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Phase II trial of bevacizumab and sorafenib in recurrent ovarian cancer patients with or without prior-bevacizumab treatment

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Abstract

Objective—To examine whether blocking multiple points of the angiogenesis pathway by addition of sorafenib, a multi-kinase inhibitor against VEGFR2/3, Raf, c-Kit, and PDGFR, to bevacizumab would yield clinical activity in ovarian cancer (OvCa).

Methods—This phase II study tested bevacizumab plus sorafenib in two cohorts; bevacizumab-naïve and bevacizumab-exposed patients. Bevacizumab (5mg/kg IV every 2weeks) was given with sorafenib 200mg bid 5days-on/2days-off. The primary objective was response rate using a Simon two-stage optimal design. Progression-free survival (PFS) and toxicity were the secondary

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Conflict of interest statement

All authors declared no conflicts of interest.

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endpoints. Exploratory correlative studies included plasma cytokine concentrations, tissue proteomics and dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI).

Results—Between March 2007 and August 2012, 54 women were enrolled, 41 bevacizumab-naïve and 13 bevacizumab-prior, with median 5 (2–9) and 6 (5–9) prior systemic therapies, respectively. Nine of 35 (26%) evaluable bevacizumab-naïve patients attained partial responses (PR), and 18 had stable disease (SD) 4 months. No responses were seen in the bevacizumab-prior group and 7 (54%) patients had SD 4 months, including one exceptional responder with SD of 27 months. The overall median PFS was 5.5 months (95%CI: 4.0–6.8 months). Treatment-related grade 3/4 adverse events (5%) included hypertension (17/54 [31%]; grade 3 in 16 patients and grade 4 in one patient) and venous thrombosis or pulmonary embolism (5/54 [9%]; grade 3 in 4 patients and grade 4 in one patient). Pretreatment low IL8 concentration was associated with PFS 4 months ($p=0.031$).

Conclusions—The bevacizumab and sorafenib combination did not meet the pre-specified primary endpoint although some clinical activity was seen in heavily-pretreated bevacizumab-naïve OvCa patients with platinum-resistant disease. Anticipated class toxicities required close monitoring and dose modifications.

1. Introduction

Angiogenesis is crucial in the persistence and the spread of cancer cells within the peritoneum in epithelial ovarian cancer (EOC) [1]. Active vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway promotes motility, migration, and dissemination of ovarian tumor cells to bordering organs and tissues. EOC has higher expression of VEGF, VEGFR-1, and VEGFR-2 than normal ovarian human tissue samples do [2, 3]. Consistently, anti-VEGF treatments have been an effective strategy for controlling tumor growth in EOC via downregulating angiogenic and other growth signaling pathways [3, 4].

Bevacizumab is a recombinant humanized monoclonal antibody that binds to all isoforms of the VEGF-receptor (VEGFR) ligand VEGF-A [3]. Single agent VEGF or VEGFR blockades have demonstrated modest activity against recurrent EOC [5], which thus led to the introduction of antiangiogenic therapy combinations with chemotherapy or other biologic agents [6]. Bevacizumab is now Food and Drug Administration (FDA) and European Medical Agency (EMA) approved, as in combination with chemotherapy for women with recurrent disease or with chemotherapy followed by maintenance as bevacizumab alone or with a PARP inhibitor olaparib for subsets of patients with newly diagnosed advanced EOC [7, 8].

One of the challenges of using VEGFR blockades is that tumor endothelial cells eventually adapt to VEGF/VEGFR pathway inhibition by promoting angiogenesis via other secondary signaling pathways, such as those induced by platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), or other cytokines [9]. Thus, it has been hypothesized that VEGF/VEGFR pathway activation and downstream signaling activation could be prevented by small molecule tyrosine kinase inhibitors (TKIs) [10]. This hypothesis has been tested in clinical trials using VEGFR TKI either alone or in combination for recurrent ovarian cancer [11].

Sorafenib is a multi-kinase inhibitor of b-Raf, c-Raf, and also targets p38, c-kit, VEGFR-2 and 3, and PDGFR- β [12]. It is therefore able to regulate metastasis, invasion, and apoptosis through inhibition of the Ras/Raf/MEK/ERK pathway and also exerts antiangiogenic effects through its activity against VEGFR and PDGFR- β [13]. Sorafenib is currently registered for the treatment in advanced renal cell carcinoma and hepatocellular carcinoma [14, 15], as well as locally recurrent/metastatic progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment [16]. We previously demonstrated the early clinical activity of the combination of bevacizumab and sorafenib in EOC with a recommended Phase II dose of bevacizumab 5 mg/kg every 2 weeks and sorafenib 200 mg bid 5 days on/ 2 days off [17, 18]. We now report the results of bevacizumab plus sorafenib in heavily pretreated recurrent EOC patients with biomarker analysis. We also report the prospectively evaluated activity of the combination treatment in those who received prior bevacizumab.

2. PATIENTS AND METHODS

2.1 Eligibility criteria

Eligible patients were aged ≥ 18 years and had histologically confirmed recurrent or metastatic EOC, fallopian tube cancer, or primary peritoneal cancer. Patients must have had measurable disease based on RECIST v1.0 criteria and at least one lesion safely accessible for a mandatory percutaneous baseline biopsy. Other key inclusion criteria included Eastern Cooperative Oncology Group performance status 0 or 1, controlled blood pressure $\leq 150/90$ mmHg and good organ function with absolute neutrophil count $\geq 1200/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, creatinine $\leq 1.5\text{mg/dL}$, and aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times institutional upper limit of normal, urinary protein/creatinine ratio (UPC) <1.0 , and normal lipase and amylase. There was no limit on the number of prior regimens. Patients who have been treated with bevacizumab either alone or in combination previously were eligible for the bevacizumab-prior cohort and must have been at least 6 weeks from the last dose of bevacizumab prior to study enrollment.

Key study exclusion criteria included anticancer therapy ≤ 4 weeks before first doses of study drugs (6 weeks for mitomycin C, carboplatin or nitrosoureas) and persistent AEs from prior anticancer therapy $\geq$ grade 2 per Common Terminology Criteria for Adverse Events version (CTCAE) version 4 with exception of stable grade 2 peripheral neuropathy. Patients with central nervous system (CNS) metastases ≤ 2 years prior to enrollment were not eligible. Additional exclusion criteria included signs and/or symptoms of bowel obstruction ≤ 28 days and thrombotic or embolic cardiovascular, pulmonary, CNS events ≤ 6 months, or concomitant or prior invasive malignancies ≤ 2 years prior to enrollment.

2.2. Study design

This open-label, single arm, investigator-initiated phase II trial was approved by the National Cancer Institute (NCI) Institutional Review Board ([NCT00436215](#)). All patients provided written informed consent before enrollment. The primary end point was the objective response rate based on RECIST version 1.0. The secondary end points included toxicity and progression free survival (PFS). The protocol was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice.

2.3. Drug administration and supportive care

Patients received sorafenib 200 mg every 12 hours on days 1–5 of a 7 day-week and bevacizumab 5 mg/kg intravenously every 2 weeks as defined by prior phase I study [17, 18]. Four weeks constituted one treatment cycle. Blood pressure was monitored at least daily for the first 2 cycles and upon therapeutic intervention for hypertension. Patients were encouraged to use emollients liberally on hands and feet to reduce severity of hand-foot syndrome (HFS) [19] and also received pyridoxine starting at 50 mg twice daily, escalating to 250 mg twice daily as tolerated and if beneficial for HFS.

2.4. Assessment

Patients were seen prior to each of the first 4 bevacizumab administrations and at least monthly during the study for history, physical examination, and safety evaluation. Reassessment imaging with computed tomography or MRI scan was done every 2 cycles, approximately 8 weeks. Hematology, blood chemistry, and liver function evaluations were performed before each treatment cycle. Toxicity was graded according to the NCI CTCAE version 4.0.

2.5. Correlative studies—Timepoints for the correlative endpoints are shown in Supplementary Figure 1a.

2.5.1. Plasma cytokine concentrations—Blood samples at baseline and on cycle 2 day 1 (+/– 2 days, approximately 4 weeks on treatment) were collected into EDTA tubes, separated within 2 hours, and stored in aliquots at –80°C until use. Quantitative analysis of plasma VEGF, IL-6, IL-8 and soluble VEGFR2 concentrations were performed using clinically validated custom V-PLEX assay plates on an electrochemiluminescence (ECL) platform, according to manufacturer's instructions (Meso Scale Discovery, Gaithersburg, MD) [20]. Purified recombinant proteins and reference samples were included in all assays for standard curves, performance validation, and for determining analyte concentrations in the plasma samples.

2.5.2. Tumor proteomics—A pre-treatment fresh percutaneous core biopsy was mandatory for all patients and second biopsy on cycle 2 day 15 (+/– 2 days, approximately 6 weeks into treatment) was optional. Biopsies were obtained by interventional radiologists under CT or ultrasound guidance using local anesthesia. Tissue samples were immediately frozen in optimal cutting temperature compound and maintained at –80°C until sectioned. Optimal quality of tissue was defined as core biopsy samples with solid tissue areas containing at least 50% tumor cells and less than 25% necrosis [21]. Tissue was lysed, frozen, and subjected to reverse phase protein microarrays (RPPA) and quantified by the MD Anderson RPPA Core facility [22] (Supplementary Table 1).

2.5.3. Dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI)—DCE-MRI was performed to assess changes in vascular permeability (K_{trans}) and perfusion (K_{ep}) at baseline and cycle 1 day 3 of treatment [20]. Region-of-interest MR measurements were obtained from one selected target lesion. MRI data were analyzed using a 2-compartment model based on the general kinetic (GKM) Kety model using commercial

software (iCAD, Nashua NH) as reported [23]. Three parameters derived from the curve fitting GKM algorithm were used to generate quantitative parameters: K_{trans} , the forward contrast transfer rate, k_{ep} , the reverse contrast transfer rate, and V_e , the extravascular, extracellular volume fraction of the tumor.

2.7. Statistical analyses

A Simon two-stage design was used with different parameters for each cohort. The bevacizumab-naïve cohort was designed to rule out a 20% response rate (RR) in favor of a 40% RR using $\alpha=0.10$ and $\beta=0.10$. A response in four or more of the first 17 patients sufficed to move to the second stage of accrual, adding another 20 evaluable patients. The regimen would be considered sufficiently interesting if 11/37 patients had a complete or partial response (PR). The target for the bevacizumab-prior cohort was to reject 5% in favor of 20%, using $\alpha=0.05$ and $\beta=0.10$. At least two responses in 21 patients were required to continue to the second stage, with 20 more patients, yielding a total of 41 patients. In this stratum, 5/41 responses would be considered interesting for further investigation.

The probability of PFS as a function of time was estimated using the Kaplan–Meier method, with a log-rank test to determine the significance of the differences. In this study, death or progression outcomes after off-treatment were not collected in some patients who were taken off study due to AE or withdrawal because follow-up ended 1 month of treatment end-date; thus, the estimates of PFS are based on the best available data. All enrolled patients were included for safety evaluation. Patients considered non-evaluable for response had either no on-treatment CT scan or discontinued within 8 weeks without clinical or radiographic progression.

Correlative study endpoints were exploratory and underwent no correction for multiple testing unless indicated. Paired T-test or Mann-Whitney U-test was used to study the effect of baseline cytokines or DCE-MRI parameters on RECIST response or clinical benefit, and also to evaluate the changes of parameters between pre- and on-treatment (Prism v6.01, GraphPad, San Diego, CA). Normalized, median-centered RPPA values for each protein were analyzed for linear correlation to duration of response for each patient using JMP9 (Cary, NC). The false discovery rate (FDR) was controlled with an alpha of 0.05 by the method of Hochberg to correct for multiple comparisons [24]. Inter-slide reproducibility for the RPPA has been examined by multiple groups and found to be high in tumor tissue and cell lines, with mean coefficients of variation across all antibodies <10% [25].

3. RESULTS

3.1. Patient characteristics

We enrolled 54 eligible women between March 2007 and August 2012, including 41 bevacizumab-naïve and 13 bevacizumab-prior patients. Figure 1 shows the CONSORT diagram for this two-cohort study and patient characteristics are presented in Table 1. Approximately 83% of patients in bevacizumab-naïve cohort and all 13 patients in the bevacizumab-prior cohort had platinum-resistant disease. All were heavily pretreated. All bevacizumab-prior patients had received bevacizumab in the recurrent disease setting, except

one who received it upfront (GOG218 trial) and again for recurrent disease. All but one had bevacizumab in combination with various chemotherapeutic drugs (Table 1).

3.2. Activity

35 bevacizumab-naïve and 13 bevacizumab-prior patients were evaluable for RECIST response because six patients in bevacizumab-naïve cohort were not evaluable for the primary response endpoint, due to small bowel obstruction without increasing size of the masses (cycle 1 [n=2] and cycle 2 [n=1]), small intestinal perforation (cycle 1 [n=1]), grade 4 hypertension (cycle 2 [n=1]) and withdrawal (n=1). Four responses were seen in the first 17 patients, reaching the pre-determined target to move to the second stage. Nine of 35 (26%) of bevacizumab-naïve patients attained PRs; thus, the study did not reach the predefined activity outcome. However, among 29 heavily pretreated platinum-resistant patients in this cohort, seven (24%) achieved a durable PR with a median duration on the study of 14.5 months (range 4 – 18.5 months). These seven patients were heavily pretreated with a median of 5 systemic prior therapies (range 4–7). Overall, the clinical benefit rate (complete response [CR] + PR + stable disease [SD] ≥ 4 months) was 77% (27/35).

No RECIST responses were seen in the previously bevacizumab-exposed patients. Seven of 13 (54%) platinum-resistant patients had SD ≥ 4 months with a median duration on the study of 6.25 months (range 4–27 months). The exceptional responder (27 months) had stage IIC clear cell ovarian cancer and received bevacizumab for recurrent disease at 3 different time points prior to enrollment, either as monotherapy or in chemotherapy combinations.

The overall median PFS was 5.5 months (95% CI: 4.0–6.8 months) (Figure 2), with 6.7 months (95% CI: 4.0–7.8 months) for bevacizumab-naïve and 4.0 months (95% CI: 2.0–6.4 months) for bevacizumab-prior patients, respectively (Supplementary Figure 2).

3.3 Toxicity

All patients who received at least one dose of therapy were evaluable for toxicity (Table 2). Toxicity is reported as the maximum grade toxicity experienced per event per patient during study treatment. Treatment-related grade 3/4 adverse events (AEs) included de novo or worsened hypertension (17/54 [31%]), venous thrombosis or pulmonary embolism (5/54 [9%]), renal arterial hemorrhage (1/54), small intestinal perforation (1/54), anal fissure (1/54), acneiform rash (1/54) and HFS (1/54). All grade 3/4 AEs were seen in bevacizumab-naïve patients, and not in the bevacizumab-prior cohort. There was one grade 4 hypertension, resulting in the discontinuation of both drugs and discontinuation of therapy on cycle 1. Approximately two thirds (36/54 [67%]) of patients required addition of, or increase in, anti-hypertensive therapy while on the study. In addition, HFS resulted in sorafenib reduction to 200mg once daily in 76% of patients at a median of 2 cycles (1–7). The frequency or patterns of hypertension, HFS, mucositis and thrombotic events were consistent with previous reports [17, 18]. There were no treatment-related deaths.

3.4 Correlative studies

Overall, no correlative study endpoints showed a significant association with clinical outcome except baseline IL-8 concentrations. While one patient in the bevacizumab-prior

cohort had a durable SD of 27 months, none of these endpoints suggested a biological cause for this exceptional responder. Supplementary Figure 1b depicts the number of patients participated in biopsy and DCE-MRI.

3.4.1. Cytokine analysis—Plasma samples were evaluated for IL-6, IL-8, VEGF, and soluble VEGFR2 (Figure 3). Pretreatment low IL8 levels were associated with clinical benefit (median 12.88 ng/ml [IQR 7.89–22] vs. 21.26 ng/ml [10.6–52.09], $p=0.031$). No relationships between other cytokines and clinical outcomes were identified. A significant increase in VEGF was observed after treatment (median 33 pg/ml [IQR 4.2–68.2] baseline vs. 204 pg/ml [IQR 10–302.2] on cycle 2 day 1, $p<0.0001$) (Supplementary Table 2).

3.4.2. RPPA—No significant relationship was observed between protein expression and RECIST response or clinical benefit at a FDR of $<5\%$. Also, no significant alterations were noted in VEGF/VEGFR signaling pathways as a function of RECIST response or clinical benefit.

3.4.3 DCE-MRI—Neither changes or baseline values of K_{trans} and K_{ep} were associated with clinical outcome. We observed no significant changes in K_{trans} and K_{ep} values before and on-treatment.

4. DISCUSSION

Angiogenesis is a complex process involving various pathways and regulatory elements within the tumor microenvironment [26]. Thus, it is not surprising that inhibition of a single element within a single pathway, such as VEGFA with bevacizumab, may not reach the level of activity originally hoped. We hypothesized that inhibition at multiple points along angiogenesis pathways could be approached safely and with improved clinical benefit for women with recurrent EOC. We elected to combine bevacizumab with sorafenib for its broader multi-kinase inhibitory activity against VEGFR2/3, Raf, c-kit, and PDGFR, all involved in different aspects of angiogenesis. We identified a dose and schedule that was tolerable and found unanticipated activity in recurrent ovarian cancer patients during our phase I study [17, 18].

Bevacizumab has gone on to be used commonly, raising the question as to whether the doublet activity as seen in the phase I study in bevacizumab-naïve patients, would extend to the patients who previously have had treatment with bevacizumab. The question of the potential benefit of bevacizumab-after-bevacizumab remains pertinent today. In this study, the level of anti-tumor activity seen did not meet the pre-specified level based on the statistical analysis plan. However, it is worth noting that seven (of 29; 24%) patients achieved a durable PR and all had heavily pretreated platinum-resistant disease, supporting the use of antiangiogenic therapies in this population.

Bevacizumab emerged as a novel targeted agent after many reports of a prognostic role of vascularity in EOC and the seminal single arm phase 2 trial in recurrent disease, GOG-0170d, showing 21% RR [27]. Subsequently, phase 3 trials have demonstrated a 2.4 – 3.8 month improvement in PFS with the addition of bevacizumab, not only for patients with

newly diagnosed ovarian cancer (GOG-0218 [3.8 months] [28], ICON7 [2.4 months] [29]), but also for recurrent platinum-sensitive disease (OCEANS [3.0 months] [30], GOG-0213 [3.4 months] [31]), and platinum-resistant disease (AURELIA [3.3 months]) [32]. Of note is that the proportion of bevacizumab-pretreated patients in each of these trials ranged from 0 – 8%, allowing the interpretation of activity in bevacizumab-naïve patients only.

This reinforces the question of when to use bevacizumab in the treatment life-time of an EOC patient and whether or not re-exposure results in second benefits. Our initial results showed 43% (6/13) RR in bevacizumab-naïve EOC patients [17], and by the time of the phase II launch, the issue of bevacizumab pre-exposure was already being questioned, leading to the design of the current trial. Numerous, mostly retrospective, studies have suggested a benefit of re-exposure in the setting of bevacizumab with chemotherapy. Only one study, MITO16B [33], a randomized phase III clinical trial prospectively assessed this question, although still in the setting of concomitant chemotherapy, showing a small but statistically significant benefit of bevacizumab re-exposure (8.8 v 11.8 months; Δ = 3.0288 months; HR=0.51, 95%CI: 0.41–0.64, $p < 0.001$). Furthermore, monotherapy with nintedanib, an oral TKI of VEGFR, FGFR and PDGFR, yielded minimal activity in bevacizumab-exposed ovarian cancer patients [34]. One patient in the current trial, with 3 prior exposures to bevacizumab had prolonged SD to the combination of bevacizumab and sorafenib. None of the correlative studies executed within this phase 2 study, in either naïve or prior treated cohorts shed light into her exceptional response. These results of no benefit in 12 of 13 prior exposed patients is not definitive but should be of concern.

We have observed the class toxicities such as hypertension and HFS, consistent with the results of the phase 1 study. The frequency of grade 3 or 4 hypertension (31% in the present study) was higher compared to each drug alone (6–25% for bevacizumab [35] and 2.5–12.6% for sorafenib [36]). Although hypertension was the most common grade 3 or 4 AE in the current study, the CTCAE grading relates to the number of blood pressure drugs needed for management. Blood pressure elevations were generally asymptomatic for the most patients, except for the one patient with grade 4 hypertension, who was not compliant with instructions for reporting and management of elevated blood pressure. In addition, three quarters of patients still had sorafenib dose reduction to 200mg daily Monday-Friday while the severe HFS was less frequently seen with an intermittent dosing schedule. Close monitoring and counseling for HFS and hypertension management were necessary for compliance.

Our biomarker data also suggest a prognostic association between initial low IL-8 concentrations and better PFS. IL-8 plays an important role in tumor growth and metastasis and is associated with worse prognosis in advanced solid tumors including ovarian cancer [37]. IL-8 activates TAK1/NF κ B signaling in preclinical models via the CXCR2 receptor, thus enhancing ovarian cancer metastatic potential [38]. Also, higher levels of IL-8 in peritoneal fluid or serum have been associated with poor prognosis in ovarian cancer patients [39]. Other circulating cytokines, including IL-6, VEGF, and soluble VEGFR, were not different between the groups in the present study, although they have been reported as prognostic biomarkers in ovarian cancer [40, 41]. Instead, we found an increase of VEGF after treatment, possibly due to counterbalancing the VEGF/VEGFR pathway inhibition, as

shown in our original phase I study [17]. We did not identify any differences in DCE-MRI parameters or proteomic endpoint changes related to the VEGF/VEGFR pathway. This could be due to the limitation of the biopsy size, intratumoral heterogeneity, tissue vs. systemic signaling, and the discriminating capacity of the assay system (DCE-MRI). It is possible that they may have provided early indications of treatment effect even before changes in size can be perceived on CT, requiring further exploration with optimal sample size and time points.

In conclusion, we report the results of the phase 2 study of bevacizumab and sorafenib in heavily-pretreated ovarian cancer patients. The study did not meet the primary end point although potential clinical activity was observed in platinum-resistant bevacizumab-naïve patients. No activity was seen in the bevacizumab-prior cohort. Thus, bevacizumab-after-bevacizumab should be used with a caution in prior exposed patients especially when bevacizumab combined with signal interrupting agents such as TKIs [42]. Further evaluation of biomarker directed therapy is also warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research highlights

- Bevacizumab and sorafenib combination showed modest clinical activity in bevacizumab-naïve recurrent ovarian cancer.
- No RECIST responses were observed in women who had prior bevacizumab.
- The toxicities of bevacizumab and sorafenib combination was manageable with dose reduction, monitoring and counseling.
- Baseline plasma low IL8 levels were associated with clinical benefit.

Figure 1.
Consort diagram

Figure 2. Progression-free survival

Median progression-free survival (PFS) for all patients was 5.5 months (95% CI: 4.0–6.8 months). The censoring times do not reflect additional follow-up; patients were followed at most 1 month post-treatment if treatment was discontinued without progression. Six patients in the bevacizumab-naïve cohort who were not evaluable for the RECIST endpoint were captured for the PFS evaluation. Median follow-up duration was 2.1 months for 9 patients who did not progress during off-treatment follow-up. Thus, these curves reflect the available data only.

Figure 3: Cytokine concentrations at baseline

Pretreatment plasma cytokine concentrations were evaluated as a function of clinical benefit (PR + SD 4months [n=37]) vs no benefit (all others [n=15]) in intention-to-treat patients. Baseline low IL-8 concentrations were associated with clinical benefit **(a)**; other cytokines **(b-d)** did not correlate with clinical outcome.

Table 1.

Patient characteristics (N = 54)

	Bevacizumab- naïve (N=41)	Bevacizumab-prior (N=13)
Age in years, median (range)	57 (27–79)	66 (40–72)
ECOG Performance Status, N (%)		
0	2 (5%)	1 (8%)
1	39 (95%)	12 (92%)
Race/Ethnicity, N (%)		
White	40 (98%)	10 (77%)
Asian	1 (2%)	2 (15%)
African American	0	1 (8%)
Hispanic	0	0
Histology		
High-grade serous ovarian cancer (HGSOC) *	38 (93%)	12 (92%)
Mixed clear cell and HGSOC	2 (5%)	0
Clear cell	0	1 (8%)
Mucinous	1 (2%)	0
Platinum sensitivity ⁺ , N (%)		
Platinum resistant recurrent disease	34 (83%)	13 (100%)
Platinum sensitive recurrent disease	7 (17%)	0
Median number of prior systemic treatment regimens (range) ⁺⁺	5 (2–9)	6 (5–9)
Prior bevacizumab treatment, N (%)	N/A	
Upfront setting only		0
Upfront and recurrent settings		1
Recurrent settings only		12
Bevacizumab monotherapy		0
Both bevacizumab monotherapy and in combination ^{**}		4
Bevacizumab in combination with chemotherapy ^{***} /a PKC inhibitor		8/1
The number of use of bevacizumab-containing regimens prior to enrollment	N/A	
1		5
2		4
3		4
The last dose of bevacizumab prior to study entry	N/A	
6 months		6
> 6 months		7

⁺ Platinum sensitive: recurs 6 or more months after cessation of platinum-based chemotherapy; platinum resistant: progression within 6 months of platinum-based therapy

* HGSOC includes epithelial ovarian, fallopian tubal and primary peritoneal cancers.

⁺⁺ Four patients received a PARP inhibitor olaparib in combination with carboplatin through a clinical trial ([NCT01445418](#)).

** Two separate courses of therapy

*** Chemotherapy combination includes gemcitabine, taxotere, vinorelbine, capecitabine plus oxaliplatin, abraxane, carboplatin, doxorubicin, carboplatin plus taxotere, carboplatin plus doxorubicin, carboplatin plus taxol, carboplatin (or cisplatin) plus gemcitabine, cyclophosphamide, enzastaurin.

Abbreviations: N/A; not applicable

Table 2:

Drug-related adverse events by maximum grade per patient (N=54)

Adverse Event	Bevacizumab- naïve (N=41)			Bevacizumab-prior (N=13)		
	Maximum Grade			Maximum Grade		
	2	3	4	2	3	4
Hypertension	5 (12%)	16 (39%)	1 (2%)	4 (31%)	-	-
Thromboembolic events*	-	4 (10%)	1 (2%)	-	-	-
Small intestinal perforation	-	1 (2%)	-	-	-	-
Anal fissure	-	1 (2%)	-	-	-	-
Renal hemorrhage (arterial)	-	1 (2%)	-	-	-	-
Rash acneiform	-	1 (2%)	-	-	-	-
Palmar-plantar erythrodysesthesia syndrome (Hand foot syndrome)	26 (63%)	1 (2%)	-	8 (62%)	-	-
Oral mucositis	4 (10%)	-	-	4 (31%)	-	-
Weight loss	2 (5%)	-	-	1 (8%)	-	-
Anorexia	2 (5%)	-	-	-	-	-
Upper respiratory infection	2 (5%)	-	-	-	-	-
Diarrhea	1 (2%)	-	-	2 (15%)	-	-
Hypothyroidism	-	-	-	2 (15%)	-	-
Fatigue	1 (2%)	-	-	1 (8%)	-	-
Weight gain	1 (2%)	-	-	-	-	-
Nausea	1 (2%)	-	-	-	-	-
Dysgeusia	1 (2%)	-	-	-	-	-
Proctitis	1 (2%)	-	-	-	-	-
Pain in extremity	1 (2%)	-	-	-	-	-
Peripheral sensory neuropathy	1 (2%)	-	-	-	-	-
Rash maculo-papular	1 (2%)	-	-	-	-	-
Urticaria	1 (2%)	-	-	-	-	-
Vaginal inflammation	1 (2%)	-	-	-	-	-
Labial cyst	1 (2%)	-	-	-	-	-
Laboratory						
AST increased	-	2 (5%)	-	-	2 (15%)	-
ALT increased	-	2 (5%)	-	1 (8%)	1 (8%)	-
Hypophosphatemia	5 (12%)	1 (2%)	-	1 (8%)	-	-
Proteinuria	3 (7%)	-	-	2 (15%)	-	-
Lipase increased	3 (7%)	-	-	1 (8%)	-	-
Amylase increased	1 (2%)	-	-	1 (8%)	-	-
Bilirubin increased	-	-	-	1 (8%)	-	-

* Two patients developed right neck jugular vein clots related to the catheter, and three developed grade 3 deep vein thrombosis and pulmonary embolism (PE) (n=2) and grade 4 PE (n=1).