombosis; Grade 4 elevated ALT and perforated bowel. In addition, one patient had Grade 3 elevated liver enzymes.

Seven (11.7%) patients discontinued ramucirumab due to adverse events (AE), including 4 (6.7%) who discontinued due to AEs considered at least possibly related to ramucirumab that included: Grade 1 increased creatinine, Grade 2 proteinuria, Grade 3 increased AST and ALT (1 patient), and Grade 4 intestinal perforation.

Antitumor activity

PFS-6 was 25.0% [95% CI: 14.7–37.9%], identified in 15 of the 60 patients who received investigational therapy (Table 3). The ORR was 5% (95% CI: 1.0–13.9%); three patients had confirmed partial responses (PRs). The durations of response for these three patients were 3.7, 5.6 and 17.5 months. One patient began ramucirumab in January 2009 and remained on study drug as of September 2013. This patient was 60 years of age with mixed serous and clear cell ovarian carcinoma and metastases involving lymph node only. Of the 33 patients (55% of population receiving ramucirumab) who experienced some degree of tumor burden reduction, 12 patients had platinum-refractory or primary platinum-resistant disease. Changes in tumor size at time of best overall response are summarized in Fig. 1C and are categorized by platinum status.

The median PFS per Kaplan–Meier calculation was 3.5 months (95% CI: 2.3–5.3) and the 6-month PFS rate was 33.5% (95% CI: 21.0–46.4%) (Table 3). The difference between the primary endpoint of PFS-6 and the 6-month PFS rate is due to nine patients whose data were censored in the Kaplan–Meier analysis before 6 months; these patients are considered as

having disease progression for the analysis of PFS-6. Subgroup analysis of the 15 patients with platinum-sensitive disease indicated a median PFS of 3.9 months (95% CI: 2.5–21.0) and PFS-6 of 20.0% (95% CI: 4.3–48.1). The median PFS in the 45 patients with platinum-resistant or refractory disease was 3.2 months (95% CI: 1.8–3.7) and the PFS-6 was 26.7% (95% CI: 14.6–41.9) (Table 3). There were 11 patients (18.2%) who received bevacizumab as prior therapy and they had a 6-month PFS rate of 18.2% (95% CI: 2.9–44.2) as estimated by Kaplan–Meier analysis with a median PFS of 3.4 months (95% CI: 1.6–3.7). The 49 patients (82%) who did not receive prior bevacizumab had a 6-month PFS rate of 37.8% (95% CI: 23.2–52.4%) and a median PFS of 3.5 months (95% CI: 2.3–6.8).

Median overall survival (OS) was 11.1 months (95% CI: 8.3–17.0) (Table 4 and Fig. 1A). Subgroup analysis of the 15 patients with platinum sensitive disease and 45 patients with platinum-resistant or refractory disease indicated a median OS of 40.2 months (95% CI: 6.5–43.9) and 10.0 months (95% CI: 7.7–15.2), respectively (Table 4 and Fig. 1B). Patients who received prior bevacizumab and patients who did not receive prior bevacizumab had a median OS of 7.7 months (95% CI: 1.9–28.5) and 13.6 months (95% CI: 9.9–17.4), respectively.

Pharmacodynamic analyses and results

Pharmacodynamic analyses were performed on the translational research population, which consists of patients from selected centers (n = 22) from whom appropriate consent was obtained and who had at least one sample (from any collection time point) assayed for pharmacodynamic levels. Trend plots reveal that serum levels of VEGF and PlGF increased following ramucirumab administration (Fig. 2A, B). Increases in PlGF were pronounced, with cycle 3 levels in some patients exceeding 10× baseline (the largest increase in VEGF was approximately 8 times baseline by cycle 3). Levels of sVEGFR-2 decreased following ramucirumab administration (Fig. 2C).

Discussion

Tumors are dependent on angiogenesis, the formation of new blood vessels and lymphatics, for nutrition and growth. This process promotes metastases and contributes to sequelae such as ascites production [16]. Because of the key role of angiogenesis in tumor progression, inhibition of the VEGF pathway is a major area of interest in the development of novel agents, but there has yet to be a demonstrable impact on survival in ovarian cancer [17]. Potential advantages of anti-angiogenic drugs include non-cytotoxic mechanism of action, slower development of resistance given the endothelium's stable genome, normalization of vasculature with potential to enhance chemotherapy, and potential promotion of tumor dormancy. Although these agents are more likely to confer SD (as opposed to response), the associated therapeutic index may be favorable because toxicity is less substantial than with chemotherapy [18,19].

Ramucirumab is a novel human monoclonal antibody that inhibits angiogenesis by binding to the extracellular domain of VEGFR-2 and has recently received approval by the U.S. Food and Drug Administration as the first VEGFR-2 antagonist to treat patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single-agent

after prior fluoropyrimidine- or platinum-containing chemotherapy. In gastric cancer, patients treated with ramucirumab experienced a statistically significant increase in median OS and PFS compared to those treated with placebo [20].

In this open-label phase II trial in patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinomas, we report an ORR of 5.0%, disease control rate of 61.7% and a PFS-6 of 25.0% (95% CI: 14.7–37.9%). Patients who received ramucirumab largely experienced expected anti-angiogenic class toxicities including an intestinal perforation. Headache was observed in 71.7% of patients (n = 43; 10.0% Grade 3, no Grade >3); this was higher than the incidence in other reported phase I and II studies with ramucirumab. Most patients recovered without any intervention or with concurrent medications; however, 9 patients reported ongoing headaches at the end of the study. Blood pressure elevations may have contributed to this; however, this is unlikely to be the sole explanation. Headache was seen in 92% of those with Grade 2 hypertension and 67% of those without. The relatively modest sample size of this single-arm Phase 2 study, in addition to the significantly lower incidence of headache observed in a larger pooled analysis of most common related AEs observed in other reported phase I and II studies with ramucirumab, makes it uncertain that the incidence of headache observed in the present study reflects the overall safety profile of ramucirumab.

Many anti-angiogenic agents are in development in ovarian cancer; the anti-VEGF humanized monoclonal antibody bevacizumab has been the most extensively studied. Bevacizumab as a single agent in recurrent disease is associated with a similar median PFS of 4.4–4.7 months [8,9]. Phase II trials are notoriously prone to selection bias, yet the response rate to bevacizumab has been similar across studies, even in relatively heavily pre-treated patients [9]. It has yet to be determined whether targeting the ligand triggers physiologic change and different resistance mechanisms relative to targeting the receptor. The rapid rise in VEGF levels observed in this study supports such a hypothesis, though many mechanisms are likely to contribute to clinical progression [21–23]. The extensive prior therapy and substantial proportion of patients with platinum refractory/primary platinum resistant disease in the current study also render cross-trial comparison difficult. At the time this study was implemented, data on the number of prior lines predicting risk of GI perforation were only emerging [9,24]. Many studies now have more stringent eligibility criteria, and the number of prior therapy lines in this study (median 3, range 1–14) very likely contributed to the risk of GI toxicity with increasing bowel involvement by peritoneal tumor.

In summary, we report activity with ramucirumab (median PFS of 3.5 months) in a relatively heavily pretreated population of patients with recurrent ovarian cancer. Although antitumor activity was observed, this study failed to meet the predetermined efficacy end-points. Future investigations with this agent in ovarian cancer are warranted if biological or clinical features associated with benefit can be identified.

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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.

Fig. 1. Overall survival and tumor change for all treated patients (N = 60). (A) Overall survival of patients receiving ramucirumab. (B) Overall survival of patients correlated with platinum sensitivity. (C) Best percent change in tumor size for all treated patients (N = 60).

Fig. 2. Fold change in serum analyte concentration levels in the translational research population (n = 22). Fold change of serum levels of (A) VEGF, (B) PlGF, and (C) sVEGFR-2 over time. Levels below the lower limit of quantitation were imputed as 0.5× minimum level of the analyte across all time points and across all patients.

Table 1

Demographics, disposition, and baseline characteristics.

	n	(%)
Number of patients		
Enrolled	73	100
Treated	60	82.2
On study therapy as of Sept 13	1	1.7
Off study therapy as of Dec 11	59	98.3
Age (years)		
18–50	11	15.1
51–60	22	30.1
61–70	28	38.4
>70	12	16.4
Median age (range)	62	27–80
ECOG PS		
0	29	48.3
1	31	51.7
Ovarian cancer grade		
Well differentiated	3	5.0
Moderately differentiated	9	15.0
Poorly differentiated/undifferentiated	38	63.3
Unknown	10	16.7
Histology		
Serous	39	65
Clear cell	7	11.7
Endometrioid	4	6.7
Mixed epithelial	4	6.7
Other — mixed serous & clear cell	2	3.3
Unknown/missing	2	3.3
Other	2	3.3
Primary platinum resistance		

	n	(%)
Platinum refractory	7	11.7
Primary platinum resistant, not refractory	19	31.7
Secondary platinum resistant	19	31.7
Platinum sensitive	15	25.0
Number of prior regimens		
Median (range)	3	1–14
Number of prior platinum regimens		
Median (range)	2	1–4
Pts with 1 prior platinum regimen	17	28.3
Pts with 2 prior platinum regimens	30	50.0
Pts with 3 prior platinum regimens	13	21.7
Previous therapy		
Chemotherapy	60	100
Surgery	60	100
Biological	12	20.0
Hormonal	6	10.0
Immunotherapy	2	3.3
Radiotherapy	3	5.0
Other	9	15.0
Site of metastatic disease (>5%)		
Lymph Nodes	40	66.7
Peritoneum	39	65.0
Liver	25	41.7
Soft tissue	21	35.0
Lung	19	31.7
Pleura	6	10.0
Bone	2	3.3

Platinum resistance was retrospectively assessed based on the following definitions: refractory = PD while on 1st-line platinum therapy. 1° resistant, not refractory = PD 0–6 months after last dose of 1st-line platinum. 2° resistance = PD on or within 6 months of 2nd-line (or beyond) platinum therapy. Sensitive = PF interval >6 months from last platinum dose.

Table 2

Treatment-emergent AEs in at 10% of patients (N = 60, safety population).

Adverse event	All grades			Grade 3/4			Grade 5		
	All TEAE			All TEAE			All TEAE ^a		
	n	%	n	%	n	%	n	%	n
Patients with AEs	59	98.3	56	93.3	25	41.7	5.0	5	8.3
Anemia	12	20.0	7	11.7	1	1.7	0	0	0
Thrombocytopenia	6	10.0	4	6.7	3	5.0	2	3.3	0
Abdominal distention	7	11.7	1	1.7	0	0	0	0	0
Abdominal pain	13	21.7	6	10.0	1	1.7	1	1.7	0
Constipation	13	21.7	5	8.3	0	0	0	0	0
Diarrhea	21	35.0	17	28.3	1	1.7	1	1.7	0
Dyspepsia	6	10.0	4	6.7	0	0	0	0	0
Gingival bleeding	6	10.0	3	5.0	1	1.7	1	1.7	0
Nausea	26	43.3	12	20.0	3	5.0	0	0	0
Stomatitis	11	18.3	10	16.7	0	0	0	0	0
Weight decreased	9	15.0	4	6.7	0	0	0	0	0
Vomiting	20	33.3	11	18.3	2	3.3	0	0	0
Fatigue	41	68.3	34	56.7	5	8.3	2	3.3	0
Peripheral edema	17	28.3	8	13.3	1	1.7	1	1.7	0
Pyrexia	9	15.0	4	6.7	1	1.7	0	0	0
Urinary tract infection	13	21.7	4	6.7	0	0	0	0	0
Anorexia	12	20.0	8	13.3	1	1.7	0	0	0
Hypoglycemia	7	11.7	4	6.7	1	1.7	0	0	0
Hypomagnesemia	6	10.0	4	6.7	0	0	0	0	0
Arthralgia	11	18.3	4	6.7	1	1.7	1	1.7	0
Back pain	9	15.0	2	3.3	0	0	0	0	0
Myalgia	7	11.7	6	10.0	0	0	0	0	0
Pain in extremity	7	11.7	3	5.0	0	0	0	0	0
Dizziness	7	11.7	5	8.3	0	0	0	0	0

Adverse event	All grades		Grade 3/4				Grade 5	
	All TEAE		Related TEAE		All TEAE		Related TEAE	
	n	%	n	%	n	%	n	%
Headache	43	71.7	39	65.0	6	10.0	6	10.0
Insomnia	7	11.7	1	1.7	0	0	0	0
Proteinuria	8	13.3	7	11.7	0	0	0	0
Cough	13	21.7	2	3.3	0	0	0	0
Dysphonia	6	10.0	2	3.3	0	0	0	0
Dyspnea	12	20.0	4	6.7	2	3.3	0	0
Epistaxis	8	13.3	8	13.3	1	1.7	1	1.7
Hypertension	16	26.7	15	25.0	2	3.3	2	3.3

Abbreviations: PT = platinum therapy; SOC = system organ class; TEAE = Treatment Associated Adverse Event.
Patients experiencing > 1 AE within a PT or SOC were only counted once for that PT or SOC for the worst grade experienced by the patient.

^aThere were no Grade 5 TEAEs related to study drug.

Table 3

Best overall response and duration of response.

	All patients		Platinum sensitivity		Prior bevacizumab	
	Safety population		Platinum sensitive		Yes bevacizumab	
	N = 60	N = 15	N = 45	N = 49	N = 11	N = 49
PFS-6 ^a	25.0%	20.0%	26.7%	18.2%	26.5%	
95% CI	14.7–37.9	4.3–48.1	14.6–41.9	2.3–51.8	14.9–41.1	
6-month PFS ^b	33.5%	33.7%	32.6%	18.2%	37.8%	
95% CI	21.0–46.4	9.4–60.6	18.8–47.3	2.9–44.2	23.2–52.4	
Median PFS	3.5	3.9	3.2	3.4	3.5	
95% CI	2.3–5.3	2.5–21.0	1.8–3.7	1.6–3.7	2.3–6.8	
Best overall response	n %	n %	n %	n %	n %	
Complete response (CR)	0 0	0 0	0 0			
Partial response (PR)	3 5.0	1 6.7	2 4.4			
Stable disease (SD)	34 56.7	11 73.3	23 51.1			
Progressive disease (PD)	20 33.3	3 20.0	17 37.8			
Not evaluable (NE)	3 5.0	0 3	6.7			
Objective response rate (CR + PR)	3 5.0	1 6.7	2 4.4			
95% CI	1.0–13.9	0.2–31.9	0.5–15.1			
Median duration of response (months)	5.6	17.5	4.7	3.4	3.5	
95% CI	3.7–17.5	n/a	3.7–5.6	1.6–3.7	2.3–6.8	
Disease control rate (CR + PR + SD)	37 61.7	12 80.0	25 55.6			
95% CI	48.2–73.9	51.9–95.7	40.0–70.4			

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; PFS = Progression Free Survival.

^aProportion of treated patients without disease progression at 6 months.

^bEstimated by Kaplan–Meier method.

Table 4

Overall survival.

	All patients		Platinum sensitivity		Prior bevacizumab		No bevacizumab	
	Safety population		Platinum sensitive		Yes bevacizumab		No bevacizumab	
	N = 60		N = 15		N = 45		N = 49	
	n	%	n	%	n	%	n	%
Number of deaths	48	80.0	8	53.3	40	88.9	39	79.6
Median overall survival time (months)	11.1		40.2		10.0	7.7	13.6	
95% CI	8.3–17.0		6.5–43.9		7.7–15.2	1.9–28.5	9.9–17.4	
1-year survival rate (%)	48.0		72.7		40.0	36.4	50.6	
95% CI	34.9–59.9		42.5–88.8		25.8–53.8	11.2–62.7	35.8–63.6	

Abbreviation: CI = confidence interval.