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A Phase I Trial of Pegylated Liposomal Doxorubicin (PLD), Carboplatin, Bevacizumab and Veliparib in Recurrent, Platinum-Sensitive Ovarian, Primary Peritoneal, and Fallopian Tube Cancer: An NRG Oncology/Gynecologic Oncology Group study

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Abstract

Objective—To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of veliparib combined with PLD and carboplatin (CD) in patients with recurrent, platinum-sensitive epithelial ovarian cancer. To determine the tolerability at the MTD combined with bevacizumab.

Methods—Patients received PLD (30 mg/m², IV) and carboplatin (AUC 5, IV) on day 1 with veliparib on days 1-7 (intermittent) or days 1-28 (continuous). Standard 3+3 design was used in the dose escalation phase with DLTs based on the first cycle. Once the MTDs were determined, cohorts of 6 patients were enrolled to each regimen with bevacizumab (10 mg/kg on day 1 and 15)

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to assess feasibility. DLTs were based on the first 4 cycles of treatment in the bevacizumab cohorts.

Results—In the dose-escalation phase, 27 patients were treated at 3 dose levels with DLTs noted in 6 patients including grade 4 thrombocytopenia (n=4), and prolonged neutropenia >7 days (n=3). At the MTD of veliparib (80 mg p.o. b.i.d. for both dosing arms), myelosuppression was the DLT. At MTD, 12 additional patients were treated with bevacizumab with 9 patients experiencing DLTs including grade 4 thrombocytopenia (n=4), prolonged neutropenia >7 days (n=1), grade 3 hypertension (n=5), and grade 5 sepsis (n=1).

Conclusions—The MTD of veliparib combined with CD is 80 mg PO BID in women with recurrent, platinum-sensitive ovarian cancer. With bevacizumab, DLTs were noted in 9 out of 12 patients. Lower doses of veliparib will need to be considered when given in combination with platinum-based therapies.

Keywords

PARP inhibitors; VEGF inhibitors; thrombocytopenia

Introduction

Ovarian cancer is the most lethal gynecologic malignancy in the United States today with over 14,000 deaths anticipated in 2015 [1]. The principal reasons for this outcome are the advanced stage at diagnosis, the high rate of disease recurrence, and the eventual emergence of treatment resistance. Patients with recurrent disease frequently undergo multiple cycles of treatment with multiple drug regimens. Treatment planning is largely based on sensitivity to platinum agents. Patients with recurrent disease are categorized as either platinum-resistant/refractory based on relapse within 6 months of platinum-based treatment, or platinum-sensitive, based on recurrence more than 6 months after completion of platinum-based therapy [2,3]. Platinum-sensitive patients are more likely to achieve a response to second line chemotherapy but even so, are rarely cured [4,5]. Even in those patients who have an excellent response to therapy, the second remission is typically significantly shorter than the first remission [4,5]. While treatment options for recurrent disease have increased, the natural history of recurrent ovarian cancer has not changed and recurrent patients are expected to die of their disease. Because of this, goals of therapy in a recurrent setting should not only focus on improving the length of life, but also include a thoughtful review of anticipated side effects and the effect on quality of life (QoL).

Randomized studies have documented that platinum-based combination therapy is superior to single-agent platinum in extending progression-free survival (PFS) and in some cases improving overall survival (OS) for patients with platinum-sensitive ovarian cancer [4,6]. Unfortunately, a majority of patients will have been treated in the initial setting with paclitaxel and suffer with residual peripheral neuropathy. Recently, a randomized, multicenter, phase III trial (CALYPSO) tested the efficacy and safety of pegylated liposomal doxorubicin (PLD) and carboplatin (CD) compared with standard carboplatin and paclitaxel (CP) in patients with platinum-sensitive, recurrent ovarian cancer [5]. In this non-inferiority trial, 976 patients were randomized to carboplatin (AUC 5) plus PLD (30 mg/m²) every 4

weeks or carboplatin (AUC 5) plus paclitaxel (175 mg/m²) every 3 weeks. With median follow-up of 22 months, PFS for the CD arm was 11.3 months vs. 9.4 months for the CP arm [HR (hazard ratio), 0.821; 95% CI (confidence interval), 0.72 to 0.94; *P* = .005]. There was more non-hematologic grade >2 toxicity with CP resulting in early discontinuation of treatment. Specifically, there was more alopecia (83.6% v 7%), hypersensitivity reactions (18.8% v 5.6%), and sensory neuropathy (26.9% v 4.9%) compared to CD. Based on the provocative results from this trial, CD was selected as the cytotoxic backbone of therapy for this phase I trial.

Poly-ADP-ribose polymerase (PARP) inhibitors are one of the most promising classes of drugs in clinical trials in recent years [7,8]. PARP enzymes function to bind damaged DNA and result in the activation of catalytic activity, causing poly (ADP) ribosylation of itself and other key proteins [9,10]. This is thought to signal recruitment of other DNA repair mechanisms to facilitate repair of both single-stranded or double-stranded DNA breaks [11,12]. Hence, PARP inhibition will result in less efficient DNA repair following a cytotoxic insult. In addition, PARP inhibitors, such as veliparib, are also known to act as sensitizing agents for a variety of DNA-damaging agents including carboplatin [13]. Overall, it was hypothesized that continuous dosing of veliparib would provide the best approach to patients with known BRCA mutations, while intermittent dosing may suffice when using PARP inhibition for chemo-sensitization in patients with homologous recombination deficiency [14].

In addition, there are data in the pre-clinical setting that would suggest a synergistic effect of PARP inhibitors when combined with angiogenesis inhibitors (15, 16). Homologous recombination repair genes appear to be downregulated with hypoxia which resets PARP inhibitor sensitivity. BRCA1 and BRCA2 are also downregulated in ovarian cancer cells with VEGF inhibition (17). At the time of the concept of this study, there had not been any clinical data to demonstrate the efficacy or toxicity of adding a VEGF inhibitor in combination with cytotoxic chemotherapy and a PARP inhibitor in patients with platinum sensitive recurrent ovarian cancer.

The objective of this study is to determine the maximum tolerable dose as defined by cycle 1 for veliparib given in an intermittent and continuous schedule in combination with CD at the time of first recurrence in a platinum-sensitive ovarian cancer population. In addition, given the increase in PFS with bevacizumab in combination with chemotherapy in both platinum-sensitive and resistant disease once the maximum tolerated dose (MTD) is established, bevacizumab will be added to determine tolerability [15,16].

Materials and Methods

Eligibility criteria

Eligible patients included those with a histologic diagnosis of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer documented by elevated CA 125, or clinically measurable disease, or non-measurable disease (defined as symptomatic ascites or pleural effusions, solid and/or cystic abnormalities on imaging that do not meet RECIST 1.1 criteria [17]. Patients must have had a platinum-free interval of at least 6 months following initial

platinum-based chemotherapy. Patients that received maintenance therapy in front-line treatment with biologics, hormones, or taxanes were eligible for the study as long as at least 6 months had passed from the initial platinum-based chemotherapy. Patients were not eligible if they had received more than one prior chemotherapy regimen, a PARP inhibitor, or PLD. Additionally, a GOG performance status of 0 or 1 was required. Laboratory criteria for eligibility included an absolute neutrophil count (ANC) $\geq 1,500/\text{mcl}$, platelets $\geq 100,000/\text{mcl}$, creatinine ≤ 1.5 times the institutional upper limit of normal (ULN), bilirubin <1.2 times the ULN, alanine transaminase and aspartate transaminase ≤ 3.0 times the ULN, and alkaline phosphatase ≤ 2.5 times the ULN and left ventricular ejection fraction (LVEF) $\geq$ institutional lower limit of normal (LLN) as determined by gated cardiac radionuclide scan (MUGA) or echocardiogram. Pretreatment neuropathy (sensory and motor) was also assessed and required to be $\leq$ grade 1 using National Cancer Institute Common Toxicity Criteria version 4.0 (NCI CTCAE v4). Additional criteria for patients treating on the bevacizumab cohort included the requirement for a urine protein of $<2+$ on urine analysis or <1000 mg on 24-hour urine. In addition, patients receiving bevacizumab could not have a serious non-healing wound, ulcer or bone fracture, a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the last 6 months, or significant cardiovascular disease. Patients that had previously received bevacizumab in first-line therapy were not excluded from participation. This study was reviewed and approved by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute. All patients gave written informed consent before study entry in compliance with institutional, state, and federal regulations.

Treatment

All patients were treated with PLD $30 \text{ mg}/\text{m}^2$ followed by carboplatin AUC 5. Veliparib was administered one hour prior to the chemotherapy at various Dose Levels (DL 1 = 50 mg; DL 2 = 80 mg; DL 3 = 120 mg) as per protocol. Subsequent doses of veliparib were taken twice daily on days 1-7 for patients on the intermittent arm and on days 1-28 for patients on the continuous arm. Patients were instructed to not take a missed dose or double the next dose if they vomited or missed a dose, but rather to continue with the assigned dosing schedule. Patient Pill Calendars were provided for all patients with instructions to record the date, time and number of veliparib capsules taken in the morning and evening, and to return the calendar and any unused pills at each appointment. Anti-emetics were recommended and given at the discretion of the treating physician. No growth factor support was allowed unless indicated by a dosing modification in the protocol. The cycles were repeated every 28 days for up to 10 cycles if the patient was still responding and tolerating treatment. Continuation of therapy beyond 10 cycles was allowed on a case-by-case basis. Once the MTD for the combination of veliparib, and CD was determined, six evaluable patients in both the intermittent and continuous arms of the study were treated with bevacizumab ($10 \text{ mg}/\text{kg}$) on days one and 15 to determine tolerability.

Evaluation of toxicity

Patients underwent weekly laboratory evaluations and toxicity assessments as graded by the NCI CTCAE v4. Dose limiting toxicities (DLTs) were defined as study drug-related adverse events during cycle 1 during the dose escalation portion of the study. For evaluation of the

bevacizumab cohorts, DLTs were examined in the first 4 cycles of treatment. Hematologic DLTs included: dose delay of >3 weeks due to failure to recover counts, febrile neutropenia, grade 4 neutropenia >7 days, grade 4 thrombocytopenia, or grade 3 thrombocytopenia with clinically significant bleeding. Non-hematologic DLTs included any grade 3 or 4 adverse event (excluding anorexia, fatigue, nausea/vomiting, diarrhea, dehydration, constipation, hypersensitivity reaction to PLD and/or carboplatin, hypokalemia, hypomagnesemia, hypocalcemia, hypophosphatemia if recovered in 48-72 hours with maximal medical management) and any drug-related death. Any dose delay for >3 weeks due to toxicity was also considered a DLT. Subsequent cycles of treatment did not begin until all toxicities were grade 1 or below. For patients with dose-limiting neutropenia or thrombocytopenia, veliparib was held until ANC recovered to 1,500 cell/mcl or 100,000/mcl, respectively.

Statistical design

In the dose escalation phase, the MTD was identified for the intermittent and continuous dosing of veliparib in combination with CD using a standard 3+3 design. Dose escalation for each cohort of three patients continued until a DLT was observed during the first cycle of therapy. If one patient out of three experienced a DLT, an additional three patients were enrolled at that dose level. The MTD was determined by the maximum dose level achieved at which 1 patient (among six) experienced a DLT. No intra-patient dose escalation occurred. No patients were enrolled at the next higher level of dose until all patients at the previous dose level had been followed through the end of the first cycle.

Results

Patient characteristics

Thirty-nine patients were enrolled from May 2012 to August 2013. The first 27 patients were enrolled in the dose escalation phase with 12 and 15 patients in the veliparib intermittent and continuous dosing arms, respectively. The mean patient age at enrollment was 62 years (range from 41-80). Baseline characteristics for all treated patients are shown in Table 1. There were no clinically significant differences in the patients enrolled in either arm. Once the MTD for both the veliparib intermittent and continuous dosing arms was determined, 12 additional patients were enrolled (six to intermittent dosing, six to continuous dosing) to assess the feasibility of adding bevacizumab to the treatment regimen of CD and veliparib.

Dose escalation phase

Three patients were enrolled at Dose Level 1 for the intermittent and continuous dosing schedule receiving oral veliparib twice daily at 50 mg in combination with IV carboplatin (AUC 5) and IV PLD (30 mg/m²). None of the three patients experienced DLTs on the intermittent arm. One patient did experience a DLT at Dose Level 1 on the continuous arm with grade 4 neutropenia >7 days. The continuous dosing cohort was expanded to an additional three patients, with no additional DLTs noted on Dose Level 1. Study participants were then enrolled on Dose Level 2 for both intermittent and continuous dosing with none of the patients experiencing a DLT. The study was then expanded to Dose Level 3. On the intermittent arm, two of the three patients had DLTs with grade 4 thrombocytopenia and

grade 4 neutropenic fever. Likewise on the continuous arm, another two of the three patients had DLTs with grade 3 hyponatremia and grade 4 thrombocytopenia. Given these findings, Dose Level 2 was expanded for another three patients on both dosing arms to determine if this was the MTD. On the intermittent arm, one patient out of a total of six patients had a DLT with grade 4 neutropenia >7 days and grade 4 thrombocytopenia. On the continuous arm, none of the six patients treated at this dose had evidence of DLT. Therefore, the MTD was determined to be 80 mg p.o. b.i.d. The most common grade 3 or 4 toxicities occurring in both regimens included gastrointestinal and metabolic adverse events. Cycle 1 DLTs for the dose escalation phase for all treated and DLT-evaluable patients are noted in Table 2. For patients treating at the MTD, 4 of 6 patients completed at least 6 cycles of therapy in the intermittent dosing arm. One patient had progressive disease after 2 cycles and was excluded from the study, and the other patient was excluded from the study due to an extended delay in treatment(> 21 days) due to thrombocytopenia after receiving cycle 5. For patients on the continuous dosing arm at the MTD, 5 of 6 patients completed at least 6 cycles of therapy. The only patient that failed to complete the study at this dosing elected to stop treating for patient preferences.

For the bevacizumab cohort, six evaluable patients were enrolled for each dosing arm with DLTs determined by the first four cycles of treatment. For the six patients receiving an intermittent dose of veliparib, four patients experienced a DLT over the course of the first four cycles of treatment including grade 3 hypertension (n=2), grade 4 thrombocytopenia (n=2), and grade 4 neutropenia >7 days (n=1). Likewise, on the continuous dosing arm, five of six patients experienced a DLT during the first four cycles of treatment including grade 4 thrombocytopenia (n=3) and grade 3 hypertension (n=3). There was one treatment-related death that occurred on the study due to grade 5 sepsis. On cycle 1, day 15 of treatment on regimen 2, the patient was admitted to the hospital for paracentesis with grade 2 dyspnea related to her ascites. At admission she was noted to have grade 4 thrombocytopenia and grade 4 neutropenia, but afebrile. During her brief hospital stay she had a witnessed aspiration which rapidly led to sepsis, multi-organ system failure, and death. Cycle 1-4 DLTs for all treated and DLT-evaluable patients for the bevacizumab cohort are summarized in Table 2.

The objective tumor response for all treated patients was also noted as a secondary outcome measure for the 25 patients that had measureable disease at the time of study entry (Table 3). Seventeen patients (68%) were noted to have a complete (n=7, 28%) or partial response (n=10, 40%) to treatment, with progression of disease in only 2 patients (8%).

Discussion

The results from the CALYPSO trial demonstrated that doublet therapy with CD was non-inferior to CP in terms of PFS (HR 0.82, $P = .005$) [4]. Importantly, this regimen was associated with less carboplatin hypersensitivity, peripheral neuropathy, prolonged neutropenia, and alopecia [18,19]. Hence, the doublet of CD emerged as a favorable option for patients in the recurrent setting. PARP inhibitors, such as olaparib, have also proven to be a very promising class of drugs for patients with ovarian cancer. Maintenance monotherapy with olaparib has been noted to result in significant improvement in median

PFS compared with placebo in patients with platinum-sensitive recurrent serous ovarian cancer (8.4 months with olaparib vs. 4.8 months with placebo; HR 0.35 [95% CI 0.25-0.49]; $p<0.001$) [20]. When patients were stratified by BRCA mutation, median PFS was significantly longer in the olaparib group compared to the placebo group (11.2 months vs. 4.3 months, respectively; HR 0.18 [95% CI 0.10-0.31]; $p<0.001$) [21]. Although the PFS difference was lower for patients with wild-type BRCA, the olaparib group still had significantly greater PFS compared to the placebo group (7.4 months vs. 5.5 months, respectively; HR 0.54 [95% CI 0.34-0.85]; $p=0.0075$).

PARP inhibitors have also been used effectively in combination with other agents in patients with recurrent, platinum-sensitive, high-grade serous or endometrioid ovarian with or without BRCA mutations. In a phase II randomized trial, patients with relapsed, platinum-sensitive, high grade serous or endometrioid tumor treated with olaparib and cediranib (VEGF inhibitor) had a median PFS of 17.7 months compared to 9.0 months for patients treated with olaparib monotherapy [22]. Grade 3 and 4 toxicity were more common in patients treating with both angiogenesis and PARP inhibitors compared to the patients who received only olaparib with hypertension as the most common event. This is consistent with the toxicity from our study noted in the bevacizumab cohort. In another randomized phase II trial, patients with recurrent, platinum-sensitive, high grade serous or endometrioid ovarian cancer treated with the combination of olaparib, paclitaxel, and carboplatin followed by maintenance with olaparib had a significantly greater PFS compared to patients receiving paclitaxel and carboplatin alone (12.2 months vs. 9.6 months, respectively; (HR 0.51; [0.34-0.77]; $p=0.012$). As noted by Lederman and colleagues, the greatest clinical benefit was noted in patients with BRCA mutations [21,23].

Although germline BRCA1 and BRCA2 mutations are currently thought to account for about 10-18% of ovarian cancers, there are a number of other proteins involved in homologous recombination repair which are now recognized to contribute to hereditary cancer risk [24,25,26]. Given that homologous recombination deficiency is prevalent in ovarian cancer and are predictive of response to platinum agents, we envisioned that the addition of a PARP inhibitor to this regimen could further extend PFS without undue toxicity for patients. Due to profound thrombocytopenia – which is presumed to be due to potentiation of the effects of carboplatin – and significant neutropenia, we were unable to increase the dose of veliparib beyond the lowest doses when combination with platinum-based therapy. In retrospect, the use of cisplatin rather than carboplatin in combination with PLD may have enabled us to safely expand the dose of veliparib without experiencing the early and significant dose limiting toxicity of thrombocytopenia, although admittedly cisplatin with its requirement for hydration extending the treatment time and its other toxicities may not be an ideal substitute for carboplatin in women with recurrent disease. Alternatively, a lower dose of carboplatin (AUC 4) was effectively used by Oza and colleagues in combination with paclitaxel and olaparib and may have resulted in less marrow suppression [23].

Our study also assessed the addition of bevacizumab to the treatment regimen at the MTD for veliparib over four cycles of treatment. In a recent phase II trial, the feasibility of PLD, carboplatin and bevacizumab was assessed in 54 patients with platinum-sensitive, recurrent

ovarian cancer. The patients received PLD at 30 mg/m² with carboplatin at AUC 5 on day 1 plus bevacizumab 10 mg/kg on days 1 and 15 of every 28 day cycle [27]. The objective response rate was 72.2% (95% CI: 58.4-83.5) with a median duration of response 11.9 months and median time to progression of 13.9 months. Three patients (5.6%) discontinued therapy due to serious adverse events (grade 4 thrombocytopenia, grade 3 bowel obstruction/perforation, and grade 3 abdominal abscess). Ninety-two percent of patients reported 1 adverse effect which was most commonly neutropenia (42.6%), hypertension (37.0%), stomatitis (37.0%), proteinuria (37%) and palmar-plantar erythrodysesthesia (27.8%), but most were able to continue treatment with no deaths reported. In our study, we added bevacizumab to the combination of PLD, carboplatin, and veliparib. However, nine of twelve evaluable patients experienced protocol defined DLTs related to this combination including thrombocytopenia, neutropenia, and hypertension.

In conclusion, our results indicate that even modest doses of veliparib in either intermittent or continuous dosing when combined with CD in a population of patients with recurrent, platinum-sensitive ovarian cancer results in significant hematologic toxicity. The addition of bevacizumab to this regimen carried the risk of additional toxicity associated with VEGF inhibitors. Given the activity of PARP inhibitors in platinum sensitive disease, further exploration of this combination administering carboplatin at a lower AUC, or administering veliparib only as maintenance therapy following treatment for platinum sensitive relapse, may be warranted.

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Table 1
Baseline characteristics – all treated patients

	All N (%)
N	40
Age Group	
40-49	4 (10%)
50-59	15 (38%)
60-69	10 (25%)
70-79	10 (25%)
80	1 (3%)
Race	
Caucasian	37 (93%)
African American	1 (3%)
Unknown	2 (5%)
Performance status	
0	31 (78%)
1	9 (9%)
Cell type	
Adenocarcinoma, NOS	1 (3%)
Clear cell carcinoma	1 (3%)
Mixed epithelial	1 (3%)
Serous adenocarcinoma	37 (93%)
Measurable disease	
No	15 (38%)
Yes	25 (63%)
Number of cycles	
< 6	13
6	11
> 6	16
Median	6
Range (min – max)	1-26 [‡]

[‡]Two patients remain on study: one on regimen I with bevacizumab who has received 20 cycles and one on regimen II with bevacizumab who has received 26 cycles.

Treatment related grade 3-4 adverse events by regimen and dose level for all evaluable patients

Table 2

System Organ Class/Term	Treatment/Adverse Event Grade											
	DL 1 (50 mg ABT-888)				DL 2 (80 mg ABT-888)				DL 3 (120 mg ABT-888)			
	Intermittent	Continuous	G3	G4	Intermittent	Continuous	G3	G4	Intermittent	Continuous	G3	G4
Blood/Lymphatics	0	0	0	0	1	1	0	0	1	0	0	0
Anemia	0	0	0	0	1	1	0	0	1	0	0	0
Gastrointestinal	0	0	0	0	1	0	0	0	1	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	1	0	0	0	0	0	0	0
Nausea	0	0	0	0	1	0	0	0	1	0	0	0
Vomiting	0	0	0	0	0	0	0	0	1	0	0	0
General and administration	0	0	0	0	0	1	0	0	0	0	0	0
Fatigue	0	0	0	0	0	1	0	0	0	0	0	0
Infections/infestations	0	0	0	0	1	0	0	0	1	0	0	0
Lung infection	0	0	0	0	0	0	0	0	1	0	0	0
Infections and infestations	0	0	0	0	1	0	0	0	0	0	0	0
Investigations	0	1	3	2	3	1	3	2	0	2	1	1
Neutrophil count decreased	0	1	1	2	3	1	4	0	0	2	1	1
Platelet count decreased	1	0	4	0	1	1	1	2	0	2	0	4
White blood cell decreased	1	0	2	1	2	0	2	0	1	1	0	1
Metabolism/nutrition	0	0	0	0	1	1	1	0	1	0	0	0
Acidosis	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0
Hyperkalemia	0	0	0	0	0	0	0	0	1	0	0	0
Hypokalemia	0	0	0	0	2	0	1	0	1	0	0	0
Hypomagnesemia	0	0	0	0	0	0	1	0	1	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	0	0	0	0
Hypophosphatemia	0	0	0	0	0	0	1	0	0	0	0	0

System Organ Class/Term	Treatment/Adverse Event Grade											
	DL 1 (50 mg ABT-888)				DL 2 (80 mg ABT-888)				DL 3 (120 mg ABT-888)			
	Intermittent	Continuous	G3	G4	Intermittent	Continuous	G3	G4	Intermittent	Continuous	G3	G4
Musculoskeletal	0	0	0	0	0	0	0	0	0	1	0	0
Muscle weakness lower limb	0	0	0	0	0	0	0	0	0	1	0	0
Respiratory/thoracic	0	0	0	0	0	0	0	0	1	0	0	0
Epistaxis	0	0	0	0	0	0	0	0	1	0	0	0
Vascular disorders	0	0	0	0	1	0	0	0	0	0	2	1
Hypertension	0	0	0	0	0	0	0	0	0	0	2	1
Thromboembolic event	0	0	0	0	1	0	0	0	0	0	0	0

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Table 3
Objective Tumor Response – All treated patients. (I – intermittent dosing with veliparib; II – continuous dosing with veliparib

	Regimen				
	All n (%)	I n (%)	II n (%)	I with Bevacizumab n (%)	II with Bevacizumab n (%)
N	25	10	8	2	5
Objective Tumor Response					
Complete Response	7	3	2	0	2
Partial Response	10	2	3	2	3
Stable	3	2	1	0	0
Increasing Disease	2	2	0	0	0
Indeterminate	3	1	2	0	0